RARE DISEASES DEVELOPMENT PLAN

1. Introduction

Source Documents at the Level of the European Union

- The Orphan Medicinal Product Regulation (EC No 141/2000 of the European Parliament and of the Council of December 1999 on orphan medicinal products) – the purpose of the regulation is to lay down the procedure applicable to orphan medicinal products.

  Criterion – medicinal products qualify as rare or orphan medicinal products when intended for diagnosing, prevention or treatment of a chronic or life-threatening diseases with a prevalence of not more than five affected persons per 10 thousand.

- The Commision Communication on Rare Diseases: Europe's challenge – adopted on 11.11.2008, highlighting three main spheres:
  - improving recognition and visibility of rare diseases;
  - supporting policies on rare diseases in the Member States;
  - developing European co-operation, co-ordination and regulation for rare diseases.

- The Council Recommendation on an action in the field of rare diseases (2009/C 151/02);

- European Commission Decision 2009/872/EC on establishing a European Union Committee of Experts on Rare Diseases;

- Directive 2011/24/EU of the European Parliament and of the Council of 9 March 2011 on the application of patients' rights in cross-border healthcare.

Definition

The European Union considers diseases to be rare when they affect not more than 5 per 10 000 persons in the European Union.

Rare diseases are diseases with a particularly low prevalence; however, the number of different rare diseases is high and therefore, the relative number of people, suffering from rare diseases, is relatively high. It is estimated that between 5 000 and 8 000 distinct rare diseases exist today, affecting between 6 % and 8 % of the population in the course of their lives. In other words, although rare diseases are characterised by low prevalence for each of them, the total number of people affected by rare diseases in the EU is between 27 and 36 million; for Estonia, this would mean between 70,000–100,000 affected people.

Most rare diseases are genetic diseases, the others being rare cancers, auto-immune diseases, congenital malformations, toxic and infectious diseases among other categories. Research on rare diseases has proved to be very useful to better understand the mechanism of incurrence of rare diseases. However, research on rare diseases is not only scarce, but also scattered in different laboratories throughout the EU. The lack of specific health policies for rare diseases and the scarcity of the expertise, translate into delayed diagnosis and difficult access to care. This result in additional physical, psychological and intellectual impairments possibly combined with Misdiagnosis and non-diagnosis, despite the fact that some rare diseases are compatible with a normal life if diagnosed on time and properly managed. There-

fore, timely diagnosis and ensuring the availability of proper treatment are the most important for thousands of rare disease patients.

European cooperation can help to ensure that scarce knowledge can be shared and resources combined as efficiently as possible, in order to tackle rare diseases.

In June 2009, the European Commission adopted Council Recommendation (EK 2009/C 151/02), which lays down current and future guidelines for the society, aimed at improving the prevention, diagnostics and availability of treatment for rare diseases within the European Union.

Rare diseases occur very infrequently and therefore, there is less knowledge available about these diseases that current development level of research would, theoretically, allow. As the consequence, patients with rare diseases suffer twice as much: first, they suffer from a rare medical condition, difficult or complex to diagnose and second, the treatment that they receive is often insufficient as the treatment may be absent altogether or is very expensive and therefore, often unavailable.

In Estonia, there is currently lack of information about the distribution of many (both genetic and non-genetic forms) rare diseases. Research has been conducted to study single condition, however, an overview of more general nature is missing.

Many rare diseases also lack a ICD-10 code or in other words, these diseases are not registered under ICD-10 classifier.

2. Definition, Coding and List of Rare Diseases

Definition

The term “rare disease” was first introduced in 1980ies. Usually, rare diseases represent medical conditions that shorten life expectancy and are characterised by low prevalence. These are less well known and studied than other medical conditions and there is often no cure available for such diseases. Another synonym, “orphan disease”, is also used to describe rare diseases.

In general, rare diseases can be divided into three larger categories:

- Genetic diseases that result from a defect or mutation of a single or several genes (monogenic diseases) or extra, missing or re-arranged copies of a chromosome of the same segment (chromosome disorders);
- Multi-factorial disorders result from the combined effect of environmental factors and mutations of different genes (congenital defects, for example, the Fallot’ tetrad or spina bifida, autoimmune diseases and tumours);
- Environmental diseases – this category includes, for example, rare infectious diseases, poisonings and radiation.

Several international organisations and databases have been established to acquire and disseminate information about rare diseases:

- Rare diseases and orphan medicinal products information website (www.orpha.net) was originally established in France and now joins more than 40 countries (incl. Estonia). The database is co-ordinated by INSERM (Institut National de la Santé et de la Recherche

Médicale, French National Institute of Health and Medical Research) in France. The website contains information about more than 5,000 rare diseases, centres of excellence that study rare diseases, tests required to diagnose rare diseases, scientific research carried out in the sphere of rare diseases, patients' organisations and registered orphan drugs. Orphanet is available in English, French, German, Italian, Spanish and Portuguese languages;

- NORD (The National Organization for Rare Disorders, www.raredisorders.org) is a US voluntary organisation that represents patients suffering from rare diseases and their family members.

