

## State of the Art of Rare Disease - Activities in EU Member States and Other European Countries

### Denmark Report

#### Definition of a Rare Disease

Denmark has adopted the European Commission definition of a rare disease concerning Orphan Medicinal Products. However, the measures within the National Strategy and in other matters use a different definition:

- A number of rare usually congenital, hereditary complex and serious diseases and conditions that require special knowledge and skills, and who needs a highly specialized especially well-planned coordinated efforts in the form of highly specialized diagnosis, treatment, monitoring and control 1-2 places in the hospital service.
- Rare diseases occur with a frequency (prevalence) of approximately 1-2 of 10,000 or less, i.e., up to approximately 500-1,000 people in Denmark. The diseases often cannot be cured, but with appropriate effort, the consequences of the diseases might be prevented, restricted or treated and patients thus ensured better quality of life and survival.
- There is no need for an absolute delimitation in Denmark as there is no attached special rights or similar to such a definition.
- The basic requirement is a long-standing and often multidisciplinary special treatment effort, organized in accordance with the known specialty planning criteria for highly specialized functions in the hospital system.
- Rare infectious and cancer diseases are not usually recognized under the term in Denmark, but will often have similar challenges. It is recommended in the organization of health services for the rare infectious and cancerous conditions, that there will be corresponding attention to that these patients are referred to the appropriate level of medical expertise including relevant specializations etc.
- As far Denmark follows and acknowledges the EU definition in the EU regulation on orphan drug regulation mv5.

#### National Plan/Strategy for Rare Diseases

Denmark has adopted a National Strategy for rare diseases.

The strategy was prepared on the basis of a five-year perspective and the Working Group suggested monitoring the situation and status evaluation of the strategy after 3 to 5 years, involving EUROPLAN recommendations.

This status evaluation is undertaken by the Danish health Authority in collaboration with the National Board of Social Services and will subsequently serve as a status report for the work on rare disease in Denmark.

The first meeting is planned to take place in October 2016. The institutions who participated in the working group of the strategy is invited to the meeting.

The Danish Health and Medicines Authority as the statutory competent authority has approved centres of expertise/referral centres for rare diseases in 2010 as part of a comprehensive planning of highly specialized hospital services in Denmark accordingly to the health care act.

Since 1993 The National Board of Health has published a list of centres of expertise designated by the National Board of Health. This list of centres has been revised regularly through the years and is now developed to the above mentioned approval system.

In 2001 the Danish National Board of Health launched a special report on rare diseases with recommendations regarding rare diseases in general and specific recommendations for 14 rare diseases to be cared for at two specialised Rare Diseases Centres. These two centres were established in Copenhagen and Aarhus respectively. The two centres work continuously on strengthening the interdisciplinary and cross professional activities. The 2001 report described an ideal general model for development of activities regarding rare

diseases in the health care sector and cooperation with other sectors. Many of the EUROPLAN-recommended elements of a national strategy for rare diseases were dealt with in this report.

On 19 November 2010, Rare Disorders Denmark in collaboration with EURORDIS held a National Conference on Rare Diseases in the context of the Europlan project in order to discuss the elaboration of a national plan for rare diseases in Denmark. In 2011 it was decided to let the National Board of Health establish a working group to elaborate a national strategy for Rare Diseases.

The strategy was developed by the National Board of Health in agreement with the Ministry of Health in order that Denmark lived up to the EU Council of Ministers' recommendation on the area and includes recommendations for both healthcare service and recommendations for social and educational initiatives.

The working group with the task to elaborate a national plan for RD has a broad representation of stakeholders and was founded at the end of 2011 and met at the start of February 2012 for the first time. The recommendations in the previous report on rare diseases from 2001 were assessed to see what was still required, what had changed and what new recommendations could be added considering the European perspective and the recommendations for a national strategy. The subject of Centres of Expertise was a key area of consideration but many other subjects were dealt with.

The working group had the task to describe and assess:

- Size and special characteristic of the patient group.
- The need for action in relation to diagnostics, treatment, care and control and rehabilitation.
- The current organization of offers, including the cooperation between sectors, based on the continuity of care.
- The need for knowledge and experience gathering, documentation and research.
- The need for dissemination of information.
- International cooperation.

The National Strategy was published by the Danish Health Authority in July 2014.

