NATIONAL PLAN RARE DISEASES LUXEMBOURG

2018 2022

LE GOUVERNEMENT
DU GRAND-DUCHÉ DE LUXEMBOURG
Ministère de la Santé

Direction de la santé

MINISTERIAL FOREWORD

A disease is defined as rare when it affects fewer than one in 2,000 people. In Europe, an estimated number of 30 million people suffer from a rare disease, around 30,000 of which live in Luxembourg.

Although rare diseases are vastly diverse, they share common features. Most often, they are severe, chronically debilitating and degenerative diseases, fatal in the short or medium term. In 50% on the cases, onset occurs during childhood. The quality of life of people with rare diseases is often impacted by their loss of autonomy and their condition also comes with psychological, social and financial consequences.

Because of their low prevalence and lesser known characteristics, rare diseases often go undetected by non-specialist doctors. On average, it takes more than four years for a person to get a diagnosis and specialist care. For some patients and their families, the diagnostic odyssey entails multiplying consultations while seeking medical advice both in Luxembourg and abroad, travelling long distances and being burdened by considerable expenses.

Once the diagnosis has finally been obtained, the patient faces another problem: 95% of rare diseases are orphan diseases, meaning no real treatment exists. At best, the progression of the disease can be curbed and the symptoms alleviated.

This highlights the need for specialised and integrated care pathways for patients with a rare disease. A global approach is necessary to address their physical, emotional, mental and social health but also to assure that their needs are met when it comes to education and professional integration, and that they are supported financially if required.

The national survey conducted by the rare diseases task force MARA from 2006 to 2011 resulted in the first mapping of rare diseases in Luxembourg and provided a fundamental contribution to developing a national plan. This first National Plan for Rare Diseases 2018-2022 aims to continue the fight against these diseases in Luxembourg by mobilising all relevant stakeholders around a national strategy.

The government and all the partners who have contributed to the elaboration of this plan are committed to alleviate the burdens of rare diseases for patients and their families by ensuring them equal access to diagnosis, provision of appropriate medical and psychological and social treatment and care, a fair and broad coverage from the health and dependency insurance and the possibility of having their educational, professional and personal needs met.

Rare diseases are a public health issue that cannot be ignored. You can count on my determination and commitment to improve the ways the needs and expectations of rare disease patients and their families are met.

My sincere thanks to the members of the Steering Committee and to all the subgroups who have contributed to bringing this plan to completion.

Lydia MUTSCH
Minister for Health

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STEERING COMMITTEE OF THE NATIONAL PLAN FOR RARE DISEASES

TITLE	SURNAME	FIRST NAME	INSTITUTION
Dr	**BERTHET**	Françoise	DIRECTORATE FOR HEALTH
Ms	**BORDE**	Patricia	LABORATORY OF NATIONAL HEALTH Vice Chairman of the Steering Committee
Dr	**CHIOTI**	Anna	LUXEMBOURG INSTITUTE OF HEALTH
Ms	**CROHIN**	Gwennaëlle	ALAN RARE DISEASES LUXEMBOURG
Pr	**DAHAN**	Karin	NATIONAL HEALTH LABORATORY
Dr	**DE BEAUFORT**	Carine	HOSPITAL CENTRE OF LUXEMBOURG
Dr	**DE PERDIGO**	Arantzazu	NATIONAL HEALTH LABORATORY
Dr	**EVEN**	Jos	ALAN RARE DISEASES LUXEMBOURG Chairman of the Steering Committee
Ms	**FEIDER**	Shirley	ALAN RARE DISEASES LUXEMBOURG
Ms	**GENOUX-HAMES**	Jacqueline	MINISTRY OF HEALTH Department of pharmacy and pharmaceuticals
Dr	**HOFFMANN**	Michel	NORTHERN HOSPITAL CENTRE
Dr	**HOLBACH**	Gérard	SOCIAL SECURITY MEDICAL INSPECTORATE
Dr	**LECHES**	Marguerite	HOSPITAL CENTRE OF LUXEMBOURG
Mr	**MOES**	Olivier	MINISTRY OF HEALTH Department of pharmacy and pharmaceuticals
Dr	**PAULY**	Fernand	HOSPITAL CENTRE OF LUXEMBOURG
Ms	**POLONI***	Francesca	NATIONAL PLAN COORDINATION
Mr	**RIES**	Marc	ALAN RARE DISEASES LUXEMBOURG
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Dr	**TABOURING**	Patrick	GENERAL PRACTITIONER
Ms	**TRIERWEILER**	Sonja	MINISTRY OF SOCIAL SECURITY National Health Fund
Dr	**WAGENER**	Yolande	HEALTH DIRECTORATE School Health Department
Dr	**ZIADE**	Bechara	HEALTH DIRECTORATE School Health Department

** Editor of the plan on behalf of the Steering Committee*

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The National Plan for Rare Diseases' website:
www.maladiesrares.lu

The National Plan for Rare Diseases 2018-2022 was approved by the Government Council on 2 March 2018.

ACRONYMS

ACRONYM	DEFINITION
ALAN	ALAN - Maladies Rares Luxembourg
BaMaRa	Banque Maladies Rares
CF	Cystic Fibrosis
CHdN	Centre Hospitalier du Nord
CHL	Centre Hospitalier de Luxembourg
CIEC	Centre d'Investigation et d'Épidémiologie Clinique
CLMMA	Centre Luxembourgeois de Mucoviscidose et des Maladies Apparentées
CNGH	Centre National de Génétique Humaine
CNMR	Comité National Maladies Rares
CNS	Caisse Nationale de Santé
COMP	The Committee for Orphan Medicinal Products
CoNGO	Conference of NGO's
DECCP	Diabetes and Endocrinology Care Clinique Pédiatrique
DSP	Dossier de Soins Partagé
EC	European Commission
ECRIN	European Clinical Research Infrastructure Network
EMA	Agence Européenne du Médicament - European Medicine Agency
E-RARE	ERA-Net for Research Programmes on Rare Diseases
ERIC	European Research Infrastructure Consortium
ERN	European Reference Networks
EU	European Union
EUCERD	The European Union Committee of Experts on Rare Diseases, founded in 2010 and replaced by the EC Expert Group on Rare Diseases in 2013
EUPATI	European Patients Academy on Therapeutic Innovation
EUROCAT	European network for surveillance of congenital anomalies
EUROPLAN	European Project for Rare Diseases National Plans Development
EURORDIS	European Organisation for Rare Diseases (recently renamed Rare Diseases Europe)
Groupe MARA	Groupe de travail Maladies Rares
IBBL	Integrated BioBank of Luxembourg
INSERM	Institut National de la Santé et de la Recherche Médicale
IRDIRC	International Rare Diseases Research Consortium
LBMCC	Laboratoire de Biologie Moléculaire et Cellulaire du Cancer
LCSB	Luxembourg Centre for Systems Biomedicine
LIH	Luxembourg Institute of Health
LNS	Laboratoire National de Santé
NCRD	National Committee for Rare Diseases
NPRD	National Plan for Rare Diseases
ORPHANET	Portail des maladies rares et des médicaments orphelins www.orpha.net
PAH	Pulmonary Arterial Hypertension
RD	Rare Diseases

SUMMARY

A disease is defined as rare in the European Union when it has a particularly low prevalence, affecting less than 1 in 2,000 people.

There is a wide diversity of rare diseases (RD) but the people affected by them share the same challenges when it comes to diagnosis, treatment and management of their condition. Special attention and global action is needed to help them through their difficult patient journey, with a diagnosis process often drawn-out by dearth of expertise and exceptional clinical expression, the burdens of a debilitating chronic condition and a treatment with heavy social and financial consequences. Over time, these circumstances compel patients and their families to take care into their own hands.

Rare diseases affect 30 million Europeans, which amounts to around 30,000 people in Luxembourg, making **RD** a public health problem that cannot be ignored. The National Plan for Rare Diseases 2018-2022 (**NPRD**) was developed is response to the recommendations set forth by the governmental programme in 2013 and by the Council of the European Union in 2009. The aim is to better meet the needs and expectations of rare disease patients and their families and to guide, coordinate and structure actions within the field of **RD** in an improved way.

FIVE AREAS OF ACTION HAVE BEEN DEVELOPED TO MEET THE OVERALL OBJECTIVE OF THE NPRD:

GENERAL

General line of action

- Implementation of a NPRD governance framework
- Improvement of the patient diagnostic journey and care pathway with the help of an orientation unit and a team of coordinators
- Development of a policy for raising awareness about RD
- Adoption of a multidisciplinary approach and a holistic vision of patient care
- Grouping of all related stakeholders in a National RD Alliance

A

Area A
Improve care and treatment

- Application of the principle of prevention to RD
- Consolidation of a genetic counselling service for RD patients and their families
- Improvement of access to medication
- Development of a care pathway for different groups of RD
- Commitment to continuity of care for those affected

B

Area B
Facilitate access to information on RD through the creation of a national platform

- Improvement of access to information on RD in Luxembourg
- Optimisation of the use of resources available in the country
- Development of international links and collaborations
- Organisation of a first support helpline for patients
- Provision of training programmes dedicated to RD

C

Area C
Enhance recognition of RD specificities and promote research

- Organisation of a national RD census
- Improvement of RD traceability in Luxembourg
- Implementation of data collection in line with European regulations
- Adoption of a system for national monitoring
- Intensification of implication in research projects at international and national level

D

Area D
Respond to the psychological and social support needs of patients and their families

- Improvement of the quality of psychological and social care for patients, their families and their carers
- Simplification of access to administrative procedures
- Commitment to ensure equity of social rights for RD patients
- Development of measures to facilitate the educational pathway of people affected by RD
- Offering of social and professional support to people with RD and their family members

Following the Government Council's approval of the **NPRD**, a detailed implementation plan including the lines of actions will be defined by the Comité National des Maladies Rares (National Committee for Rare Diseases, **NCRD**).

1. Introduction

In Luxembourg's 2013 government programme, it was stated that "a national plan for rare diseases will be developed together with national and international organisations such as EURORDIS".

The aim of this plan is to improve how the needs and expectations of rare disease patients and their families are being met and to provide better guidance, coordination and structure to activities within the field of RD.

The rare diseases task force MARA was created in 2005. The results of the national survey[1] it carried out were published in 2011 and enabled a first assessment of the experiences and needs of rare disease patients in Luxembourg. The EUROPLAN conference[2], which took place in November 2013 in Luxembourg, allowed to identify the main areas to be included in this plan.

The National Plan for Rare Diseases (NPRD) follows the recommendations made by the Council of the European Union (EU) in 2009[3] as well as those put forward by EUROPLAN in 2010[4].

1. "Rare diseases: Survey on the situation of people with rare diseases in the Grand Duchy of Luxembourg". *Study carried out by the Rare Diseases Working Group (MARA), date of publication: February 2011, Editor: Ministry of Health - Health Directorate*
2. "Luxembourg EUROPLAN National Conference - Final Report", *19-20 November 2013, Luxembourg. Source: https://www.eurordis.org/sites/default/files/ flags/finalreport-luxembourg.pdf*
3. "Council recommendation of 8 June 2009 on an action in the field of rare diseases" (2009/C 151/02)
4. "Recommendations for the development of national plans for rare diseases - Guidance document", *8 March 2010, EUROPLAN.*
Source: http://download.eurordis.org/europlan/ 2_EUROPLAN_Guidance_Documents_for_the_ National_Conference/3_EUROPLAN_Draft_ Recommendations_8%20March_10.pdf

2. Rare Diseases (RD) in Europe

A DEFINITION AND ORIGIN OF RD

A disease is defined as rare when it has a particularly low prevalence. In Europe, the rate of prevalence adopted–including by the European Regulation on Orphan Medicinal Products–is less than 1 in 2,000 individuals[5].

Most RD have a genetic component. However any disease whether it is infectious, neoplastic or auto-immune can by definition be considered as rare if its prevalence is less than 1/2000 and no easily available treatment is known.

RD are often debilitating and can be life-threatening on the short or medium term.

They require complex medical, paramedical and psychological and social care, with attention not only to the patients themselves but also to the people who support them. In half of the cases, RD develop in childhood and it is estimated that they are responsible for over 30% of infant mortality.

Furthermore, it should be noted that a number of syndromes without a name are most probably also RD that are currently unknown.

Around 80% of RD are genetic in origin and affect 3%-4% of newborns. A list of all RD recorded to date was recently published[6]. In certain cases, the term orphan diseases is also used.

B DIVERSITY AND HETEROGENEITY OF RD

Currently, it is estimated that about 30 million Europeans in 27 EU-countries are affected by a rare disease[7]. Though they have a low prevalence individually, it's important to stress that RD are significant contributors to a number of serious health outcomes and public health issues.

According to the European Medicines Agency (EMA) between 5,000 and 8,000 RD have been identified in the EU. It is estimated that European populations have a 6%-8% lifetime prevalence of having a rare disease[8]. And as new diagnostic methods and genetic and biochemical testing methods are being made available, more and more RD are identified.

On average, five new RD are described each week in scientific publications and the number of people affected is steadily increasing. The growing interest in RD from the medical and scientific communities witnessed these past 20 years reflects the heightened awareness[7].

5 Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products.

6 The Orphanet notebooks: *List of rare diseases and their synonyms: Listed in alphabetical order with their code in the Orphanet nomenclature. July 2017.*

7 *Source :* http://www.who.int/medicines/areas/priority_medicines/BP6_19Rare.pdf . Background Paper 6.19 Rare Diseases Priority Medicines for Europe and the World "A Public Health Approach to Innovation" *S. van Weely, and Prof. H.G.M. Leufkens. 12 March 2013.*

8 *Source :* http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000029.jsp. *Data accessed on 31 October 2017.*

C COMMON CHARACTERISTICS OF RD

Despite their great diversity, RD share a distinct set of common traits[9].

- RD are severe, chronic, often degenerative and life-threatening in the short or medium term
- The onset of the disease occurs in childhood for 50% of RD
- The quality of life of RD patients is often compromised by the lack or loss of autonomy and their condition also comes with psychological, social and economic consequences. For the families and carers of people suffering from a RD, the burden is also heavy.
- Only in certain cases can a RD be treated and the treatment is then rarely curative. At best, the progression of the disease can be curbed and the symptoms alleviated.
- RD are extremely difficult to manage for the families who not only encounter difficulties in finding a medical team capable of forming a proper diagnosis but also have to face the lack of an adequate treatment. After a more or less long-lived diagnostic odyssey, the RD patients and those supporting them have to learn to live with their debilitating condition on an everyday basis while putting in place whatever helping measures and assistance they can find.

Over time, patients and their families are compelled to take care into their own hands.

D DIAGNOSTIC ODYSSEY PHENOMENON

The diagnostic odyssey is the succession of steps patients and their families go through from the onset of their symptoms to an actual diagnosis of the disease[10]. The route through endless consultations and examinations can be difficult and long, with many patients having to make 'medical pilgrimages' in the hope of finding an accurate diagnosis.

The average length of time from symptom onset to diagnosis is four years and 30% of patients suffering from a RD never get a precise diagnosis for their condition.

Excessive delays in diagnosis are not without medical, paramedical, psychological and social implications for the patients and their families. The delays mean that opportunities for timely interventions can be missed while symptoms worsen. The misdiagnoses many patients receive along the way also result in inappropriate treatments, which in turn can lead not only to aggravating the symptoms but also to premature death. The lack of information concerning the hereditary genetic origin of some conditions is also a tragedy for families who might have several affected children.

9 *Source :* https://www.eurordis.org/sites/default/files/publications/princeps_document-EN.pdf . "Rare Diseases: understanding this Public Health Priority". EURORDIS, November 2005.

10 Bernard BARATAUD, « RARE DISEASES», *Encyclopædia Universalis [online],], accessed 18 octobre 2017. URL :* http://www.universalis.fr/encyclopedie/maladies-rares/

In France, the measures developed in the first (2005-2008)[12] and second (2011-2014)[13] national plans on rare diseases have led to a significant improvement, noticeable since 2010.

The creation of national networks for RD in the second national plan aims to improve care of patients and their families. Patients are moved into a suitable hospital structure quicker.

While a quarter of them once had to wait for more than four years, by 2016 this period was just two years. This progress is based on increased awareness on the part of public and health professionals.

In the case of RD, the complexity of the symptoms and their singularities is one of the reasons why it often takes time to form a diagnosis. The suffering of patients and their families is further exacerbated by the fact that 95% of RD are orphan diseases, which means no treatment is known or available yet[7].