3. Epidemiology, Registers and Supervision

The World Health Organisation (WHO) has classified approximately 6,000 to 7,000 diseases and conditions as rare diseases (www.orpha.net). In medical literature, approximately five new rare diseases are described every week. Most of the rare diseases are genetic and most genetic diseases are rare diseases. However, not all rare diseases are genetic. For example, rare occurring infectious diseases, autoimmune diseases and poisonings can be classified as rare diseases. People are born with genetic rare diseases; however, the symptoms may only show in late childhood or even as an adult. Several rare diseases manifest themselves during early childhood (for example, spinal muscular atrophy, *osteogenesis imperfecta*, chondrodysplasia or Rett syndrome) and approximately 30% of the children, suffering from rare diseases, will die before reaching their fifth birthday. However, approximately 50% of rare diseases usually only appear in adults, for example, the Huntington's disease, Charcot'-Marie-Tooth disease, amytorophic lateral sclerosis, Kaposi's sarcoma or thyroidal cancer.

Genetic Centre of Joint Laboratory of Tartu University Hospital has a database that includes information of patients, having consulted with medical genetics, since 1990. The database belongs to the Genetic Centre; however, information can be supplied against information requests. It would be highly reasonable to continue to develop the current database but additional funding would be needed for that purpose. The database will contribute to better organisation of supervision over the occurrence of rare diseased and their prevalence/spread.

Activities:

- ensuring the funding required for supplementing and processing the rare diseases database and linking it to various other register, where appropriate;
- establishment of rare diseases centre of expertise (hereinafter the RDCE) with committee of experts on rare diseases, operating at the centre.

4. Scientific Research in the Sphere of Rare Diseases

The population of Estonia is small – according to the information, available from Statistics Estonia, 1,286,479 people lived in Estonia on 1 January 2013. Therefore, for us it's highly important to participate in various international clinic research programmes.

RDCE must keep information about all the studies in the sphere of rare diseases, conducted in Estonia.

Implementation of the e-health system and the new ICD 11 (RHK-11) will contribute to the mapping of the situation in the sphere of rare diseases: how many patients who suffer from (and which) rare diseases do we have in Estonia. The information will be used to create various databases (registers) that are to be administrated and co-ordinated by the RDCE. This will contribute to the planning of health care services in Estonia, allowing to involve majority of Estonian patients in various clinical studies.

The current experiences of the Transgenic Technology Laboratory of University of Tartu in creating the animal model for Wolfram syndrome shows that Estonia can be highly successful in the sphere of development of animal models for rare diseases, hence helping to understand the pathogenesis of such diseases, and establish the foundation required to develop treatment and medicinal products to cure the diseases. Continued and extended international co-operation is highly important in this sphere.

Activities:

- updating and modification of the information, introducing Estonia, at the http://www.orpha.net/national/EE-ET/index/avaleht/ website;
- establishment of a database for basic research and clinical scientific research at the RDCE;
- defending at least on doctoral thesis per every five years in the sphere of rare diseases.

5. Centres of Expertise and European Reference Networks for Rare Diseases

Definition: centres of expertise are expert structures for the management and care of rare disease patients in a defined catchment area, preferably national, and at international level if necessary (EUCERD Recommendations, Quality Criteria for Centres of Expertise for Rare Diseases in Member States).

Centres of expertise bring together, or coordinate, within the specialised healthcare sector multidisciplinary competences/skills, including paramedical skills and social services, in order to serve the specific medical, rehabilitation and palliative needs of rare diseases patients.

Co-ordinated co-operation between different levels of health care sector is considered important for centres of expertise. The development of centre(s) of expertise depends on the concentration of competences. In Estonia, the competence in the sphere of rare diseases (diagnostics, treatment, research work) is mostly concentrated under the University of Tartu, where doctors are also educated, using the resources of the Tartu University Hospital. The research potential is also concentrated under the same institution. Tartu University Hospital also runs the Genetic Centre of Joint Laboratory of Tartu University Hospital that offers studies and advice in the sphere of clinical genetics in its departments in both Tartu and Tallinn.

We must emphasise that centre of expertise fulfils both the role as co-ordinator of the activities and distributor of information.

Functions of the RDCE:

- contribution to improved establishment of diagnosis of rare diseases, using all the available resources;
- development of co-operation between medical establishment and specialties for the

purpose of improved diagnosis and treatment of rare diseases;

- dissemination of information, required by patients for coping with the diseases and treatment, also ensuring the availability of initial information about the available social services;
- provision of diversified information about rare diseases to medical workers and the population in general;
- making proposals to the Ministry of Social Affairs on the improvement of screening programmes for the newly born.