The National Strategy contains around 100 recommendations for a coherent and strengthened effort in a number of areas including i.e. timely diagnosis, treatment, follow-up and rehabilitation, multidisciplinary cooperation in hospitals, multidisciplinary and intersectoral coordination between sectors, more readily available valid information on diseases, research, registration and databases, training and skills development of professional and patient -empowerment and patient education.

The National Strategy was presented at a EUROPLAN Conference held by Rare Diseases Denmark in January 2015.

There is no associated funding for the National Strategy. Current expenditure for rare diseases, as for all other diseases, is within the general health system budget of the regions and municipalities. Similarly there is no dedicated budget for the activities of the National Strategy, this is incorporated into the general budget.

The National Strategy does address the coding of rare diseases.

A dedicated body exists to oversee the drafting and implementation of the National Strategy. The strategy was prepared on the basis of a five-year perspective and the Working Group suggested monitoring the situation and status evaluation of the strategy after 3 to 5 years, involving the EUROPLAN recommendations.

The status evaluation is undertaken by the Danish health Authority in collaboration with the National Board of Social Services and will subsequently serves as a status report for the work on rare disease in Denmark.

The first meeting has taken place in October 2016. The institutions who participated in the working group of the strategy were invited to the meeting.

Composition of the group:

- Phenylketonuria Association,
- Rare Diseases Denmark,
- Danish Regions (Danske Regioner),
- Local Government Denmark (Kommunernes Landsforening),
- National Board of Social Services,
- Danish Health Authority,
- Ministry of Health,
- Danish Pediatric Society,
- Danish Society of Medical Genetics,
- The Danish College of General Practitioners,
- Organization of Danish Medical Societies,
- The Capital Region of Denmark,
- Region Zealand,
- The Region of Southern Denmark,
- Central Denmark Region,
- The North Denmark Region.

In 2016, the main achievements of the National Strategy have been purported by the national alliance, Rare Diseases Denmark. These include:

- Preparation and implementation of a Rare Disease Helpline aimed at PLWRD and their relatives. The Helpline opened in October 2016, see section 9.
- Marking of Rare Disease Day, see section 14.

In October 2016 an evaluation process concerning the National Strategy has been initiated from which an action oriented report will be produced.

### **Organisation of Rare Disease Health and Social Care**

#### **Centres of Expertise**

There is an official national policy in Denmark for the designation of Centres of Expertise for rare diseases.

The Danish Health Authority has the jurisdiction to approve Centres of Expertise in accordance with the Health Care Act.

As mentioned above two Centres of Expertise specific for rare diseases have been functioning officially since 2001 in the health care system in Denmark at university hospital level. There are also a number of other established referral centres/Centres of Expertise approved by the Danish Health Authority with the task of maintaining a specific or several specific rare diseases.

The two centres, the Centre for Rare Diseases CSS RH in Copenhagen and the Centre for Rare Diseases – CSS AUH in Aarhus, were established in 2001. These Centres are responsible for 14 specific diagnoses. The special remit of these centres is the co-ordination of patient-care programs, treatment protocols and databases, and taking care of medical highly specialized tasks in agreed partnerships. Two years after the establishment of the centres, Rare Diseases Denmark conducted a survey that revealed that 75% of patients felt they had received better and more coherent treatment when treated at the centres. The two centres also have an important function in assessing patients, who do not have an official diagnosis, but were suspected to have a rare disease. Today the centres take care of many more different diagnoses, which do not have another nominated Centre of Expertise.

According to the Danish Health Care Act from 2007 the National Board of Health (now Danish Health Authority) began the task of going through the organization of specialized diagnoses, treatments and medical technologies across 36 surgical, medical and diagnostic specialties. The main goal was to improve quality

through sufficient volumes of patients and experienced professionals. The general criteria for establishing Centres of Expertise in this context are rareness, complexity, multidisciplinary and costly technologies. In 2009 public and private hospitals could apply to the National Board of Health for approval to maintain specific specialized treatments. In 2010 those hospital departments which had been approved were listed in accordance with their specific area of medical expertise. The two Centres of Rare Diseases have also been approved in this context. The departments that host the two Centres of Rare Diseases have also been approved for a number of different rare diseases, e.g. in Copenhagen for inborn errors of metabolism (IEM).

The number of Centres of Expertise for a single condition or for groups of conditions depend upon rarity (estimated number of patients), competence and available technology. A specific condition might thus be treated at only one specialised hospital department or up to five different hospital departments. Some geographical considerations will usually play a role in the decision making process if there is room for more than one centre. For instance, the approved departments are required to secure and develop their expertise, establish a quality improvement program, document their activities and take part in teaching and research activities. The system is focused on the treatment of patients.