The diagnostic odyssey is characteristic of RD. Faced with 'atypical' symptoms, doctors and medical teams are unable to make a timely diagnosis and do not know which structures to turn to for further investigation.

It happens consistently that a patient's concerns and complaints are no longer taken into account by their doctor or their family and friends and they find themselves isolated and alone with their disease and suffering.

A 2004 survey by EURORDIS (Eurordiscare 2)[11] looked at the delay in diagnosis for eight RD in 17 different European countries.

A delay in diagnosis also delays access to an adequate treatment and may have serious implications for the patients and their health.

THE EXTENT OF THE PROBLEM AS HIGHLIGHTED BY THE EURORDIS SURVEY:

25% of patients had to wait between 5 and 30 years from early symptoms to confirmatory diagnosis of their disease.

40% of patients first received an erroneous diagnosis, others received none. This led to medical interventions (including surgery and psychiatric treatments) that were based on a wrong diagnosis.

25% of patients had to travel to a different region to confirm their diagnosis and 2% had to travel to a different country.

In **33%** of cases, the diagnosis was announced in unsatisfactory terms or conditions. In 12.5% of cases, it was announced in unacceptable ones.

The genetic nature of the disease was not communicated to the patient or family in **25%** of cases.

There was genetic counselling in only **50%** of cases.

11 "Survey of the delay in diagnosis for 8 Rare Diseases in Europe ('Eurordiscare 2')", *Fact Sheet 17/04/07.*

12 "Plan national maladies rares" *2005-2008, Minister of Health and Solidarity, France.*

13 "Plan national maladies rares – Qualité de la prise en charge, Recherche, Europe : une ambition renouvelée" *2011-2014, Minister of Health and Solidarity, France.*

E MEDICAL AND SOCIAL IMPACTS[14]

The dearth of knowledge about the diseases and their impact on everyday life explains a great deal of the physical, psychological and social suffering encountered by the patient and the patient's family and carers.

The deficit of medical and scientific knowledge, the absence of curative treatments and the physical and/or psychological issues inherent to the field of RD cannot be ignored by public health policies. RD patients and their families all face the same challenges in their quest for a diagnosis: going through multiple consultations in order to find the qualified team and the way towards an appropriate treatment. Loss of autonomy is another problem RD patients often have to confront, as are their social, educational and professional inclusion and their existence as citizens. Those affected by RD are more vulnerable, not only psychologically and socially but also economically and culturally.

This highlights the need for a coordinated, holistic approach to patient care in order to take into account the RD patients' physical, mental, emotional and social health, but also to offer assistance for education and professional inclusion, plus financial support if needed.

F CURRENT CHALLENGES[15]

For many RD, basic knowledge such as the cause of the disease, pathophysiology, natural course of the disease and epidemiological data is limited or unavailable.

This alarming fact explains why it is so difficult both to diagnose and to treat RD adequately. People affected by RD are in search of answers and expertise, regardless of the location or the country where the referral centre is. This leads to care pathways that are scattered and fragmented. Medical expertise on each of these diseases is a scarce resource and treatment is currently not equally available to everyone, which is unacceptable in Europe today.

To address the many challenges linked to lack of knowledge about RD, investments in resources in Europe is fundamental. The following are particularly important:

- The introduction of an internationally recognised RD classification and coding system to help generate reliable epidemiological data and provide information for further research into the natural history, causes and evolution of RD.
- Fundamental research should allow the development of new screening tests, early identification tests and diagnostic and follow-up tests (biomarkers) for RD. On the long term, these will improve the knowledge and treatment of RD patients and their families.

14 *Source:* http://www.orpha.net/consor/cgi-bin/Education_AboutRareDiseases.php?lng=EN

15 *Source:* http://www.who.int/medicines/areas/priority_medicines/MasterDocJune28_FINAL_Web.pdf "Priority Medicines for Europe and the World - 2013 Update", Warren Kaplan et al. WHO publications, 9 July 2013.

- Clinical trial funding programmes remain essential for the development of new (orphan) medicinal products that appear less attractive for the pharmaceutical industry. Within the public health system, the individual burden of disease encountered by RD patients must prevail over the profit-generating opportunities of the pharmaceutical industry.
- Targeted therapies, such as those blocking specific mecanisms in cancer cells, could be developed for smaller disease groups like RD. It is critical to continue funding the research of these highly innovative therapies, and the same applies to the practice of 'drug repurposing'[16].
- Evidence-based clinical practice for rare diseases should be facilitated by collecting clinical data in databases and registries, taking into account the particularities of RD (selecting appropriate study designs adapted to small populations). This implies transparency and the possibility to link and access data under well-defined conditions[17].

16 **Definition of drug repurposing (also known as drug repositioning, reprofiling of drugs, therapeutic switching):** Drug repurposing is the application of known drugs and compounds to treat new indications (i.e., new diseases). A significant advantage of drug repositioning over traditional drug development is that since the repositioned drug has already passed a significant number of toxicity and other tests, its safety is known and the risk of failure for reasons of adverse toxicology are reduced. More than 90% of drugs fail during development, and this is the most significant reason for the high costs of pharmaceutical R&D. *Source: https://en.wikipedia.org/wiki/Drug_repositioning. Accessed 3 November 2017*

17 **Rath A. et al. A systematic literature review of evidence-based clinical practice for rare diseases:** what are the perceived and real barriers for improving the evidence and how can they be overcome? Trials201718:556. *Source : https://doi.org/10.1186/s13063-017-2287-7*

3. The regulatory context in Europe

European cooperation is critical for the sharing of knowledge, expertise, available research and treatments, all of which are often scarce and scattered[18].

The first initiatives aimed at combatting RD on EU level materialised in the nineties.

The EU dimension and the cooperation between Member States can make a difference for tackling RD issues, for example by pooling together knowledge and expertise, fostering concerted, complementary and coordinated research and cooperation and granting the authorisation of the best possible medicines so they are available in all European countries. EU action on RD provides high added value. The EUROCAT project, founded in 1979[19] to provide epidemiological information on congenital anomalies in Europe, owes its success to its European implementation and collaborative network for research, prevention of congenital anomalies and treatment and care of patients.

RD were identified, for the first time, as a priority field for public health action in the EU, in the Commission Communication of 24 November 1993[20]. This was followed by providing support for several projects as well as by setting up the RD Task Force.

In 2008, the Commission adopted an overall strategy to support Member States in diagnosing, treating and caring for EU citizens with RD: the *Communication on Rare Diseases: Europe's challenge.*

THE COMMUNICATION FOCUSES ON THREE MAIN AREAS:

- Improving the recognition and visibility of rare diseases
- Supporting policies on RD in the Member States for a coherent overall strategy
- Developing cooperation, coordination and regulation for RD at EU level

18 *Source :* https://ec.europa.eu/health/sites/health/files/rare_diseases/docs/2014_rarediseases_implementationreport_fr.pdf . Implementation report on the Commission communication entitled "Rare diseases: a challenge for Europe". Brussels, 5 September 2014, COM(2014) 548 final.

19 *Source :* http://www.eurocat-network.eu/aboutus/whatiseurocat/whatiseurocat

20 Commission Communication on the framework for action in the field of public health. COM (93) 559 final, 24 November 1993.

21 « Les maladies rares : un défi pour l'Europe » COM (2008) 679 final, 11 November 2008.

Along with the Communication, a Council Recommendation on an action in the field of RD[3] was adopted a few weeks later, inviting Member States to put national strategies in place.

THE COUNCIL RECOMMENDATION FOCUSES ON:

- Definition, codification and inventory of RD
- Research
- European reference networks
- Gathering expertise at EU level
- Empowerment of patient organisations
- Sustainability

Article 13 of Directive 2011/24/EU[22] on the application of patients' rights in cross-border healthcare also addresses RD. It states that the Commission shall support Member States, in particular by making health professionals aware of the tools available to assist the diagnosis of RD, and by making stakeholders aware of the possibilities offered by Regulation 883/2004[23] for referral of RD patients to other Member States.

According to Article 12 of the same Directive, the *"Commission shall support Member States in the development of European reference networks between healthcare providers and centers of expertise in the Member States, in particular in the area of rare diseases"*. These European reference networks pursue, among others, the goal of helping *"to facilitate improvements in diagnosis and the delivery of high-quality, accessible and cost-effective healthcare for all patients with a medical condition requiring a particular concentration of expertise in medical domains where expertise is rare"*.

22 "Directive 2011/24/EU on the application of patients' rights in cross-border healthcare", OJ L 88, 4.4.2011, p. 45-65.

23 Regulation (EC) No 883/2004 of the European Parliament and of the Council of 29 April 2004.

A THE EUROPLAN PROJECT AND THE LINK WITH EUCERD

EUROPLAN is a European project co-funded by the EU Commission for developing RD National Plans or Strategies. The aim is to promote and implement National Plans to meet needs of RD patients and to share relevant experiences within countries, linking national efforts with a common strategy at European level.

The project, which ran from April 2008 to March 2011, involved representatives of national health authorities from 21 Member States and brought together 57 stakeholders from 34 countries. Fifteen EUROPLAN conferences were organised in collaboration with the EURORDIS Council of National Alliances and patient associations. The conferences were conceived around common themes, linked to chapters of the Council Recommendation.

The project resulted in a report on indicators for monitoring the implementation and evaluating the impact of national plans or strategies for RD. It also served as a basis for the adoption of the EUCERD recommendations (The European Union Committee of Experts on Rare Diseases, set up in 2010 and replaced in 2013 by the EC Expert Group on Rare Diseases[24]) on core indicators for RD national plans or strategies[25].

EUROPLAN has now taken the form of a movement that encourages and promotes national plans and strategies and helps implement EU RD policies & recommendations.

Thanks to the EUCERD Joint Action (2012 - 2015)[26], 25 other EUROPLAN conferences have been organised by the National Alliances, including one in Luxembourg in November 2013.

B THE IMPORTANCE OF ORPHANET

Orphanet was established in France in 1997 by INSERM (The National Institute of Health and Medical Research). The initiative became a European endeavour from 2000, supported by grants from the European Commission. Orphanet has gradually grown into a consortium of 40 countries, within Europe and across the globe.

Orphanet is an online database that provides information about rare diseases and accessible orphan medicinal products. It aims to contribute to improving the diagnosis, care and treatment of patients with RD, whether they are genetic, autoimmune, infectious, rare cancers or diseases without a precise diagnosis. The website provides services tailored to the needs of patients and their families, health professionals, researchers, associations, institutions and industries.

To date, Orphanet is the largest RD and orphan medicinal products database at European level, with around 6,000 listed diseases.

Furthermore, Orphanet has played a key role in the development of a coding system for RD (Orphanet nomenclature, with ORPHA Code identifiers), which is essential for improving the visibility of RD in health and research information systems. According to a survey conducted by RD Action[27] in 19 European countries (from 26 April to 18 August 2017), ORPHACode was the main coding system used for RD in hospitals and elsewhere.

24 Commission Decision of 30 July 2013 setting up a Commission expert group on rare diseases and repealing Decision 2009/872/EC.

25 EUCERD Recommendations on Core Indicators for Rare Disease National Plans/Strategies, 6 June 2013.

26 *Source:* http://www.eucerd.eu/?page_id=54

27 RD Action, Work Package 5 - Survey#2 "Implementation of rare disease patient coding across member states".

C THE EUROPEAN REFERENCE NETWORKS (ERNs)

European Reference Networks are virtual networks involving healthcare providers across Europe. They were created to address complex or rare diseases and conditions that require highly specialised treatment and concentrated knowledge and resources.

The purpose of the ERNs is to reduce inequalities in access to diagnosis, treatment, follow-up for people affected by these diseases, to offer patients and doctors across the EU access to the best expertise without having to travel to another county, to foster European cooperation and coordination and to support national plans for rare diseases.

The Directive on Patients' Rights in Cross-Border Health Care[28] defines the governance and coordination of these networks as well as the criteria and conditions required to participate in them. The role of the national health authority is to integrate ERNs in the country's health system and to approve the application of health-care providers and members.

Applications are voluntary and must meet general criteria (required for all providers) and specific criteria (required for the field covered by each ERN). They are approved by an independent body. There are currently 24 thematic ERNs approved by the Board of Member States[29].

Once affiliation criteria have been met and the procedures for national designation and integration into existing ERNs have been defined and approved by the Member States, Luxembourg will be able to integrate these networks and the wealth of opportunities they hold into its national health system.

SMALL COUNTRIES SUCH AS LUXEMBOURG, WHO MAY NOT HAVE A FULL MEMBER IN ONE (OR MORE) ERN(S), CAN DESIGNATE "ERN AFFILIATED PARTNERS" IN THE FORM OF:

"Associated National Centers" focusing in the provision of healthcare

"Collaborative National Centers" focusing on the production of knowledge and tools to improve the quality of care

"National Coordination Hubs" with the remit to engage with all established ERNs or pertaining to a specific ERN

28 Directive 2011/24/UE "Patients' rights in cross-border healthcare" (Article. 12).

29 *Source:* https://ec.europa.eu/health/ern/board_member_states_en

D PATIENT ASSOCIATIONS, EURORDIS

In the field of RD, EURORDIS[30] is the largest umbrella organisation in Europe. It was founded in 1997 and is a non-governmental, patient-driven alliance of patient associations representing 765 RD patient associations in 69 countries (including 28 in Europe).

EURORDIS seeks to improve the quality of life of people living with RD in Europe through advocacy at European level, support for research and medicines development, facilitating networking amongst patient groups, raising awareness, and many other actions designed to reduce the impact of RD on the lives of patients and family.

EURORDIS is attracting an increasing number of patient organisations outside of Europe and is gaining traction at raising awareness about RD at the international level. The aim is to unite, expand and reinforce the RD movement of patient associations and patient advocates around the world.

EURORDIS membership map
Map data of 2017 (Source: https://www.eurordis.org/fr/international)

EURORDIS is recognised for its achievements as a partner of the European Commission, the European Parliament, the EU Council and EMA. EURORDIS is also a founding member of the NGO Committee for RD (United Nations, New York)[31], which is a substantive committee established under the umbrella of the Conference of NGOs in Consultative Relationship with the United Nations (CoNGO).

30 *Source : https://www.eurordis.org/fr/a-propos-d-eurordis*

31 *Source : https://www.ngocommitteerarediseases.org/about-us/*

4. National plans in neighbouring European countries

In the EU Council Recommendation, Member States committed themselves to adopt a plan or strategy to address RD as soon as possible and by the end of 2013 at the latest. In 2009, a focus on RD was relatively new and innovative in most Member States and only a few had national plans in place. These were Bulgaria, France, Portugal and Spain.

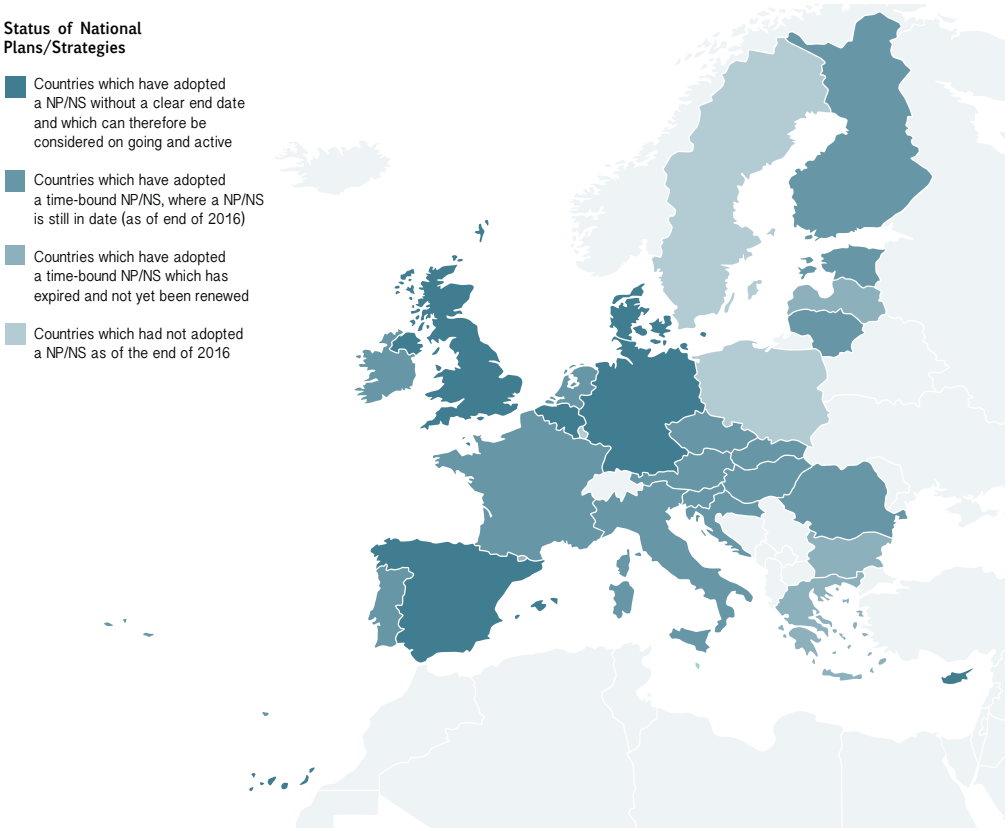
Though, countries vary considerably in the level of implementation of their national plans and strategies[32 33], Member States have made significant progress.