Timely establishment of a diagnosis will provide the pre-requisites for correct treatment of patients, thus improving both their life quality and life expectancy.

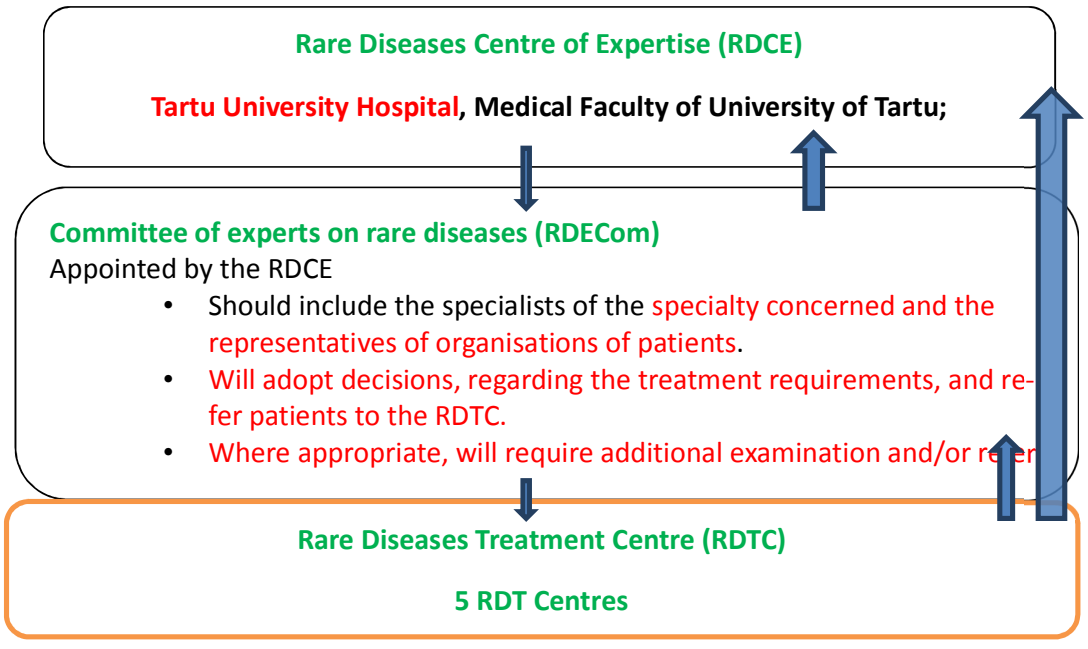
In Estonia, the role of RDCE would be fulfilled by the Tartu University Hospital in co-operation with University of Tartu.

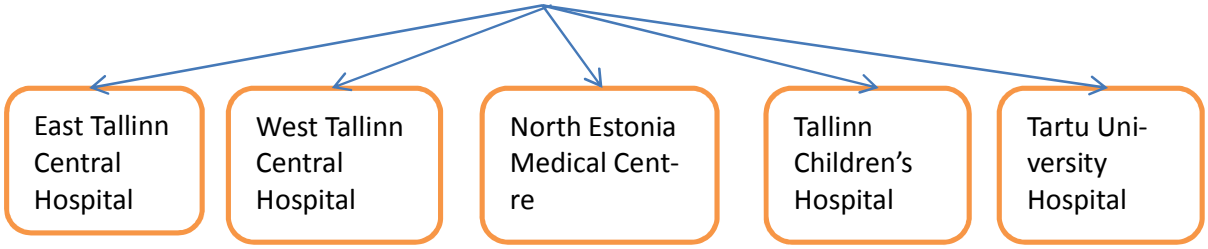
Rare Disease Treatment Centre (hereinafter the RDTC) – as the treatment of rare diseases is a long-term process, often life-long, the treatment should take place as close to the place of living of the patients as possible – in the Tartu University Hospital, Tallinn Children's Hospital, East-Tallinn Central Hospital, West-Tallinn Central Hospital, North Estonia Medical Centre. The patient's family doctor must be also involved in the process of treatment.

Rare Disease Expert Committee is a professional body of co-operation that fulfils the role of diagnosing rare diseases and providing the treatment of more specific fields (for example, eye diseases, children's neurology etc) or specific disease, involving different specialists, where appropriate. Competence committees will be established, with the co-ordination by the RDCE, and will also operate at either the RDCE or the RDTC. The RDCE will report both to the RDCE and the RDTC.

Activities:

- appointment of the RDCEs and the RDTCs by the Minister of Social Affairs;
- establishment of the position of the RDCE and ensuring the availability of public funding;
- participating in the development and organisation of legislation on rare diseases, incl. improving the availability of orphan medicinal products.