The National Board of Health has in the National Plan for highly specialised hospital services issued about 1100 approvals of medical highly specialised functions and estimates that between 100 -120 of these are related to various diseases or groups of diseases which can be classified as rare. In general the approvals will last for a limited time, approximately 3-4 years.

A review process of these services began in 2014 with established working groups for 36 medical specialties. The revised National Plan was ready in the summer of 2015 and from then until January 2016 public and private hospitals could apply to the Danish Health Authority for approval to maintain specific specialized treatments. The revised National Plan will be announced and become effective in March 2017 with the approved hospital departments in listed as per their medical specialty.

Currently in Denmark there are two Centres complying with the national policy. These Centres of Expertise are dealing with many different diagnoses and in addition there are more centres that are focused on a specialist area of diagnoses.

The number of Centres in Denmark divided by million inhabitants 2,800,000. The number of Centres fulfilling the EUCERD criteria is 2.

A holistic approach to care is intended but has not yet been fully established.

### European Reference Networks (ERNs)

Denmark has in place a formal process for the endorsement of Health Care Providers to participate as members or coordinators of an ERN. All Danish applications sent to the DMA have been coordinated by representatives from other member states; however this is not clearly stated in the applications sent to the DMA.

At present there are 4 HCPs participating as full members in 11 ERNs.

Members	European Reference Networks (ERNs)
Aarhus University Hospital	Endo-ERN ERN LUNG ERN eUROGEN
Copenhagen University Hospital Rigshospitalet	Endo-ERN ERN EYE ERN LUNG ERN eUROGEN ERN GUARD-HEART MetabERN ERN PaedCan ERN RARE-LIVER

	ERNICA
Odense University Hospital	ERN Skin ERNICA VASCERN
Zealand University Hospital	ERN Skin

### Rare Disease Registration

No single centralized register for rare diseases currently exists in Denmark. There are however, of those which deal with rare disease, a number of registries and biobanks although there is currently no public register providing an overview of this information. The Serum Institute has hosted the registry and biobank of all newborn screening blood samples since 1980. The Kennedy Centre maintains biobanks on specific rare disorders, such as Menkes disease and various genetic eye diseases. All visually handicapped children are registered until the age of 18. Furthermore, several research departments have registries of rare diseases patients.

The Raredis database which collects clinical data has been developed in Denmark in accordance to the recommendations within the Danish report of rare diseases from 2001 and has been in function since 2007 at the two Centres of Rare Diseases in Denmark. For the moment a few other departments can also report to the database.

It is planned that all the departments of clinical genetics in Denmark be granted permission to report to the database in the future. Centres of rare diseases in the Nordic countries use a local version of Raredis for collecting clinical data. The collected information can be used for research purposes and bench marking at a Nordic level for different rare diseases.

The Danish National Patient Registry (NPR) has existed since 1977 and collects systematic information on diagnoses, surgical treatment, and various demographical parameters on all patients admitted to hospital or similar institutions within Denmark. The Danish personal identity number provides healthcare professionals with the opportunity to follow patients through the years and combine data with other national registries, such as the Cancer Registry, the Registry for Cause of Death etc. and to clinical databases and more specific registries.

Danish teams contribute to some European registries such as EURO CARE CF, EIMD, EMHG and EUROCAT.

### Genetic Testing

Genetic testing is performed in departments of clinical genetics departments across all regions of Denmark. However some genetic tests are performed by Clinical Biochemical Departments.

Diagnostic tests in Denmark are available for more than 500 genes and more than 500 diseases in the Orphanet database. NGS/exome sequencing is now available in Denmark

Genetic testing for medical reasons is part of the national health care system and is free of charge.

Genetic testing abroad is possible and is mediated by the departments of clinical genetics. State reimbursement of costs for tests abroad can be effected after approval from the Danish Health Authority.

### Neonatal Screening

National neonatal screening schemes are in place for phenylketonuria, congenital hypothyroidism, congenital adrenal hyperplasia, maple syrup urine disease, ASL, carnitine transporter defect, medium chain acyl-CoA dehydrogenase deficiency, long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency, very long chain acyl-coA dehydrogenase deficiency, glutaric acidemia type 1, methyl malonic acidemia, propionic acidemia, multiple carboxylase defect, arginino succinic aciduria, tyrosinemia type 1 and biotinidase defect.