At the end of 2016, 24 countries had a national plan or strategy for RD:

- 18 of these countries have adopted a time-bound national plan or strategy: Austria, Croatia, Czech Republic, Estonia, Finland, France, Hungary, Ireland, Italy, Lithuania, Netherlands, Portugal, Romania, Slovakia, Slovenia, Bulgaria, Greece and Latvia.
- 6 of these countries have adopted a national plan or strategy without a clear end date and which is therefore considered to be ongoing (according to data available in 2016): Belgium, Cyprus, Denmark, Germany, Spain, United Kingdom.

32 Rodwell C., Aymé S., eds., "2014 Report on the state of the art of rare disease activities in Europe – Part II: Key deveolpments in the field of rare diseases in Europe in 2013". EUCERD Joint Action, July 2014.

33 "Overview Report on the State of the Art of Rare Disease Activities in Europe", 2016 Version, RD-Action WP6 Output, Authors: V. Hedley; H. Murray; C. Rodwell, S. Ayme.



Status Quo of National Plans and Strategies for Rare Diseases in EU MS, as of end of 2016. Source: "Overview Report on the State of the Art of Rare Disease Activities in Europe", 2016 Version, RD-Action WP6 Output.

- At the end of 2016, the following countries had not yet adopted a RD national plan or strategy: Luxembourg, Malta, Poland and Sweden.

France was the first European country to implement a national plan for RD, in 2005, and is a pioneer in this field. The second French national plan was presented in 2011 and was intended to end in 2014 but was extended to 2016. A third national plan is to be implemented to build upon the advances reached with the two first ones.

CENTERS OF EXPERTISE

The concept of centers of expertise as defined and promoted by EUCERD is key to the field of RD as it encompasses the objective of both mapping and understanding the existing expertise in a country. It also allows to implement quality criteria in highly specialised care.

In 2006, a number of criteria were defined to designate and evaluate RD centers of expertise, based on the experiences of the European countries who were in the process of implementing them[34]. On these grounds, EUCERD developed and adopted a series of recommendations in 2011[35].

In Belgium, centers of expertise for cystic fibrosis, metabolic disorders and haemophilia were created through a substantial budget allocation (EUR 2 million). Genetic counselling is done via a multidisciplinary approach and is funded through a special convention that covers Belgium's eight approved centers of human genetics.

In France, individual centers of expertise are grouped by the RD national health sectors to increase collaboration within the country. These sectors focus on homogeneous RD groups, including reference centers, research and diagnostic laboratories, imaging centers, psychosocial services and patient associations.

Putting centres of expertise into place in small countries remains a challenge because of the critical lack of patients necessary to generate the specific skills domestically. Cyprus is currently considering an official designation procedure for the centers of expertise, whereas it is not yet known what steps Malta will take.

34 *Source*: http://www.eucerd.eu/?post_type= document&p=1334 . "Centers of Reference for rare diseases in Europe: State-of-the-art in 2006 and recommendations of the Rare Diseases Task Force. A technical and scientific report from an expert group of the Rare Disease Task Force". December 2006.

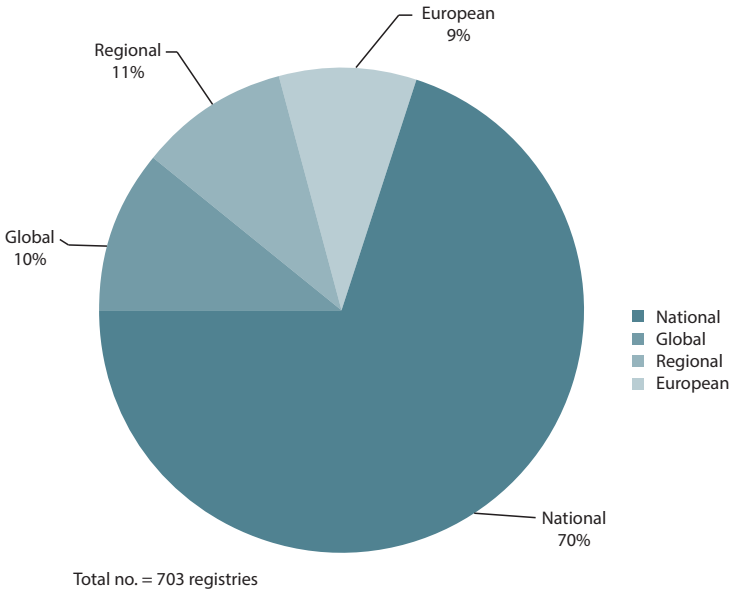
35 *Source:* http://www.eucerd.eu/?post_type=document&p=1224 . « EUCERD Recommendations on Quality Criteria for Centers of Expertise for Rare Diseases in Member States », 24 October 2011.

REGISTRIES

On its own, no country can sample a sufficient number of patients with a very rare disease to fully understand the condition epidemiologically, the reported symptoms, the process of the disease and draw significant, reliable scientific conclusions.

The registries provide information on patients affected by a particular group of RD. By combining information on a maximum number of cases at regional, national, European and/or global level, the power of the data collected increases exponentially. Registries are therefore of paramount importance in recording the natural history of RD, and they focus on the epidemiology of the disease. The data they pool can help find the best diagnostic method for a given disease, demonstrate the effectiveness of different therapeutic options and achieve sufficient sample size, which is invaluable for clinical research.

ACCORDING TO THE ORPHANET REPORT OF MAY 2017[36], THERE ARE 703 RD REGISTRIES IN EUROPE, DISTRIBUTED AS FOLLOWS: 61 EUROPEAN, 77 GLOBAL, 496 NATIONAL AND 69 REGIONAL.



Distribution of European Rare Disease Registries by geographical 'scope', according to the Orphanet database. Source: 'Rare Disease Registries in Europe'. Orphanet Report Series May 2017.

36 *Source*: http://www.orpha.net/orphacom/cahiers/docs/GB/Registries.pdf . 'Rare Disease Registries in Europe'. Orphanet Report Series May 2017.

In Belgium, the Central Registry of RD, which collects genetic data on the country's RD patients, has gradually been implemented since 2013. The registry supports research into RD and the development of orphan medicinal products.

France created a national registry in 2006 as part of its first national plan to improve the epidemiological knowledge of RD. In line with the objectives defined in the second national plan, a national database with 'a minimal data set' was introduced in its Rare Disease Bank (BaMaRa) via the centers of expertise. An interoperability regulation was introduced in 2013.

Germany set up a web portal of registries. It represents the interface to communicate with the European registry platfrom of the EU Commission Joint Research Centre in Ispra, Italy.

The national German plan further recommends the development of a disease-specific registry of RD.

The Italian national registry was established as part of the first national plan and covers 97% of the RD data collection in the country. The implementation of a monitoring system for collecting data has led to a significant improvement in coverage in the country (from 62% in 2009 to 97% in 2012).

RESEARCH

Over EUR 620 million was invested in over 120 research projects during the FP6 and FP7 programmes and Horizon 2020, covering the years 2002-2020. From 2014 to 2015, Horizon 2020 provided approximately EUR 200 million funding for RD research across 40 projects.

From 2016 to 2017, Horizon 2020 focused on two specific RD subjects: diagnostic characterisation of RD (SC1-PM-03–2017) and new therapies for RD (SC1-PM-08–2017) . A report by the IRDiRC (International Rare Diseases Research Consortium)[37] provides an overview of the state of play of research in the field of RD.

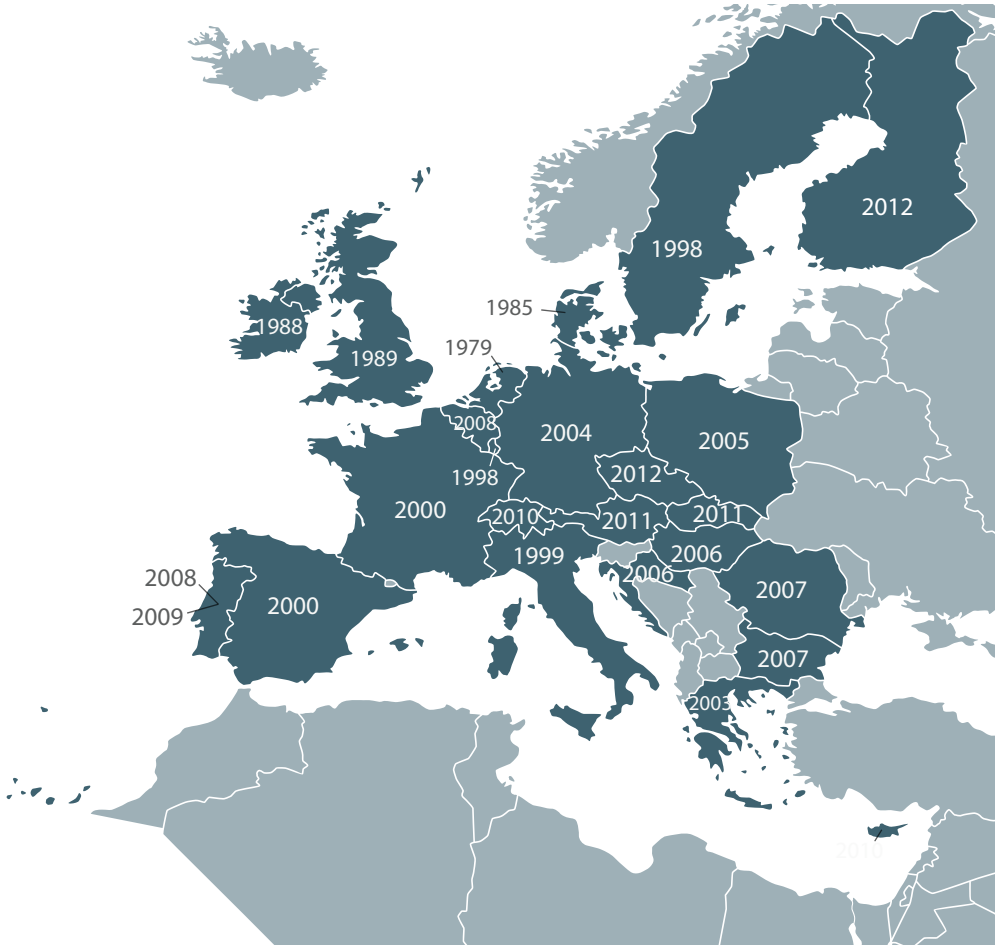
The set-up of the European Joint Programme Co-Fund for Rare Diseases was initiated late 2016 to serve as tool for the strategic organisation of RD research. It is operated by ministries and research funding organisations in conjunction with other relevant stakeholders (e.g. patients' associations, regulatory bodies and private sector).

The goal is to support translational research in the RD arena (from bench to bedside and back again). Efforts are being led by France because of the country's significant implication in RD research.

37 *Source:* http://www.irdirc.org/reports-guidelines/state-of-play-reports/

NATIONAL ALLIANCES

National alliances of RD patient associations are important structures for this key group of stakeholders at Member State level. They provide patients with a common voice and the presence needed to have an impact on national policy. Therefore, these alliances play an essential role in elaborating the national plans or strategies for RD.



National alliances and year of foundation (Source: EUCERD report 2013).

5. The situation in Luxembourg

With the available data showing that over 30 million people in Europe are affected by RD, it can be estimated that approximately 30,000 individuals are concerned in Luxembourg, directly or indirectly.

AVAILABLE DATA

Currently, the main source of data available in Luxembourg is the information collected by ALAN (ALAN Rare Diseases Luxembourg, non-profit association, formerly called Luxembourg Association of Assistance to People with Neuromuscular Diseases and Rare Diseases).

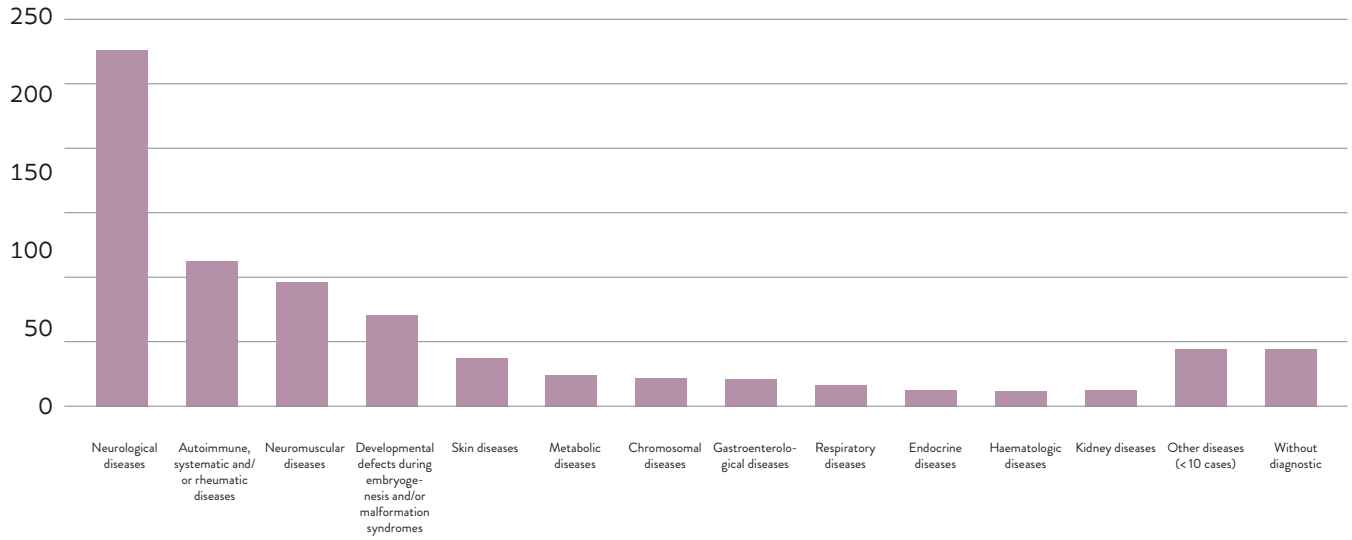
The data collected, which is a reflection of ALAN's activities, is coded using the Orphanet RD nomenclature and indicates the presence of the following three main categories of diseases in Luxembourg:

- Neurological diseases
- Autoimmune, systematic and/or rheumatic diseases
- Neuromuscular diseases

However, a survey of people affected by RD and relatives of people with RD who contacted ALAN between 2006 and 2016[38] led to the identification of several other categories.

Source: ALAN. Non-exhaustive list of cases from 2006 to 2016. Note that some diseases are not identified.

RD PATIENTS HAVING CONTACTED ALAN



38 *Source:* ALAN. Non-exhaustive table.

With regard to respiratory RD, in particular cystic fibrosis, patient care is managed by the Luxembourg Centre for Cystic Fibrosis and Related diseases (CLMMA) within the Centre Hospitalier of Luxembourg (CHL). A recent study published in Luxembourg[39] shows that the population affected by this disease consists of adult and paediatric patients with CF (cystic fibrosis/mucoviscidosis), CFTR-RD (other diseases also related to the cystic fibrosis transmembrane conductance regulator gene (CFTR) that can appear in older children and adults and are grouped under the name CFTR-RD for CFTR-Related Diseases) and related disorders (ReD).

THE REPORTED DATA ON THE CASES MONITORED AT CLMMA IN 2016 IS AS FOLLOWS:

Patient monitored at CLMMA	Number of patients	% TOTAL
CF	**38**	**61.3%**
CFTR-RD	**8**	**12.9%**
ReD	**16**	**25.8%**
* Ciliary dyskinesia	8	
* Severe bronchiectasis of undetermined etiology	8	
TOTAL patients	62	100%

Mutations of CFTR are far from the only causes that can explain symptoms, which further increases the difficulties of diagnosing these diseases.