6. Strengthening the Patients' Organisations

6.1. Network of Patients' Organisation and Umbrella Organisation

Organisations that join the patients who suffer from rare diseases operate in Estonia at the Estonian Chamber of Disabled People (hereinafter the ECDP). ECDP is an organisation that was established in 1993 and has consistently operated as a third sector organisation, protecting public interests, being the umbrella organisation for organisations of disabled people all over Estonia. The ECDP network includes 16 regional cambers of disabled people and 30 disability-specific associations, including organisations that join people who suffer from rare diseases (e.g. Estonian Association of Phenylketonuria, Estonian Association pf Haemophilia, Estonian Association of Coeliac Disease, Estonian Association of Cystic Fibrosis, the Prader-Will Syndrome Association etc). The ECDP represents 420 organisations of disabled people, having, in total, approximately 22 000 members.

The main functions of the patients' organisations include the improvement of coping, life quality and social cohesion of their respective target groups, increasing awareness both among the target group and in the society in general, fulfilling the functions that can't be fulfilled by any other level or organisation.

Activities:

- concentration of organisation of patients suffering from rare diseases at the ECDP, facilitation of the establishment of new organisations.

6.2. Funding of Patients' Organisations

Considering the size of Estonia the organisational capabilities of organisations of patients who suffer from rare diseases is small, within the scope of one disease or a group of diseases, as the probability of the presence of some families that are more active and with more organisational abilities among the few is relatively small. Patients with rare diseases with higher prevalence (from 1 : 10,000), who are probably more capable of establishing their own organisation, enjoy certain advantages here. In the case of more rare diseases (< 1 : 10 000) it is highly unlikely that the next of kin, gathered around 10-20 patients, will be capable of establishing their own organisation and get it funded from their own resources. Therefore, the capabilities of organisations of patients with rare diseases will depend, apart the availability of human resources, also from direct subsidies from the state. Currently, patients' organisations are funded in accordance with project-based rationale, from the allocations made by the Gambling Tax Council of the Estonian Chamber of Disabled People. Both the size of the applying organisation and the additional funding, raised by the organisation itself, will be taken into considerations according to this funding principle and therefore, the organisations of patients with rare diseases inevitably lose the game. The

current financing model will ensure certain funding on annual bases, however, small organisations will be unable to develop and remain sustainable. The financing model needs to be adjusted to consider the specificities of small organisation.

Activities:

- updating project-based financing model of the Estonian Foundation of Disabled People, currently available to organisations of patients with rare diseases, to accommodate the specificities of smaller organisations;
- development and implementation of principles for supported activities.

6.3. Activities of Patients' Organisations – Custody

Despite the difficulties, organisations of patients play a highly important role in supporting the patients who suffer from rare diseases and their family members and increasing the awareness of such diseases in the society in general. Although each and every diseases is only suffered by a relatively small proportion of the society, the number of all the people, involved in rare diseases, is considerable, starting from the closest family members, up to nurses/caretakers, teachers, medical doctors and many others. Therefore, a viable patients' organisation should involve not just the patients and their next of kin, but also professionals working with specific disease or welfare services in general. For the patients, the participation of professionals in the work of the organisations is highly important, for both ensuring the feeling of security, created by the network, and real assistance in communication with institutions (hospitals, schools, rehabilitation establishments etc.).

Activities:

- increasing the awareness of new patients with rare diseases and their family members through the activities of the existing organisations;
- facilitation of establishment of new, joint organisations of unorganised patients, involving patients with different diagnosis, their next of kin and specialist, especially in the situations where the low occurrence of the disease won't allow to establish a separate organisation;
- promoting the co-operation of existing patients' organisations and contribution to the development of custody abilities in the line of the ECDP (family-centred requirements, development of disability specific and general support schemes, ensuring the availability of services, considering one disabled child to be equivalent to three healthy children, development of new support services etc.);
- establishment of a rare diseases' counselling centre, incl. a helpline (telephone, Internet) and development of novel e-solutions with the purpose of providing counselling services all over Estonia. Such a helpline would also be an additional supporting tool for social welfare specialists. It's important to improve the awareness of specialists who work with the patients;
- facilitation of international co-operation, incl. increasing awareness of new trends and practices (participation in conferences, acquisition of information, translation and adaptation of materials, training courses etc.);
- consolidation of all the information about rare diseases onto a single website, as the result of the co-operation between different organisations (for example, a sub-page of the

ECDP); the website should be easily available and understandable for the patients and their next of kin, providing links to different organisations, operating in the sphere concerned (the Agrenska Foundation, the RDCE, hospitals, the Rapsody network, different patients' organisations etc.);

- facilitation of establishment and running of disease-specific support groups in different places all over Estonia;
- development of information leaflets and educational materials in co-operation with different specialists (doctors, teachers, social welfare specialists).

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