Since 2016 newborns are also tested for cystic fibrosis. The timing for drawing the blood samples (done by heel-prick) is within 48-72 hours following birth, allowing for earlier intervention and treatment. Neonatal hearing screening is also part of the national policy.

### **Guidelines and Training Activities**

#### **Clinical Practice Guidelines (CPGs)**

The 2001 report from the National Board of Health laid down guidelines concerning 11 specific rare diseases. These guidelines also serve as a template for other rare diseases. Health care professionals consult published international guidelines.

#### **Training and Education**

Within the National Strategy for Rare Diseases (2014) a list of initiatives was made, but so far no new initiatives have been carried out.

The two Rare Diseases Centres participate in educational activities for nurses and doctors. Furthermore, they provide teaching for other health care professionals, families, teachers and caretakers.

A Masters degree in Medicine from the University of Southern Denmark is currently under review. In addition to the joint training for all medical students, it will be possible for medical students to work and study within the Clinical Genetics Department, where they will focus on genetics, counselling and the diagnosis of patients with rare diseases will be on genetics and counseling and diagnosing patients with rare disease.

Specialist medical education, available within clinical genetics, has recently been revised with a targeted focus on knowledge and systematic training in rare diseases. Specialists in the handling of specific patient cases and participation in courses, obtain skills in examination and diagnosis of rare diseases and mastery of interdisciplinary collaboration with other specialties.

### **Information Resources for Rare Diseases**

#### **Orphanet Activities**

Denmark does not currently have an operational national Orphanet team. John Østergaard is an Orphanet representative, however without funding he cannot take part in the meetings nor can he deliver information to the Orphanet database.

#### **National Helplines**

A helpline is in place dedicated to rare diseases in Denmark, it is privately funded and there is a current application for public funding. Within the framework of a four year project, Rare Diseases Denmark opened a Helpline on October 1<sup>st</sup> 2016. The Helpline is operated by professionals and volunteers, who are capable of supporting people living with rare diseases with information, guidance and counselling via phone and e-mail. The Helpline team is supported by a group of experts. The Helpline is situated in the secretariat of RDD and the opening hours are similar to the opening hours of the secretariat plus three hours, all in all 22 hours per week. The estimated number of enquiries are between 200 – 400 per year. The RDD Helpline has applied for membership of the European Network of Rare Disease Helpline, ENRDHL.

#### **Official Information Centres**

There are no official or unofficial information centres for rare diseases in Denmark.

### **Rare Disease Research Activities**

#### **Existence of rare disease research programmes/projects**

There are currently no specific programmes or projects to fund and facilitate rare disease research in Denmark. At the moment there are no plans to conduct social or social-economic research. There are no specific programs or calls/grants dedicated to rare diseases research in Denmark. Although there are no

specific initiatives to support research into rare diseases in Denmark, Danish researchers are active in the field and there are resources in place (biobanks, registries, databases) for rare disease research.

### **Participation in E-rare and International Research Initiatives**

At present Denmark participates in neither E-rare nor IRDiRC.

### **National Alliance of Patient Organisations and Patient Representation**

There is a national alliance of rare disease patient organisations in Denmark.

Rare Diseases Denmark (RDD) is the National Alliance in Denmark with 52 member organizations, covering app. 200 diagnoses. The member organizations hold app. 12,500 members (individuals and families). Also, RDD hosts the NURD – Network of Ultra Rare Diseases, with 570 individual members (patients and relatives) covering app. 170 diagnosis are not covered by the member organisations.

In 2015, RDD had a number of achievements:

- Hosting an EUROPLAN Conference for presentation of the Danish National Strategy for Rare Diseases
- Implementing the project Rare Navigators granted by the Danish Health Authority. The project aims at educating and employing volunteer Navigators in order to equalize disparities and promote health and health literacy in the most vulnerable PLWRDs in the Danish Healthcare system.
- Publication of the results from the Premium Customer Survey on the needs and satisfaction levels of PLWRD regarding social services, information and more
- Audiences with the Danish Parliament Committees for Health and for Social Affairs in order to advocate the implementation of the national strategy
- The first face-to-face meeting for NURD-members – and secure permanent funding for the NURD from the Danish Ministry of Social Affairs

In 2016, the main achievement of RDD is to prepare and implement a Rare Disease Helpline aimed at PLWRD and their relatives. The Helpline opens October 2016, see section 9. Also, marking of Rare Disease Day was an important achievement, see section 14.