Cases of pulmonary arterial hypertension (PAH) and idiopathic pulmonary fibrosis have also been reported in Luxembourg. Luxembourg is part of the PROOF-registry[40], a prospective observational registry aimed at describing the evolutionary disease course and outcomes of idiopathic pulmonary fibrosis patients.

The data collected from the Kriibskrank Kanner Foundation in Luxembourg is another valuable source of information on the situation of rare childhood cancers in Luxembourg. In 2016, 185 families received support in cases of cancer (81%) and life-threatening RD (19%). The latter concerned 36 children, of which 26 were Luxembourg residents. In comparison with 2015, four new RD cases were identified in 2016[41].

39 Schlesser M. et al. "La mucoviscidose au Luxembourg" ("Cystic fibrosis in Luxembourg") Bull Soc Sci Med Grand Duche Luxemb. 2017;(1):65-82.

40 ERS International Congress 2014, Munich, Germany, 6–10 September, Poster: "PROOF-registry: a prospective observational registry to describe the disease course and outcomes of idiopathic pulmonary fibrosis patients in a real-world clinical setting", Authors: Wim Wuyts, Caroline Dahlqvist, Marc Schlesser, Christophe Compere, Hans Slabbynk, Benjamin Bondue, Marianne Berrens, Christophe Giot, Paul DeVuyst.

41 *Source:* Press release of 15.02.2017 Kriibskrank Kanner Foundation.

LUXEMBOURGISH EXPERTISE

Luxembourg's close geographical proximity to its neighbouring countries and their centers of expertise is a source of potential collaborations.

Luxembourg is a small country but it has nevertheless created and implemented the Diabetes and Endocrinology Care Clinique Pédiatrique (DECCP) at the Centre Hospitalier of Luxembourg (CHL), which became a member of an ERN on rare endocrine diseases (RareEndoERN) in 2016. A multidisciplinary team is dedicated to the care of diabetic children and adolescents, including those suffering from RD-related conditions.

RESEARCH IN LUXEMBOURG

Despite the lack of critical mass of patients for some diseases and the difficulties of collecting national data with no national codifying system, Luxembourg shows some research activity. In fact, several national institutions and organisations are involved in RD research projects (preclinical and/or clinical).

According to an informal survey led by the Integrated BioBank of Luxembourg (IBBL), several institutions in Luxembourg are conducting research projects concerning some fifty RD, including: the University of Luxembourg, the Luxembourg Centre for Systems Biomedicine (LCSB), the Centre Hospitalier of Luxembourg (CHL), the Luxembourg Institute of Health (LIH), the Laboratory of Molecular and Cellular Biology of Cancer (LBMCC), the Luxembourg Centre for Cystic Fibrosis and Related diseases (CLMMA) and the Diabetes and Endocrinology Care Clinique Pédiatrique (DECCP). Collaborations have been initiated abroad and/or with the pharmaceutical industry, for example with the company Théracule, that develops RD medicinal products in the context of personalised medicine.

At the academic level, LIH's Centre for Investigation and Clinical Epidemiology (CIEC) is a scientific partner of the European Clinical Research Infrastructure Network (ECRIN)[42], a nonprofit, intergovernmental organisation that facilitates multinational clinical trials in Europe, with a focus on RD.

This collaboration gives Luxembourg the opportunity to take part in clinical trials, such as the VISION-DMD[43] project, which received a EUR 6 million grant from the EU to investigate a new treatment for patients with Duchenne muscular dystrophy. ECRIN has had the legal status of a European Research Infrastructure Consortium (ERIC) since 2013 and for Luxembourg to continue to be eligible for as a partner country for future projects, it needs to become a full member.

42 *Source*: http://www.ecrin.org

43 *Source*: http://cordis.europa.eu/project/rcn/199721_en.html

A THE MARA TASK FORCE'S FINDINGS AND RECOMMENDATIONS

The MARA task force was founded in 2005. The national survey it carried out, in full compliance with the Eurordis Care[2] methodology[11], was published in 2011[1] and provided a first assessment of the situation of people with RD in the country. A detailed questionnaire about medical, social and psychological care was used and 222 responses analysed. This helped identify the problems in Luxembourg, common to all RD, as shown in the table below:

THE BIGGEST PROBLEMS	N	%
Difficulties obtaining a diagnosis	102	53,4%
Lack of treatments and therapies	97	50,8%
Change or loss of leisure activities	71	37,2%
Family's and friends' lack of understanding	67	35,1%
Change of professional life	45	23,6%
Marital problems	43	22,5%
Change of financial situation	33	17,3%
Sexual problems	20	10,5%
Problems raising children	17	8,9%
Other	44	23,0%

The results of the Luxembourg survey resemble those of the 2004 EurordisCare2[11] European survey, which led to the conclusion that the challenges in Luxembourg are similar to those described elsewhere in Europe.

The results of the survey led the MARA task force to conclude that the following six points should be addressed as a priority:

- Difficulties obtaining a diagnosis
- Lack of scientific knowledge
- Lack of appropriate care and therapies
- Lack of psychological and social support
- Expensive care
- Social consequences (isolation, education problems, less professional options...).

The following recommendations were made:

- Elaboration of a national plan for RD to guide, coordinate and structure actions in the field of RD in Luxembourg
- Consolidation of RD recognition, adopting the EU definition and participating in EU projects and actions on RD traceability at national health system level
- Improvement of information and awareness of RD
- Guarantee of equal access to diagnosis, care and treatment
- Provision of specific help services for patients with RD and their families
- Support of the creation of new RD patient associations and a national alliance
- Promotion of international collaboration for RD projects at EU level, particularly in the field of research
- Planning of a funding and sustainability system for the future national plan in Luxembourg.

B THE EUROPLAN CONFERENCES IN LUXEMBOURG

The first EUROPLAN conference in Luxembourg, which took place on 19 and 20 November 2013, was organised by ALAN, the country's main RD patient association.

The conference was organised around the following themes:

- Methodology and governance of a national plan
- Definition, codification and inventorying of RD
- Research on RD
- Care: Centers of expertise / Cross-border health care
- Orphan medicinal products
- Social services

The main conclusions drawn by topic were the following[44]:

- **Methodology and governance of a national plan**
  - Having a national plan for RD in Luxembourg is considered a priority.
  - The creation of a national alliance of RD patient associations is key to support the development of the national plan and promote the exchange of information and resources on an international level.
  - It is essential to provide specific resources, a budget and coordination capacity as well as a "RD reference person" within the Ministry of Health.
- **Definition, codification and inventorying of RD**
  - At the time of the conference, the MARA survey was the only existing initiative made to collect and record data on RD in Luxembourg. An essential step is therefore the creation of a national registry.
  - It will be necessary to define the "common data sets" which are to be extracted when collecting and recording data on RD.
  - In order for professionals to encode the right way, proper training needs to be addressed. RD codification is complex and the fact that it is completed by different people carries a risk of interpretation.

Research on RD

- Both national and international research projects are conducted in Luxembourg with human biospecimens. They involve multiple actors: the National Health Laboratory (LNS), IBBL, LCSB, the eHealth Agency and LIH.
- Several initiatives should be considered in the future, such as: E-RARE (ERA-Net for Research Programmes on Rare Diseases), IRDiRC, EUCERD, EURORDIS and COMP (The Committee for Orphan Medicinal Products).
- Collection of RD patient data raises the issue of data protection. It must comply with the legal framework currently in place.

44 Luxembourg Europlan National Conference final report, 19-20 November 2013

- **Care: Centers of expertise / Cross-border health care**
  - There is no centre of expertise in Luxembourg as defined on European level. However, there are experts for certain RD and several doctors participate in European or international research projects.
  - The creation of a platform for RD to guide professionals and patients and their families is the best option for Luxembourg. Among other things, this platform would help provide psychological and social support and organise training for health professionals.

- **Orphan medicinal products**
  - Reimbursement for orphan medicinal products is not guaranteed and prior approval from the competent authority is often required.
  - "Off-label use"[45] and "compassionate use"[46] of medicinal products require clarification and a legal framework.
  - The situation is even more complicated if a new molecule has not yet obtained the European recognition (EMA).

- **Social services**
  - Social resources in Luxembourg are insufficient or do not always address the specific needs of RD patients, although patient associations exist that provide support to children and families.
  - There is no global approach and the information available on which procedures to follow is limited and non-specific (for example via www.guichet.lu). A lack of coordination between existing institutions has also been identified.
  - The actions proposed were as follows:
    - *a) Define a specific 'RD status' at the level of the national health insurance fund (CNS)*
    - *b) Implement a Central Office to provide information on all available possibilities*
    - *c) Simplify social and administrative rights procedures*
    - *d) Facilitate the transition in the social system between child- and adulthood*

45 «Off-label» use refers to any intentional use of an authorised product that is not covered by the terms of its marketing authorisation and therefore not in accordance with the Product Characteristics Summary (PCS). For example, this may be the use for a different indication, the use of a different dosage, a different frequency or duration of use, the use of a different method of administration or the use by a group of different patients (e.g. by children).
Source: Study on off-label use of medicinal products in the European Union, https://ec.europa.eu/health/sites/health/files/files/documents/2017_02_28_final_study_report_on_off-label_use_.pdf

46 Definition of «compassionate use»: Compassionate use applies when a disabling, chronic or serious illness or a life-threatening illness cannot be treated by a registered medicinal product but could be treated by a medicinal product that is not registered in Luxembourg. «Compassionate use» is defined in Article 83 of Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (Text with EEA relevance).
Source: http://www.cner.lu/fr-fr/proc%C3%A9dures/demandedavispouruncupnotificationdunmnp.aspx

This conference gave the opportunity to widen the debate around the development of a NPRD and to gather the views and proposals of the different stakeholders.

A second EUROPLAN conference took place in Luxembourg on 8 November 2017. Among the main themes discussed were: social services (the "INNOV-care-social care" project) and European Reference Networks (ERNs).

The following remarks were made:

- Psychological and social services are well-structured in Luxembourg and the support ALAN and other patient associations provide patients and their families with is considerable. However, despite being accessible, theses services are not available due to insufficient resources, which results in long waiting lists and a long wait for patients in need of help.
- The coordination between the various health and care professionals and institutions needs to be improved. There is also a lack of knowledge and skills in the field of RD. Awareness raising campaigns, targeted training and use of communication tools would be ways of achieving progress in these areas.
- The implementation of ERNs provides a response to problems put forward by a number of professionals (e.g. the difficulty of diagnosis, inadequate care and significant financial constraints).
- Given the current national context and the size of the country, it is suggested that Luxembourg apply as an Affiliated Centre ("Hub") in order to benefit from the many advantages offered by ERNs.

C SUMMARY OF THE ASSESSMENT IN LUXEMBOURG

The surveys and conferences in Luxembourg reveal inequalities in access to diagnosis, to multidisciplinary care (medical, psychological and social) and to treatment for RD patients. Following this assessment an action plan was elaborated and each point raised is developed in the NPRD.

The intervention of the public health system is required in several areas:

- The challenges linked to the diagnostic odyssey are one of the most dramatic for patients and their families. The patient journey is long from the onset of the symptoms to an actual diagnosis but it doesn't stop there. Once a diagnosis is made, treatment and follow-up takes over and leaves patients to their own devices. The NPRD's general line of action addresses this issue specifically with the creation of a central guidance office ('cellule d'orientation').
- The lack of reference centers capable of supporting families of RD patients is partly linked to the size of the country. Expertise exists in Luxembourg but no structured networks and/or care pathways are accessible to professionals. The area B of the NPRD aims to facilitate access to information on RD in Luxembourg and to foster networks of existing centers of expertise.
- The RD genetic counselling service is dispersed and needs to be ramped up. Its development is part of the goals outlined in area A of the NPRD: improvement of care and treatment.
- There is a lack of coordination between the various health professionals and institutions involved in the medical, but also psychological and social care of RD patients. The NPRD's general line of action aims to develop a better multidisciplinary collaboration between the different stakeholders.
- The existing prenatal and neonatal screening programmes consist of a limited number of tests[47] [48]. The range of tests made available needs to be re-assessed.
- When a RD diagnosis in possible outside these programmes, patients and their families are not monitored within a set care pathway for the RD in question. The area A of the NPRD takes this into account by the implementation of improved programmes and follow-up.
- The refund rate for care, medicinal or other, is insufficient. Orphan medicinal products are classified as medicines that can only be delivered by hospitals and remain very expensive. Compassionate use is possible but it is necessary to define a legal frame. Other types of care (physical therapy, occupational therapy, etc) are not fully reimbursed. Area A of the NPRD also aims to review the current procedures in place for RD care and medicine.
- RD knowledge is limited among those who care for patients. It is essential to provide clinicians with more information. Area B of the NPRD is dedicated to raising awareness and improving access to targeted information.
- Currently, no comprehensive, reliable and readily accessible source of data exists. The CNS only has records regarding medical refunds. The reasons for transfers abroad are not recorded and the outcomes of consultations not known. Discharge diagnoses after a hospital stay are not detailed enough. Every year, ALAN establishes a list of existing diseases in Luxembourg which is published in its annual activity report. This list could be a good starting point for the inventory of RD in Luxembourg.

47 *Source* : http://www.sante.public.lu/fr/legislation/remboursements/remboursement-prestations/suivi-mere-enfant/convention-progr-depistage-prenatal-2007-06-01-conv-etat-ucm-programme-depistage- prenatal-anomalies-congenitales/index.html

48 *Source* : http://www.sante.public.lu/fr/publications/d/depistage-nouveau-nes-lux-fr-de-pt-en/index.html

- Likewise, it is essential to implement a coding system that integrates what is underway in Luxembourg. Ambulatory medicine should also be included in this procedure, as it does not use codification. Area C of the NPRD is dedicated to making RD data available in Luxembourg et includes setting up a coding system in line with what is used in Europe.
- Psychological and social support does not cover the needs of RD patients in Luxembourg (there is a waiting list to access intensive care provided by ALAN's socio-therapeutic counselling service). Area D of the NPRD is entirely dedicated to meeting the support needs of people with RD and their families.
- The facilities that provide paramedical care like physical therapy, dietetics, counselling and social support are not always adapted to the specific characteristics of rare diseases. Patients and their families are "left to their own devices" when faced with decision making. Moreover, there is an acute shortage of available places in care facilities and sheltered workshops. Specific measures of the NPRD, still within the context of area D, will make it possible to address the specificities of psychological and social care.
- Employees with RD must often agree to reduce their hours in order to keep their job, thus giving up part of their salary. They have to take time off to receive care and the disease is often "invisible" to those around them, none of which simplifies their situation in the workplace. The access to work and the working conditions of people affected by RD need to be reviewed in order to be better adapted. Similarly, the working conditions of caregivers must also be improved. Targeted measures in terms of socio-professional support will make it possible to meet the requirements of labour law (NPRD area D).

All of the above observations were guidelines in the development of the NPRD.

6. Organisation, methodology and objectives of the national plan

A AIM OF THE NATIONAL PLAN FOR RARE DISEASES (NPRD)

The main objective of a NPRD is to recognize RD as a national health public priority.

To define specific strategies that will reduce the burden of these RD on patients, their families and carers,

To guarantee rare disease patients' access to timely and adequate medical and psycho-social care,

To promote innovation an ensure universal access to quality care, equity and solidarity in health...

B METHODOLOGY USED

The first stage in preparing the NPRD was to take stock of the situation in Luxembourg (as described in chapter 5), taking into consideration existing surveys and conference reports.

The main stakeholders in the fight against RD in Luxembourg were gathered on 8 February 2017 in a steering committee set up by the Directorate for Health. The committee's roles and missions were pre-defined by the Directorate for Health.

THE STEERING COMMITTEE

The Steering Committee is a cross-sector coordination group consisting of professionals who are experts and/or involved in the fight against RD in Luxembourg. It includes representatives from the Directorate for Health, the Ministry of Social Security, physicians involved in the fight against RD, representatives of patient associations and members of various key institutions in Luxembourg such as LNS and LIH.

A dedicated NPRD coordination structure was made available by the Directorate for Health to support the members of the Steering Committee in their work developing the national plan. The committee's mission was to define the overall strategy of the NPRD, using the conclusions of the EUROPLAN 2013 conference[24] and the recommendations made by the MARA task force in 2011[1] as a starting point. Strategic areas and general goals were defined and entrusted to specific working groups.

THEMATIC WORKING GROUPS

The working groups were mandated to determine the necessary measures and actions to be included in the NPRD for each objective set by the steering committee. The composition of each group was decided by the steering committee based on RD involvement, competence and interest. Members of these groups are listed in Appendix 1.

THE FOLLOWING FOUR THEMATIC WORKING GROUPS WERE SET UP

Area A working group: Care and treatment system

Area B working group: Creation of a national RD information platform

Area C working group: Coding, registry and RD research

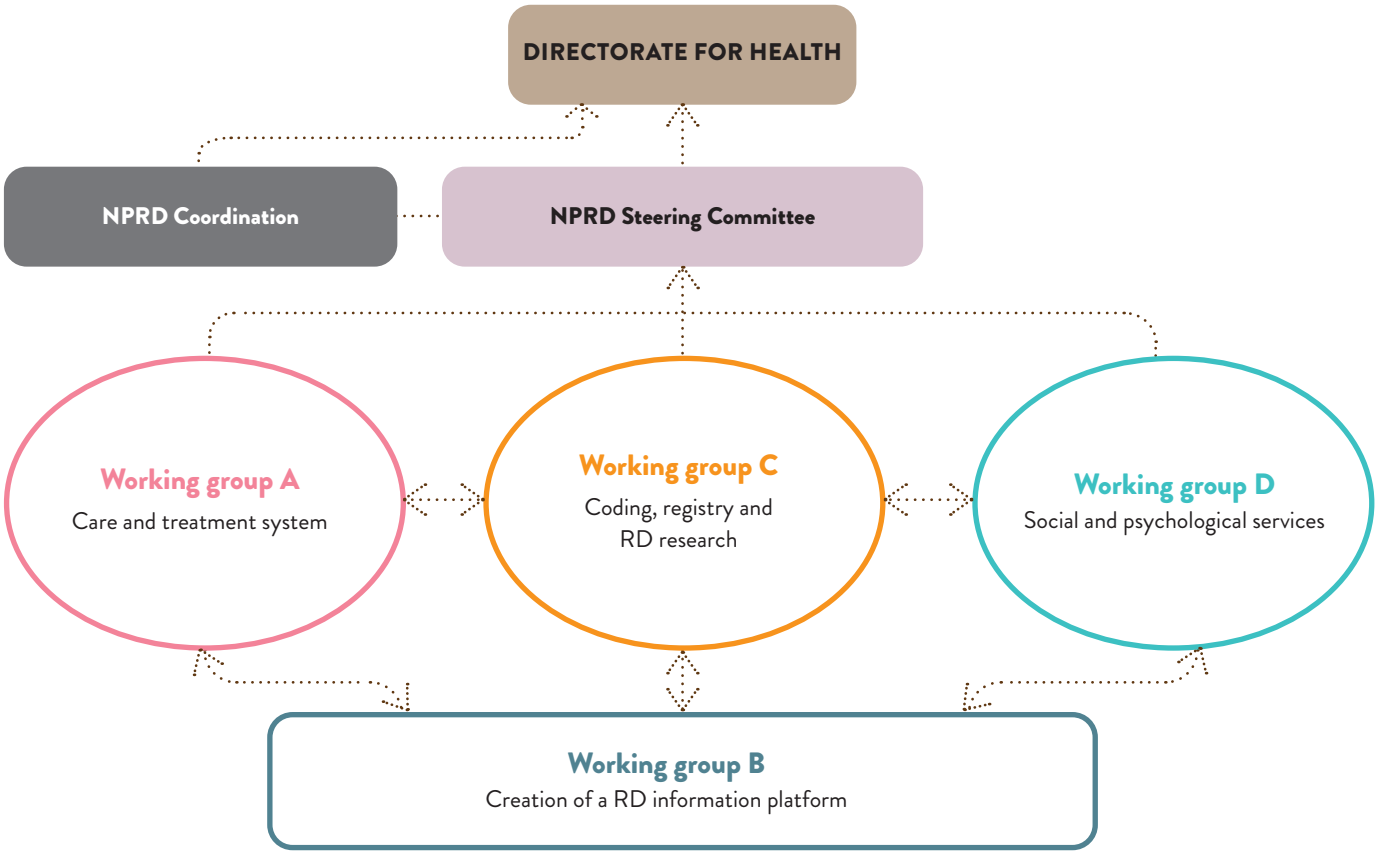
Area D working group: Social and psychological services

The groups met three to four times after the first kick-off meeting was held at the Ministry for Health on 16 June 2017[49]. At the end of all of the meetings, measures and actions to be implemented within the context of the plan were elaborated and validated by the steering committee in alignment with the recommendations of the EU Council[3].

49 *Source:* http://www.sante.public.lu/fr/actualites/2017/06/plan-national-maladies-rares/communique-de-presse-plan-nationalmaladies-rares.pdf. Press release 26.06.2017, "Une Première pour le Plan National Maladies Rares (16.06.2016)"

ORGANISATION

The operating mode of the Steering Committee and the different working groups is represented in the diagram below:



The working groups interacted and exchanged about the plan thanks to the NPRD coordination structure, under the supervision of the steering committee. The results of this were centralised by the steering committee.

C NPRD OBJECTIVES: MAIN GUIDING PRINCIPLES

THE OBJECTIVES OF THE NPRD CAN BE DIVIDED INTO 5 MAIN AREAS
General line of action
Area A – Improve care and treatment system
Area B – Facilitate access to information on RD through the creation of a national platform
Area C – Enhance recognition of RD specificities and promote research
Area D – Meet the social and psychological need of patients and their families

D NPRD INDICATORS

For each area, indicators for monitoring the NPRD have been defined, in line with EU recommendations[50]. Indicators can be structural, result-based or related to the implementation of the NPRD and are instrumental in assessing the progress of the different areas and objectives of the plan.

50 "EUCERD Recommendations on Core Indicators for Rare Disease National Plans/Strategies", 6 June 2013.

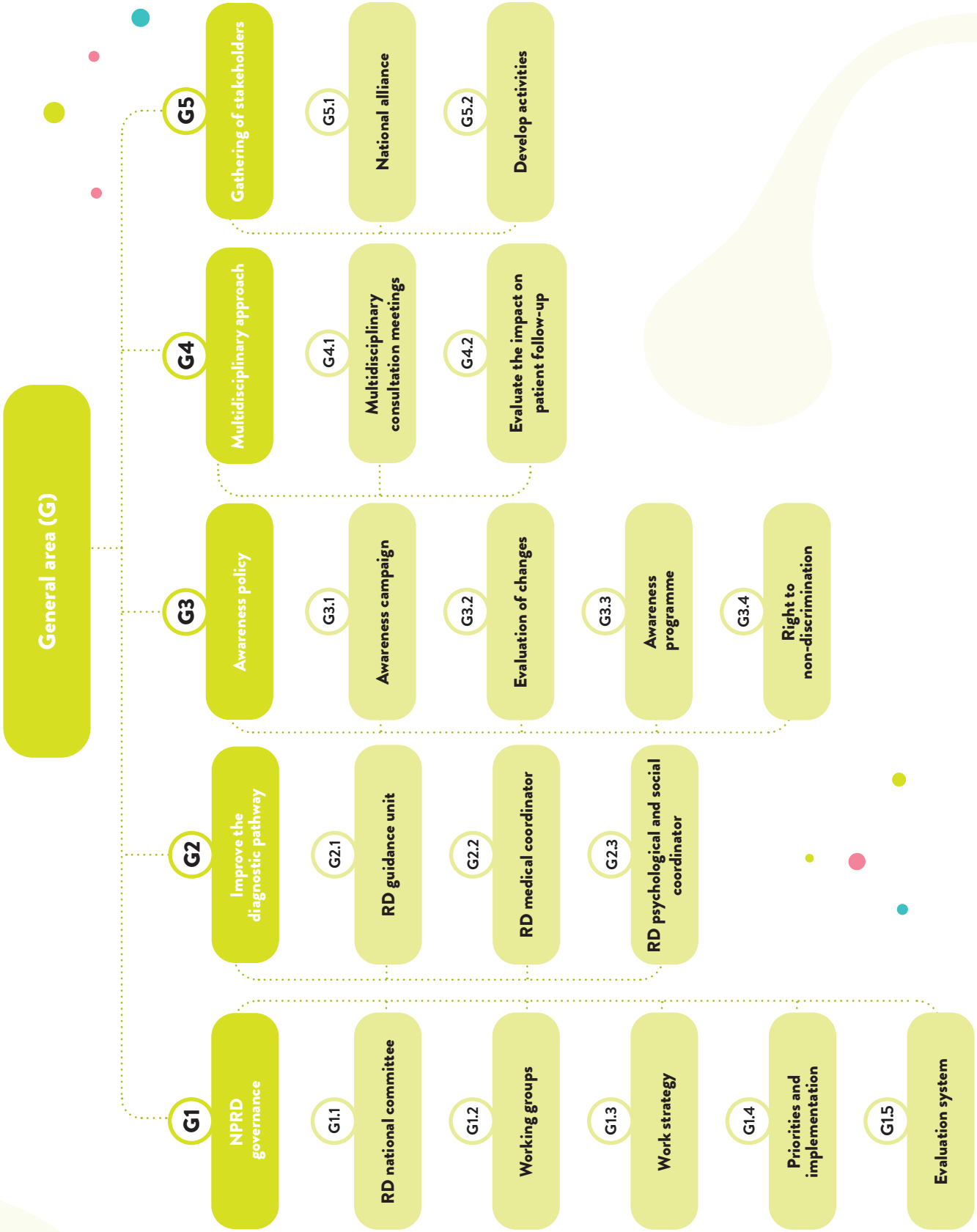
7. General line of action

A general line of action has been developed spanning the different areas of intervention in the NPRD to achieve all the goals related to the holistic care of RD patients.

The following objectives and measures are part of this line of action:

- Implementation of a NPRD governance framework, through the creation of a RD national committee, the formation of working groups dedicated to each goal, the definition of a work strategy and priorities, the development of an implementation plan and the establishment of an external monitoring system for the NPRD.
- Improvement of the patient diagnostic journey and care pathway through the creation of an orientation unit and a team of RD coordinators (medical, psychological and social).
- Development of a policy for raising awareness about RD through targeted campaigns, including the notion of the right to non-discrimination and integrating this approach to all public policies.
- Adoption of a multidisciplinary approach and a holistic vision of patient care by setting up multidisciplinary consultation meetings.
- Grouping of all related stakeholders in a national RD alliance and developing activities within patient associations.

ORGANISATIONAL CHART OF GOALS AND MEASURES



GOALS

GOAL G1

IMPLEMENTATION OF A NPRD GOVERNANCE SYSTEM

To implement, coordinate, monitor and assess the outcomes of the plan

MEASURE G1.1

CREATE A NATIONAL COMMITTEE FOR RD (NCRD)

The NCRD is responsible for following the proposals put forward by the working groups regarding measures and actions to be implemented.

ACTION G1.1.1

Define the role, missions, operation and expected results

ACTION G1.1.2

Formally appoint the members of the NCRD.

MEASURE G1.2

SET UP WORKING GROUPS (WG)

These technical working groups are assigned to each goal of each strategic area of the NPRD to provide the expertise required for setting up and implementing activities related to the plan.

ACTION G1.2.1

Define the mission of each WG.

ACTION G1.2.2

Formally appoint WG members.

MEASURE G1.3

DEFINE A NPRD WORKING STRATEGY

Once the NCRD is in place, a global work strategy must be defined to address every complex and diverse aspect of RD.

ACTION G1.3.1

Define RD families according to established criteria and make models / work tools based on them.

MEASURE G1.4

DEFINE PRIORITIES AND A NPRD IMPLEMENTATION PLAN

For each NPRD goal, measure and action, the priorities must be defined in a time frame between 2018 and 2022.

ACTION G1.4.1

Define the priority goals.

ACTION G1.4.2

Prepare an implementation plan including the resources needed for its implementation.

MEASURE G1.5

ESTABLISH AN EXTERNAL NPRD EVALUATION SYSTEM

External NPRD evaluation is essential to identify areas for improvement throughout the plan and over its implementation period (2018-2022).

ACTION G1.5.1

Identify a commission of independent experts from existing institutions in Europe in the field of RDs.

ACTION G1.5.2

Conduct a mid-term (2020) and late (2022) NPRD assessment.

GOAL G2

IMPROVEMENT OF THE DIAGNOSTIC AND CARE PATHWAY

Diagnostic and therapeutic odyssey is addressed in this key goal of the NPRD, which aims to improve the way RD patients, their families and the professionals treating them are orientated towards existing sources. The coordination between the various stakeholders is ensured by the creation of two positions (one medical, the other psychological and social). They will work in close collaboration.

MEASURE G2.1

CREATE AN RD ORIENTATION CELL

This unit, based on the information available, will be responsible for referring patients, their families and health professionals to specialists and/or specialised RD teams in the country or abroad. Its main role is to facilitate the process of diagnosis and care management.

ACTION G2.1.1

Define the status, missions and operation of the unit

ACTION G2.1.2

Define the necessary resources and a sustainable development plan (including funding).

ACTION G2.1.3

Recruitment and implementation of the orientation unit.

MEASURE G2.2

DESIGNATE A RD MEDICAL COORDINATOR

This person will be responsible for coordinating everyone involved around a patient and their family, regardless of their speciality, without overtaking the role of the attending doctor. This person will work closely with the psychological and social RD Coordinator.

ACTION G2.2.1

Define the job description including roles and responsibilities, and its integration at the health system level.

ACTION G2.2.2

Define the necessary resources and a sustainable development plan (including funding).

ACTION G2.2.3

Recruitment and implementation of the position.

MEASURE G2.3

DESIGNATE A RD PSYCHOLOGICAL AND SOCIAL COORDINATOR

This person, in close collaboration with the RD medical coordinator, will be the link between the various services of the medical, psychological and social network and the other parties concerned. This position will have national coverage and will help harmonise the health journey of the patient and their family.

ACTION G2.3.1

Define the job description with roles and responsibilities as well as its integration into the psychological and social network.

ACTION G2.3.2

Define the necessary resources and a sustainable development plan (including funding).

ACTION G2.3.3

Recruitment and implementation of the position.

GOAL G3

IMPLEMENTATION OF A RD AWARENESS POLICY

The goal is to raise and develop public awareness of RD-related issues, and to reduce the risk of discriminatory behaviour by encouraging exchanges and openness.

MEASURE G3.1

SET UP RD AWARENESS CAMPAIGNS

Set up awareness campaigns in hospitals, long-stay facilities, rehabilitation centers, schools and in the community.

ACTION G3.1.1

Define the target population, the message and campaign frequency.

ACTION G3.1.2

Involve professionals in the development of campaigns.

ACTION G3.1.3

Conduct systematic "employer" campaigns to raise awareness of RD and employment-related issues.

MEASURE G3.2

EVALUATE BEHAVIOURAL CHANGES FOLLOWING AWARENESS CAMPAIGNS IN TARGET POPULATIONS

ACTION G3.2.1

To be defined when setting up a dedicated working group.

MEASURE G3.3

INTEGRATE A RD AWARENESS PROGRAMME IN ALL PUBLIC POLICIES

This would enable people affected by RD to live in supportive environments.

ACTION G3.3.1

To be defined when setting up a dedicated working group.

MEASURE G3.4

GUARANTEE THE PATIENTS THE RIGHT TO NON-DISCRIMINATION

ACTION G3.4.1

Reflection work on public awareness of non-discrimination

GOAL G4

DEVELOPMENT OF A MULTIDISCIPLINARY APPROACH TO PATIENT CARE THROUGHOUT THEIR ILLNESS

The goal is to reach a 'holistic' vision of patient care in order to ensure that all actions are consistent and complementary.

MEASURE G4.1

ESTABLISH MULTIDISCIPLINARY CONSULTATION MEETINGS (MCM) FOR RD

This would ensure quality care, where each party is consulted before the start of the treatment(s).

ACTION G4.1.1

Define the MCM mission and how it works.

ACTION G4.1.2

Define the clinical situations that will be the subject of a national and/or international MCM.

ACTION G4.1.3

Provide MCM with national management software.

MEASURE G4.2

EVALUATE THE IMPACT OF MCM ON PATIENT MONITORING

ACTION G4.2.1

Put in place a national MCM monitoring system.

GOAL G5

GATHERING OF ALL STAKEHOLDERS AROUND RARE DISEASES

Federate the major RD stakeholders, and especially the patient associations in Luxembourg.