Patient organizations are, in general, consulted regarding legislation concerning issues relevant to rare diseases and handicap, they also participate in the relevant boards and working groups. In 2015, RDD participated in five different boards/working groups hosted by the Danish Ministry of Social Affairs / The National Board of Social Services. Also, RDD put forward a limited number of hearing statements linked to new laws and consolidation acts in the area of social policy and health policy.

### **Integration of Rare Diseases to Social Policies and Services**

The field of rare diseases is diverse. It is therefore not possible to give one answer to this question. It is possible to roughly divide rare diseases into three groups: There is one group of rare diseases, fx. Spielmeyer – Vogt syndrome, PKU, Rett SYNDROME, Huntington diseases and a range of neuromuscular disorders, with have specialized centre/teams with competence dedicated on diagnose.

Then there is one group of rare diseases, which can benefit from other competence areas (e.g. People with albinism can get support from a Communication Centre). Finally there is a group of people with rare diseases who does not have “their own” specialized service, but receives a more general service.

No, there are no specific measures in place to support the integration of rare disease specificities at the national level. There is an ambition though at more local level – in the municipalities – to work more in a direction, where each citizen is being described in a holistic way – and the system used to do so, is the WHO-developed system of ICF (International classification of functionality). This way of working has also been integrated in the digital journals in many municipalities called BUBU (children) and VUM (adults).

It is decided that the National Board of Social Services in collaboration with the National Board of Health Services will produce a National Guideline (forløbsbeskrivelse) on a group of people with rare diseases in 2016/17. The specific target group has not yet been selected.

### **Orphan Medicinal Products**

75 OMPs are marketed in Denmark. Out of 91 orphan medicinal products with an EU market authorisation, 75 are approved in Denmark and are on the Danish national formulary of medicines. The remaining 16 are approved but not on the Danish national formulary of medicines.

No distinction is made in Denmark as to whether the medicinal product is intended for the treatment of rare diseases or not. Special publication lists are not prepared.

Lists of currently available marketed products (including orphans) are updated every two weeks and can be accessed here: [medicinpriser.dk](http://medicinpriser.dk). This page is only available in Danish.

No incentives are provided at present to support research into and the development of (designated or potential) Orphan Medicinal Products and there doesn't appear to be any plans for future incentives.

As for other disease states and where there is a medical need, the compassionate use program can be made available for rare diseases. Compassionate use is not new in Denmark. No other measures are planned.

### **Rare Disease Day**

In 2015, Rare Diseases Denmark organised a pilot Race for Rare Diseases in the Copenhagen area and hosted an exhibition of drawings – the exhibition was witnessed by the Patron of RDD, HRH Crown Princess Mary of Denmark.

In 2016, RDD organized a full sized Race for Rare Diseases in the Copenhagen and in the Aarhus Areas, with approximately 1,200 participants all in all. Also, RDD awarded the Rare Price to two persons who have contributed with extraordinary effort for people living with rare diseases.

### **Other**

Denmark has achieved much since 2014:

The Raredis-database is planned to be rolled out to all Clinical Genetics Departments and the economy seems be in place.

There is an increased focus and action concerning adult patients with rare diseases and also the transition between childhood and adulthood.

### *Conferences*

- Europlan Conference, January 2015
- Nordic Rarelink Conference on rare diseases in Copenhagen, September 2016.

### *Publications*

- New mapping of the area for rare disabilities in Scandinavia (2016) (Ny kortlægning af området for sjældne handicap i Skandinavien). (<http://socialstyrelsen.dk/nyheder/2016/ny-kortlaegning-af-sjaeldne-handicap-i-skandinavien>)
- Support and advice in everyday life. A study of social work for people with rare diseases and their relatives. Gold Customer survey 2014 – 2015 (Støtte og rådgivning i hverdagen. En undersøgelse af den sociale indsats overfor borgere med sjældne diagnoser og deres pårørende. Guldkunde undersøgelse 2014 – 2015). (<http://viden.sjaeldnediagnoser.dk/wp-content/uploads/2014/03/Guldkunde-2015.pdf>)
- People living with rare handicap (2014) (Mennesker med sjældne handicap). (<http://socialstyrelsen.dk/udgivelser/mennesker-med-sjaeldne-handicap>)





Since 2014 the continuous updating of specifications of rare diseases and the process of making new specifications has been turned over from the National Board of Social Services to The Danish Health Authority.

In October 2016 an evaluation process concerning the National Strategy has been initiated and this will lead to an action oriented report.