MEASURE G5.1

CREATE A RD NATIONAL ALLIANCE (NA)

A confederation where each association, while retaining its specific nature, can exchange and share information and means.

ACTION G5.1.1

Define the status and mission of the NA.

ACTION G5.1.2

Set up the NA.

MEASURE G5.2

DEVELOP ACTIVITIES LINKING THE NA TO PATIENT ASSOCIATIONS

ACTION G5.2.1

Identify all patient associations in Luxembourg, and link them to the NA.

ACTION G5.2.2

Develop NA activities in the country and internationally.

INDICATORS:

Structural:

- NCRD regulations;
- Main stakeholders' attendance of NCRD at RD level;
- Patients are officially represented at NCRD and WG level.

Result-based:

- RD medical coordinator and psychological and social coordinator positions in place;
- Run at least one awareness campaign per year;
- Set up the NA.

Process-based:

- The definition of RD according to the EU has been adopted;
- The MCM in the field of RD are established.

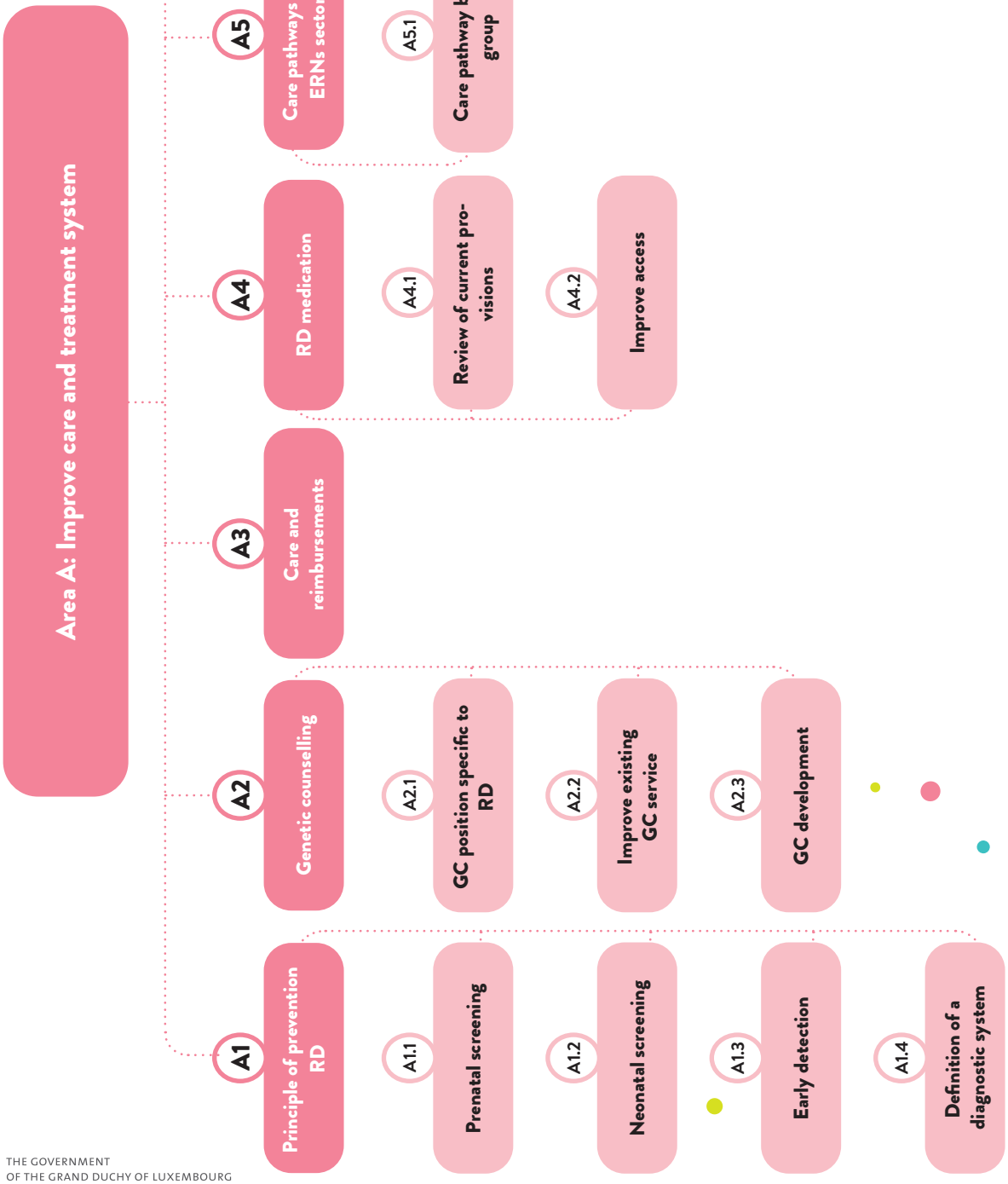
8. Area A - Improve care and treatment system

Area A is dedicated to improving the care and treatment system of RD. Reaching the goals and putting into place the defined measures and actions will ensure quality monitoring while optimising resources available in the country.

This area includes the following goals and measures:

- Application of the principle of prevention, targeting current screening programmes (prenatal and neonatal) and adopting early RD detection measures. The goal includes the definition of diagnostic pathways to improve care after detection.
- Consolidation of a genetic counselling service for RD patients and their families, creating a new position specific to RD and improving the current service.
- Improvement of coverage and of reimbursement of consultations, medication, medical devices, food supplements and any additional means.
- Improvement of access to RD medicine, reviewing what is currently in place by implementing a task force dedicated to orphan medicinal products.
- Development of a care pathway for different groups of RD, according to the sectors laid down by the ERNs and using expertise available in Luxembourg (affiliated centers) and in European ERNs.
- Commitment to continuity of care for those affected, creating a paediatric/adult RD care unit to ensure a transition of care between the different institutions, at the level of school and work health services.

ORGANISATIONAL CHART OF GOALS AND MEASURES



GOALS

GOAL A1

APPLICATION OF THE PRINCIPLE OF PREVENTION[51]

This applies to prenatal and neonatal screening and to any situation of early RD detection, for the patients and/or their family, in line with current practices [52 53]

MEASURE A1.1

IMPROVE THE CURRENT PRENATAL SCREENING PROGRAMME

ACTION A1.1.1

Evaluate the current prenatal screening programme, including provisions on abortion on medical grounds (AMG), pre-implantation diagnosis (PID), and non-invasive prenatal testing.

ACTION A1.1.2

Introduce adjustments and/or improvements consistent with national and international bioethical principles.

MEASURE A1.2

UPDATE THE NEONATAL SCREENING PROGRAMME

Optimise neonatal screening through an initial assessment of the current screening system, the possible integration of new tests or the expansion of screening for other diseases in line with international scientific recommendations and evidence, and possible adjustments at the various stages, in line with international recommendations on the subject[54].

ACTION A1.2.1

Review the current programme in place in Luxembourg and other European countries, in accordance with the technical possibilities and therapeutic options (a screening programme applies to the entire population).

ACTION A1.2.2

Adjust the type and number of genetic screening tests in accordance with existing technologies.

ACTION A1.2.3

Include sensory screening tests in the programme.

MEASURE A1.3

SET UP EARLY RD DETECTION MEASURES THAT REMAIN ACTIVE THROUGHOUT A PERSON'S LIFE

By setting up a system that triggers specialised consultations from the first symptoms.

ACTION A1.3.1

To be defined when setting up a dedicated working group.

ACTION A1.3.2

Extend the arrangement to any other member of the patient's family concerned.

MEASURE A1.4

DEFINE A DIAGNOSTIC SYSTEM FOR THE CARE OF RD DETECTED DURING SCREENING, LINKED TO PSYCHOLOGICAL AND SOCIAL SERVICES

This measure is closely linked to the implementation of multidisciplinary consultation meetings (MCM, measure G4.1) and the development of a care pathway (measure A5.1).

ACTION A1.4.1

To be defined when setting up a dedicated working group.

51 *Explanatory note: The principle of prevention is to anticipate and take steps to avoid or reduce a risk to a person or a community (in this case a biological family), to identify a disability or illness early, to set up adequate measures to anticipate adverse health consequences.*

52 « Principes et pratique du dépistage de maladies », Wilson & Jungner, OMS Genève 1970.*Source:* Press release of 15.02.2017 Kriibskrank Kanner Foundation.

53 *Source:* http://www.who.int/bulletin/volumes/86/4/07-050112/en/« Revisiting Wilson and Jungner in the genomic age: a review of screening criteria over the past 40 years ». Anne Andermann, Ingeborg Blancquaert, Sylvie Beauchamp, Véronique Déry, Bulletin of the World Health Organization, Volume 86, Number 4, April 2008, 241-320.

54 *Source :* https://ec.europa.eu/health/rare_diseases/screening_en

GOAL A2

CONSOLIDATION OF GENETIC COUNSELLING (GC) SERVICE FOR RD

Consolidation of a RD "Genetic Counselling detection and care" service to ensure the care of patients throughout the genetic diagnosis process. This service will be located at the National Centre for Human Genetics (CNGH) (which is in the implementation phase for the National Cancer Plan at LNS level).

MEASURE A2.1

CREATION OF GC POSITION SPECIALISED IN RD

ACTION A2.1.1

Define the job description, with roles and responsibilities and its integration at CNGH level.

ACTION A2.1.2

Define the necessary resources and a sustainable development plan (including funding).

MEASURE A2.2

IMPROVEMENT OF CURRENT GC SERVICE

ACTION A2.2.1

Review the operation of the current service.

ACTION A2.2.2

Guarantee psychological and social support from the beginning of care.

ACTION A2.2.3

Put in place measures to avoid drop-off owing to psychological and social reasons.

MEASURE A2.3

GC DEVELOPMENT

ACTION A2.3.1

Develop GC on hereditary RD, detectable at various stages of life (preconception, prenatal, paediatric and adults).

ACTION A2.3.2

Develop an ethical guide for clinical practice in accordance with the legal framework of bioethics legislation.

GOAL A3

IMPROVEMENT OF COVERAGE AND REIMBURSEMENT OF CONSULTATIONS, MEDICATION, MEDICAL DEVICES, FOOD SUPPLEMENTS AND ANY ADDITIONAL MEANS

The request for coverage will be justified by what is "useful and necessary". A list of priorities will be established in terms of the pathologies to be considered first, according to the needs. This goal includes the coverage and refund of diagnostic tests.

ACTION A3.1.1

Review existing reimbursements, according to a patient's needs, by drawing up a list of the 'problems' related to health insurance coverage that have been identified.

ACTION A3.1.2

Extension/adjustment of benefits refunded online with a personalised medicine approach.

GOAL A4

IMPROVEMENT OF ACCESS TO RD MEDICINE

The procedures currently in place to ensure access to new therapies will be reviewed and an expert committee set up to assess the most complex situations. Achieving this goal will be in accordance with the legal framework of bioethics established in Luxembourg.

MEASURE A4.1

REVIEW CURRENT PROVISIONS ON RD MEDICINES

ACTION A4.1.1

Create a task force composed of experts in the field of orphan medicinal products, who will work in accordance with the bioethical provisions in force in Luxembourg.

ACTION A4.1.2

Review the current provisions for RD medication.

ACTION A4.1.3

Review the provisions for compassionate use.

MEASURE A4.2

IMPROVE ACCESS TO RD MEDICATION

ACTION A4.2.1

Introduce measures to improve access to orphan medicinal products in Luxembourg.

ACTION A4.2.2

Improve supply systems for orphan medicinal products, including their reimbursement rate.

ACTION A4.2.3

Facilitate the participation of Luxembourg patients in clinical RD studies in Europe.

ACTION A4.2.4

Set up a committee of experts to review the arrangements to be made in the most complex situations.

GOAL A5

DEVELOPMENT OF A CARE PATHWAY, ACCORDING TO THE SECTORS LAID DOWN BY THE ERNs

This goal aims to elaborate a care pathway simplifying a patient's arrival to an expert centre (affiliated centre) located in Luxembourg or in Europe (ERNs), thus limiting diagnostic odyssey and delayed care. By establishing a care unit (Goal A6), this pathway will ensure the link between primary healthcare, associations, school health services and the existing expert centers in Luxembourg (Goal B2). When creating care pathways, access to local medical care will be preferred when possible.

MEASURE A5.1

DEFINITION OF A CARE PATHWAY BY RD GROUP

ACTION A5.1.1

Identify current clinical practices at the level of RD groups.

ACTION A5.1.2

Define a care pathway for RD groups with expertise available in Luxembourg (affiliated centers).

ACTION A5.1.3

Define a care pathway for RD groups requiring European expertise available through ERNs.

GOAL A6

CONTINUITY OF CARE FOR AFFECTED PATIENTS

This goal will be achieved through the creation of a care unit, with a paediatric section and another section for adult care. They will work closely together to ensure an adequate transition from the paediatric age to adulthood. The principle of continuity of care applies to the cooperation of health professionals at the hospital, the rehabilitation centre and/or in a private practice and to the coordination of the care necessary for a good educational and/or professional integration.

MEASURE A6.1

CREATION OF RD PAEDIATRIC/ADULTS CARE UNIT

ACTION A6.1.1

Definition of the unit's roles, responsibilities and inter-connections.

ACTION A6.1.2

Definition of a care transition programme between paediatric age and adulthood.

ACTION A6.1.3

Establish the unit (pilot phase in hospitals), in connection with the pathway of the referring doctor (paediatrician or GP), in accordance with the existing tools (shared record of care, DSP).

MEASURE A6.2

ENSURING CONTINUITY OF CARE BETWEEN DIFFERENT INSTITUTIONS/ FACILITIES

ACTION A6.2.1

Definition of a care transition programme between the different actors.

MEASURE A6.3

ENSURING CONTINUITY OF CARE IN SCHOOL HEALTH SERVICES

ACTION A6.3.1

To be defined with school health services when setting up a dedicated working group.

MEASURE A6.4

ENSURING CONTINUITY OF CARE IN WORK HEALTH SERVICES

ACTION A6.4.1

To be defined with work health services when setting up a dedicated working group.

INDICATORS:

Structural:

- Create a task force consisting of experts in the field of orphan medicinal products;
- Hire a new consultant in RD genetic counselling.

Result-based:

- Update the panel of screening tests;
- Assess the effectiveness and sufficiency of the insurance coverage and refunds of medical and paramedical consultations.

Process-based:

- Establish a follow-up procedure after screening;
- Define RD care pathways in Luxembourg and collaboration with ERNs;
- Formalise patient access to ERNs.

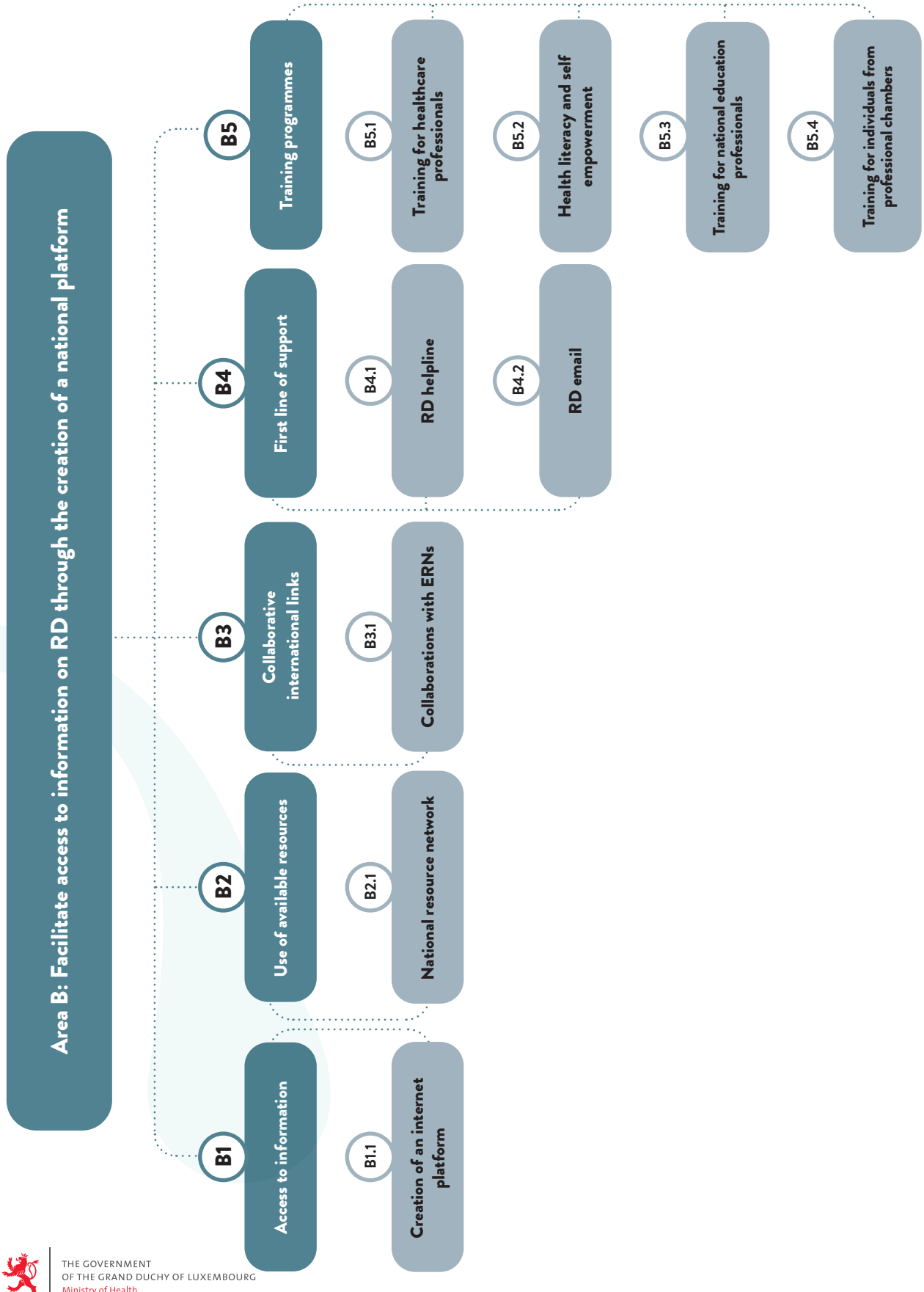
9. Area B - Facilitate access to information on RD through the creation of a national platform

The creation of a national information platform for patients, their families and RD professionals will facilitate access to information and be training relevant to them? It will also add Luxembourgish characteristics to the existing information platforms in Europe.

This area includes the following goals and measures:

- Improvement of access to information on RD in Luxembourg, through the creation of a country-specific online platform.
- Optimisation of the use of resources available in Luxembourg, by developing national networks of expertise in the country.
- Development of international links and collaborations, especially at the level of ERNs.
- Organisation of a first support line for patients, setting up a dedicated RD helpline and a specific email address.
- Provision of training programmes dedicated to RD, targeted at healthcare and national education professionals and individuals from professional chambers. Programmes also include health literacy and self empowerment modules for patients and patient associations.

ORGANISATIONAL CHART OF GOALS AND MEASURES



GOALS

GOAL B1

IMPROVEMENT OF ACCESS TO INFORMATION ON RD IN LUXEMBOURG

The creation of a RD online information platform in Luxembourg is essential. The platform will be accessible to patients and to all professionals involved. It will centralise information and resources gathered, including internationally, and will work closely with the helpline (Goal B4).

MEASURE B1.1

CREATE A RD ONLINE PLATFORM

ACTION B1.1.1

Define the characteristics of the platform: type of information disseminated, user profiles, access rights, etc.

ACTION B1.1.2

Define the organisation, operation, required resources and accessibility of the platform (with the contribution of a webmaster).

ACTION B1.1.3

Define a secure, certified exchange and contact platform in liaison with the helpline.

ACTION B1.1.4

Check the relevance of existing information (RD-specific) on other European websites (especially Orphanet) and create links demonstrating national resources.

ACTION B1.1.5

Identify and update the available research tools in terms of information sources (Orphanet, ELIXIR, Matchmaker exchange, etc.) and list them on the platform.

GOAL B2

OPTIMISATION OF THE USE OF RESOURCES AVAILABLE IN LUXEMBOURG

Once this goal has been reached the information on the national resources will be identified on the online platform (Goal B1) and available via the helpline (Goal B4).

MEASURE B2.1

DEVELOP A NETWORK OF NATIONAL RESOURCES

ACTION B2.1.1

Connect and update existing network resources by RD group.

ACTION B2.1.2

Connect and update existing network resources by RD group.

ACTION B2.1.3

Develop collaborative links with existing ERNs.

GOAL B3

DEVELOPMENT OF CLOSE INTERNATIONAL LINKS AND COLLABORATIONS

Cooperating with the European Reference Networks (ERNs) will facilitate access to healthcare channels, meaning Luxembourg teams will be involved at European level as affiliated members.

MEASURE B3.1

DEVELOP COLLABORATIONS WITH ERNs

ACTION B3.1.1

Prepare and support the "affiliated member" application(s).

ACTION B3.1.2

Create preferential and active cooperation with these ERNs based on existing RD groups.

ACTION B3.1.3

Prepare and support the candidate(s) as an "affiliated member".

GOAL B4

ORGANISATION OF A FIRST LINE OF SUPPORT FOR PATIENTS

With the introduction of a RD support helpline and a dedicated email address, patients and healthcare professionals will have access to a first line of contact. This service will be integrated in the RD orientation unit planned in Goal G2.

MEASURE B4.1

CREATE A RD HELPLINE

ACTION B4.1.1

Define the helpline's missions within the RD orientation unit.

ACTION B4.1.2

Define the organisation, operation and resources required.

ACTION B4.1.3

Implement and evaluate the helpline according to indicators (to be defined when setting up a dedicated working group that will accompany its gradual launch).

MEASURE B4.2

CREATE A DEDICATED RD EMAIL ADDRESS

ACTION B4.2.1

Define the missions of the email address within the RD orientation unit.

ACTION B4.2.2

Define the organisation, operation and resources required.

ACTION B4.2.3

Implementation and evaluation of email messages, according to the indicators selected at launch.

GOAL B5

PROVISION OF TRAINING PROGRAMMES DEDICATED TO RD

These general training programmes provide support to healthcare professionals looking for further information on RD. Specialised training for specific issues is the responsibility of the centers of expertise. The online platform will provide links to courses offered abroad (Goal B1). This goal includes health literacy and self-empowerment training for patients, in line with the recommendations of the EU[55].

MEASURE B5.1

TRAINING PROGRAMMES FOR HEALTH CARE PROFESSIONALS

ACTION B5.1.1

Identify training needs in the area of RD.

ACTION B5.1.2

List the courses available in Luxembourg and abroad.

ACTION B5.1.3

Create training programmes, quantify resources.

ACTION B5.1.4

Create a continuing education programme for encoders.

MEASURE B5.2

HEALTH LITERACY AND SELF-EMPOWERMENT TRAINING FOR PATIENTS

ACTION B5.2.1

Identify training needs with patient associations.

ACTION B5.2.2

List the courses available in Luxembourg and abroad. Identify expert patient and support peer groups.

ACTION B5.2.3

Create specific online training courses and/or partnership with EURORDIS.

MEASURE B5.3

TRAINING FOR PROFESSIONALS IN NATIONAL EDUCATION

ACTION B5.3.1

Provide continuing professional development training for all national education professionals.

ACTION B5.3.2

Conduct targeted actions to raise RD awareness within the entire school system.

MEASURE B5.4

TRAINING FOR INDIVIDUALS FROM PROFESSIONAL CHAMBERS

ACTION B5.4.1

Conduct targeted actions to raise RD awareness within professional groups.

INDICATORS:

Structural:

- National online platform in place
- Implementation of the helpline

Result-based:

- Participation in Orphanet Joint Action
- Preparation of information leaflets in the national languages
- Number of affiliated members (ERNs)
- Number of expert centers

55 *Source :* https://ec.europa.eu/health/ph_threats/non_com/docs/rare_com_en.pdf

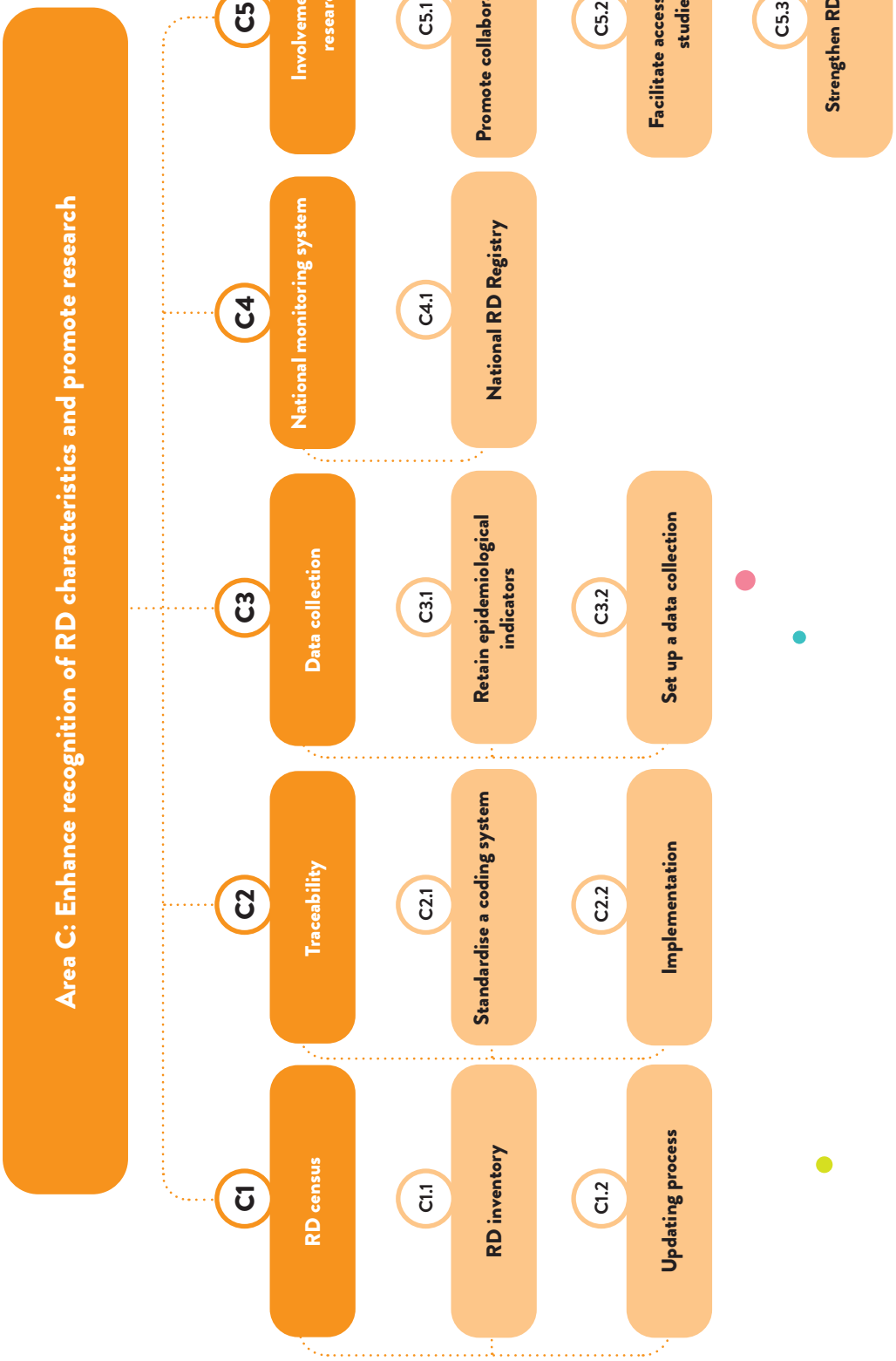
10. Area C - Enhance recognition of RD characteristics and promote research

The recognition of the specificities of RD implies putting in place the measures and actions necessary to establish an inventory, a dedicated coding system and a RD registry that will allow data collection in line with studies done in Europe. The overall aim is to promote research activities in this area.

This area includes the following goals and measures

- Organisation of a national RD census, creating an inventory and implementing a system to update all existing information.
- Improvement of RD traceability in Luxembourg, standardising a single RD coding system and implementing it within institutions involved.
- Implementation of data collection in line with European regulations: the epidemiological indicators necessary for RD monitoring must be maintained, and a collection of data put in place in order to implement them.
- Adoption of a system for national RD monitoring, by setting up a dedicated national registry.
- Intensification of Luxembourgish implication in research projects and/or other RD-related areas, at national and international level, by promoting collaboration models in Luxembourg and abroad, facilitating patient and professional access to clinical studies in Europe, and strengthening research in the areas that require funding.

ORGANISATIONAL CHART OF GOALS AND MEASURES



GOALS

GOAL C1

ORGANISATION OF A RD CENSUS IN LUXEMBOURG

MEASURE C1.1

CREATING A RD INVENTORY

ACTION C1.1.1

List all RD present in Luxembourg using currently available sources (data from patient associations and other entities).

ACTION C1.1.2

Create a list of disease groups.

MEASURE C1.2

SETTING UP A SYSTEM TO UPDATE THE EXISTING INVENTORY

ACTION C1.2.1

To be defined by a dedicated working group that will be set up.

GOAL C2

IMPROVEMENT OF RD TRACEABILITY IN LUXEMBOURG

This goal concerns the development of a coding system in line with what is done in other European countries, and taking into account, if possible, the systems currently used in Luxembourg.

MEASURE C2.1

STANDARDISING A SINGLE CODING SYSTEM FOR RD

The coding system must be in line with what is done in other European countries, and taking into account, if possible, the systems currently used in Luxembourg.

ACTION C2.1.1

Set up the ICD10-CM (and then ICD11 as soon as available) coding system to code diagnostics, and Orphacode to code the RD.

ACTION C2.1.2

Identify the specific skills needed to encode RD and put in place the necessary resources.

ACTION C2.1.3

Develop a quality control system that can validate/verify the coding.

MEASURE C2.2

IMPLEMENT THE CODING SYSTEM WITHIN INSTITUTIONS INVOLVED

ACTION C2.2.1

Develop a step-by-step implementation plan in hospitals (with a pilot phase in one hospital).

ACTION C2.2.2

Assign dedicated resources for implementation (staff, hardware, computer system etc.).

GOAL C3

IMPLEMENTATION OF RD DATA COLLECTION

Define the "epidemiological indicators" in order to follow the development of RD in Luxembourg. Such as: identification of new cases, evaluation of the quality of care (according to the guidelines by disease, if available), time required for diagnosis and mortality rate. This goal provides for the establishment of data collection tools in accordance with the European recommendations[56].

MEASURE C3.1

RETAINING THE "EPIDEMIOLOGICAL INDICATORS" NECESSARY FOR RD MONITORING

ACTION C3.1.1

Define a list of indicators (descriptive epidemiology and quality of care) and their characteristics.

MEASURE C3.2

SETTING UP A DATA COLLECTION TO MEET THE DEFINED INDICATORS

ACTION C3.2.1

Collect data on mortality, disability, social, educational and vocational integration of people with RD.

ACTION C3.2.2

Define the resources necessary.

ACTION C3.2.3

Define a validation and quality control system.

GOAL C4

ADOPTION OF A SYSTEM FOR NATIONAL RD MONITORING

Create a national registry to allow long-term RD monitoring. This registry will constitute a main coordination structure to bring together data elements that are common to all RD and ensure the interoperability of existing registries.

MEASURE C4.1

ESTABLISHING A NATIONAL RD REGISTRY

ACTION C4.1.1

Create a main coordination structure (and infrastructure) linking the existing registries.

ACTION C4.1.2

Harmonise the common RD dataset in line with European recommendations[57].

56 "EUCERD Report on Health indicators for rare diseases: II - Conceptual for the use of health indicators for the monitoring of quality of care", L. Fregonese, C. Rodwell, S. Aymé, September 2011. Source: http://www.eucerd.eu/?post_type=document&p=1353

57 European commission joint research centre. set of common data elements for rare diseases registration.

GOAL C5

INTENSIFICATION OF LUXEMBOURGISH IMPLICATION IN RESEARCH PROJECTS AND/OR OTHER RD-RELATED AREAS, AT NATIONAL AND INTERNATIONAL LEVEL

This purpose of this goal is to set up a networking system. The starting point is the creation of a list of researchers specialised in RD research in Luxembourg.

MEASURE C5.1

PROMOTE MODELS OF COLLABORATION ON RD IN LUXEMBOURG AND ABROAD

ACTION C5.1.1

To identify institutions/researchers in Luxembourg involved in RD research projects/ collaborations.

ACTION C5.1.2

Networking with relevant centers in Europe or elsewhere.

MEASURE C5.2

FACILITATING PATIENT AND PROFESSIONAL ACCESS TO CLINICAL STUDIES IN EUROPE

ACTION C5.2.1

Review existing provisions on access to clinical studies to facilitate patient inclusion procedures in Luxembourg.

MEASURE C5.3

STRENGTHEN RD RESEARCH IN LUXEMBOURG

ACTION C5.3.1

Identify weak RD fields at funding level.

ACTION C5.3.2

Prioritise the measures to be put in place in the "Research and Development" sector.

INDICATORS:

Structural

- Set up the coding system

Result-based

- Implement a comprehensive RD inventory, updated annually

Process-based

- Implement a data collection system
- Participate in international research projects
- Participate in clinical trials
- Process data from the National RD Registry

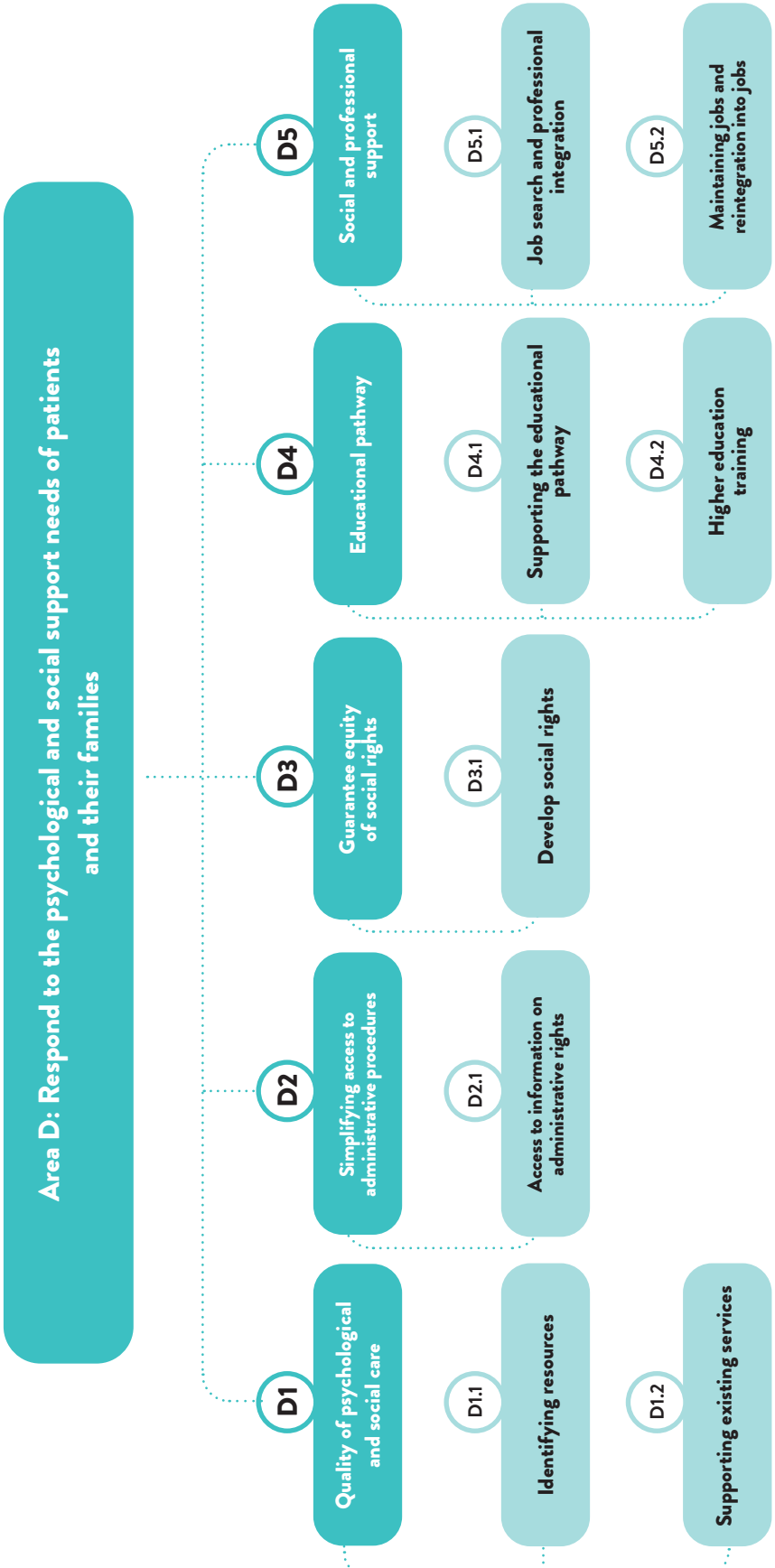
11. Area D - Respond to the psychological and social support needs of patients and their families

This last area aims to improve, develop and consolidate the psychological and social care given to patients and their families so as to better respond to their support needs. Achieving the goals of this area will reduce inequalities in the social, professional, educational and personal spheres.

This area includes the following goals and measures:

- Improvement of the quality of psychological and social care given to patients and their families, through the identification of current resources and the support of existing services specific to RD.
- Simplification of access to administrative procedures, improving access to information through a practical guide, the RD online platform and the creation of a one-stop desk.
- Commitment to ensure equity of social rights for RD patients, by developing current rights.
- Development of measures to facilitate the educational pathway of people affected by RD, supporting the schooling process and boosting access to higher education programmes.
- Offering of social and professional support to people with RD and their family members, supporting placement and job search measures for young workers, and maintaining employment and reintegration into employment for people with RD and affected family members.

ORGANISATIONAL CHART OF GOALS AND MEASURES



GOALS

GOAL D1

IMPROVEMENT OF QUALITY OF PSYCHOLOGICAL AND SOCIAL CARE OF PATIENTS AND THEIR FAMILIES

The planned measures will make existing resources and their optimisation more accessible. The expected results of this goal will be closely related to Goal B2 (Develop a network of accessible national resources).

MEASURE D1.1

IDENTIFY CURRENT RESOURCES IN RD PSYCHOLOGICAL AND SOCIAL CARE

ACTION D1.1.1

Map specialised psychological consultations and social monitoring.

ACTION D1.1.2

Define the role of the services/institutions with regard to patients with RD.

ACTION D1.1.3

Identify specificity and resource requirements with regard to existing supply and demand.

MEASURE D1.2

SUPPORT EXISTING SERVICES SPECIFIC TO THE RD PSYCHOLOGICAL AND SOCIAL CARE

ACTION D1.2.1

Support the specialised national RD support service.

ACTION D1.2.2

Identify the coordination mechanisms in place at service/institution level and take the necessary measures to optimise them.

ACTION D1.2.3

Optimise care of people with RD in reception facilities.

ACTION D1.2.4

Provide comprehensive care for the family by developing the support for carers, among other things.

GOAL D2

SIMPLIFICATION OF ACCESS TO ADMINISTRATIVE PROCEDURES

MEASURE D2.1

IMPROVE ACCESS TO INFORMATION ABOUT ADMINISTRATIVE RIGHTS

ACTION D2.1.1

Update and publish a practical guide on the subject.

ACTION D2.1.2

Guarantee access to clear information (RD online platform).

ACTION D2.1.3

Creation of a one-stop desk.

GOAL D3

COMMITMENT TO ENSURE EQUITY OF SOCIAL RIGHTS FOR RD PATIENTS

MEASURE D3.1

DEVELOP THE SOCIAL RIGHTS OF PATIENTS WITH RD

ACTION D3.1.1

Identify current limits to rights for patients with RD and those around them.

ACTION D3.1.2

Suggest and develop possible adjustments to social rights legislation.

GOAL D4

DEVELOPMENT OF MEASURES TO FACILITATE THE EDUCATIONAL PATHWAY OF PEOPLE AFFECTED BY RD

These measures will provide for personal fulfilment within the national education system, ensuring equal rights of access to schooling and higher education training programmes. This goal is closely linked to the work performed by school healthcare in terms of continuity of care (Measure A6.3).

MEASURE D4.1

SUPPORT THE EDUCATIONAL PATHWAY

ACTION D4.1.1

Offer specific and specialised support for inclusive education and a school pathway that meets the specific needs of a child.

ACTION D4.1.2

Review the existing school offer and suggest adjustments that meet the unique needs of children with RD.

ACTION D4.1.3

Increase extracurricular activities and the offers of support for children.

MEASURE D4.2

BOOST ACCESS TO HIGHER EDUCATION PROGRAMMES

ACTION D4.2.1

Encourage and support people with RD on their paths to and through higher education.

GOAL D5

OFFERING OF SOCIAL AND PROFESSIONAL SUPPORT TO PEOPLE WITH RD AND AFFECTED FAMILY MEMBERS

This goal aims to meet demands of the right to employment for people affected by a disease but also for the members of their family professionally affected by RD. It therefore aims to reduce the financial impact the disease has on family life. This goal is closely linked to the work performed by occupational medicine with regard to continuity of care (Measure A6.4).

MEASURE D5.1

SUPPORT PLACEMENT AND JOB SEARCH MEASURES FOR YOUNG WORKERS

ACTION D5.1.1

Evaluate use of existing measures.

ACTION D5.1.2

Facilitate career guidance through specific and specialised RD support.

ACTION D5.1.3

Support professional integration specific to RD.

MEASURE D5.2

IMPROVE MEASURES FOR MAINTAINING EMPLOYMENT AND REINTEGRATION INTO EMPLOYMENT FOR RD PATIENTS AND AFFECTED FAMILY MEMBERS

ACTION D5.2.1

Evaluate use of existing measures.

ACTION D5.2.2

Suggest new alternatives according to needs.

ACTION D5.2.3

Guarantee support for the identification of suitable training and employment opportunities as part of a career change.

INDICATORS:

Result-based

- Perform targeted actions to support the national educational pathway of people with RD.

Process-based

- Existence of psychological and social support measures in RD care.
- Implementation of measures for professional integration and job maintenance specific to RD.

12. The implementation phases of the NPRD

After the NPRD 2018-2022's presentation and validation by the Government Council, it will be implemented and conducted by the National Committee for Rare Diseases (NCRD) under the aegis of the Minister for Health. The NCRD will be supported by a coordinator responsible for mobilising and assisting partners in carrying out actions.

If necessary for the implementation of the NPRD 2018-2022, legislative work will be enacted by the public authorities in parallel.

The provisions of the plan, as well as their implementation, fall under the Ministry of Social Security and will therefore be subject to the laws and regulations in force.

ESTABLISHMENT OF WORKING GROUPS (WG)

Working groups consisting of representatives from different institutions and various other stakeholders will be set up following a provisional timetable (Appendix 2) and will serve as a reference to measure the progress of the implementation of the NPRD 2018-2022.

Each measure or action foreseen in the NPRD 2018-2022 will be carried out under the supervision of a delegated member of the NCRD and with the partners involved, according to the defined content and the planned schedule. The coordinator, in cooperation with the delegated member of the NCRD, will be in charge of: developing and implementing the measures and actions in consultation with the involved stakeholders; accounting for the progress of the work and the results obtained; reporting on the difficulties encountered and requesting the necessary support for the progress of the work.

A summary table of the NPRD areas and goals is given in Appendix 3. Adaptations of the NPRD 2018-2022 may be decided by the NCRD depending on the difficulties encountered or contextual changes.

PRIORITIES

The NCRD will be responsible for defining a strategic plan for the priority actions to be implemented. For the year 2018, the Steering Committee considers the following as priorities: implementation of the NPRD governance at the launch of the plan; improvement of the diagnostic path with the creation of an orientation unit and a coordination team to reduce the phenomenon of diagnostic odyssey; start of RD identification work through the creation of an inventory and the establishment of a specific coding system to ensure traceability; improvement of visibility and access to information through the creation of an online platform and a helpline service; improvement of the quality of psychological and social care.

FUNDING

An application for funding has already been made to the Health Directorate for the NPRD 2018-2022, based on the funds needed for its implementation. The budget for 2018 was approved in December 2017. For the subsequent years, a provisional budget has been drawn up to cover the necessary funds. If needed, this can be renegotiated and adjusted each year.

13. Appendices

Appendix 1:

Membership list of working groups that participated in the conceptual stages of the NPRD in 2017.

Appendix 2:

Creation of working groups by goal: provisional timetable.

Appendix 3:

Organisational chart of the NPRD's areas and goals.

Appendix 1 - Membership list of working groups that participated in the conceptual stages of the NPRD in 2017

TITLE	SURNAME	FIRST NAME	INSTITUTION
Dr	**ALLARD**	Serge	CHL
Ms	**BAHLAWANE**	Christelle	IBBL
Ms	**BAILLOEUIL**	Emilie	CHL-SERVICE SOCIAL
Mr	**BARGE**	Hervé	AGENCE eSANTÉ
Dr	**BECKER**	Regina	LCSB
Mr	**BECKERS**	Mike	ASSOCIATION DE PATIENTS : ALLM (CYSTIC FIBROSIS)
Ms	**BINTENER**	Vera	INFOHANDICAP
Dr	**BOISANTE**	Catherine	CNER
Ms	**CHEF**	Séverine	CHL-SERVICE SOCIAL
Dr	**COLLET**	Agnès	LABORATOIRES RÉUNIS
Ms	**CONTER**	Stéphanie	HELP-AIDES ET SOINS
Dr	**COUFFIGNAL**	Sophie	LIH
Ms	**DA SILVA FERREIRA**	Sonia	APEMH - SOCIAL SERVICE
Ms	**DEBACKER**	Martine	MINISTRY OF HEALTH, CURATIVE MEDICINE DIVISION
Dr	**DE REKENEIRE**	Nathalie	MINISTRY OF HEALTH, EPIDEMIOLOGY SERVICE
Dr	**FELLMANN**	Florence	LNS
Ms	**GAPENNE**	Catherine	HELP – AIDES ET SOINS
Ms	**GARZARO**	Denis	ASSOCIATION OF PATIENTS: MARFAN SYNDROME
Mr	**GILSON**	Georges	CHL
Ms	**GOERES**	Anne	FOUNDATION OF PATIENTS: KRIIBSKRANK KANNER FOUNDATION
Mr	**HAAS**	Frédéric	AGENCE eSANTÉ
Ms	**HACHEMI**	Hafida	ASSOCIATION OF PATIENTS: WAERTVOLLT LIEWEN ASBL
Dr	**KARASI**	Jean-Claude	AGENCE eSANTÉ
Mr	**KOCH**	Alain	HELLEF DOHEEM
Ms	**KOLB**	Pascale	ASSURANCE DÉPENDANCE
Mr	**LEPANTO**	Olivier	AGENCE eSANTÉ
Dr	**LÜCK**	Jacques	ASSURANCE DÉPENDANCE
Ms	**LUX-COLLETTE**	Diane	ASSOCIATION OF PATIENTS: EEN HÄERZ FIR KRIIBSKRANK KANNER

Ms	**MAGAR**	Stéphanie	ALAN
Dr	**MAJERY**	Nicole	OCCUPATIONAL MEDICINE
Ms	**MARQUES**	Patricia	KRAIZBIERG
Ms	**MEDINGER**	Nadine	TRICENTENAIRE
Mr	**MULLER**	Erny	ONE
Mr	**PEREIRA**	José	REHAZENTER
Dr	**ROLLAND-PORTAL**	Isabelle	MINISTRY OF SOCIAL SECURITY - GENERAL INSPECTORATE OF SOCIAL SECURITY
Mr	**SALVI**	Patrick	RED CROSS - SOCIAL OFFICES
Mr	**SATAGOPAM**	Venkata	LCSB
Mr	**SCHEER**	Jean-Marc	ASSOCIATION OF PATIENTS: WÄERTVOLLT LIEWEN ASBL
Dr	**SCHLESSER**	Marc	CHL
Mr	**SCHMIT**	Jean-Philippe	RED CROSS - CENTRE OF CONVALESCENCE
Dr	**SCHNEIDER**	Reinhard	LCSB
Mr	**SCHWEBAG**	Mike	HEALTH MEDIATOR
Ms	**STURM**	Isabelle	RED CROSS - SOCIAL OFFICES
Dr	**VAN WYMERSCH**	Didier	CHL
Mr	**VITALI**	Sylvain	FHL
Ms	**WAGNER**	Gaby	ADEM
Ms	**ZAHNER**	Nadine	HELLEF DOHEEM
Ms	**ZOLLER**	Sandy	MINISTRY OF FAMILY

Appendix 2 - Creation of working groups by goal: provisional timetable

*PRIORITY GOALS

Appendix 3 - Organisational chart of the NPRD's areas and goals

NOTES

NOTES

NATIONAL PLAN
RARE
DISEASES
LUXEMBOURG