EMRADI PROJECT
Explanation of the Selection Process of the eight Rare Diseases to focus on

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GENERAL DESCRIPTION OF THE DECISION STRATEGY AND PROCESS

The EMRaDi Project was launched in October 2016 for a 3-year duration with the main objective to improve the quality of life of Rare Disease Patients in the Euregio Meuse-Rhine (EMR) and beyond. A big advantage of the project is that a lot of stakeholders from different countries and institutions come together. Among them are representatives of patient organizations, hospitals and mutual health insurance funds.

The project team has formulated the following objectives when writing the application in the field of Rare Diseases:

1) Increase the transparency of needs and availability of services in the field of rare diseases in the EMR
2) Develop EMR models of RD patient pathways in order to elaborate patient-oriented recommendations in synergy with national and European developments
3) Improve the network of health care providers, mutual health insurance funds and patient organizations and raise (public) awareness for rare diseases

Long term general aim is to improve the quality of life of these patients.

As the field of Rare Diseases (RD) is very large and diverse, one of the major aspects when starting the project was to decide which RDs to focus on. This was of course not an easy task as not only the RDs are diverse but also the partners. They have different expertise, backgrounds, approaches and cultures. Through different meetings with all representatives of partners from the start of the project (October 2016) until June 2017, the selection criteria and the list of potential RD to focus on were discussed, argued and compared. The consortium of partners succeeded in reaching a consensual decision on the RD selection in June 2017, based principally on the cooperation possibilities and preferences expressed by the different partners. Choosing specific RD was difficult but was necessary as it will enable to have as concrete results as possible for these diseases.

The partners also expect that the choice has a positive impact on other rare diseases (for example thanks to a better information and training of the health insurance funds and of the health experts) and hope that the EMRaDi project is a first step to a larger and long-term cooperation in the RD field in the EMR, to help as much RD patients as possible.

It should also be stressed explicitly here, that although in this start phase only the three EMR University Hospitals were involved from the Health Care Provider side, an enlargement to

other hospitals and resident doctors in the EMR is foreseen already within the project's runtime and an important condition to reach the project's objectives.

It should be mentioned that all three participating countries have "National plans of action for people with rare diseases" and have realized or plan to realize a certification process for centers for Rare Diseases. Whereas Belgium and Germany are still in the preparatory phase, only the Netherlands already have formally designated centers of expertise, appointed by the Minister of Health.

When writing the application, it became clear that a project of this scope and funding should focus on a small set of diseases. An important part of the improvement possibilities for RD patients in the EMR is based on medical expertise. Therefore, it became clear that this expertise should be present at least at one of the partner's institutions.

It was a discussion already at the time of writing the application on which groups to focus (this is of course a little bit artificial as RDs often do not belong to one RD group only, what can be seen when looking at the Orphanet classification (www.orpha.net)). Rare neurological, rare hematological and rare syndromal diseases were defined quite quickly – with rare metabolic diseases as a further candidate group – by the participating University Hospitals in consensus with the other partners. In order to get a good representation of the diversity of rare diseases and a good overview of this field, it was decided to select two diseases per group, resulting in eight diseases altogether.

This EMRaDi project has a huge scope: the aim is to develop models, to organize a close contact with patient organizations, to write or revise patient guidelines[1] tailored to the EMR situation, to organize information sessions for professionals, to improve networking, etc. Therefore the project partners had to restrict themselves to a small number of RDs.

After this process was finished and once the project started, a further strategy was elaborated. It was – to make a long story short – a) to define criteria which should be used for the decision and b) to collect data for the candidate RDs (around 70 diseases in a long list) in order to c) come to a consensual and final solution in the steering committee of the project, where the leaders of the EMRaDi work packages, other representatives of the different institutions and further members of the project convene regularly. The project's task force of medical experts from the participating University Hospitals was included in data collection.

Selection criteria encompassed:

- At least one of the participating hospitals should have expertise as a lot of results will depend on answers for medical questions.

[1] Please note that the word "guideline" is not directly connected with the dutch word "richtlijn". The term "guideline" in this text is a summary term for all types of information papers either for patients and relatives or health professionals.

- There should be a sufficient number of patients to be expected in the EMR – best from childhood and adulthood – for the field study and to help the most patients possible.
- There should be a balance between the type of symptoms (mental/physical impairments) and a wide range of difficulties/ challenges for the patients resulting in a need for coordination between different types of health care/professionals.
- The point of existing patient organizations was taken into consideration as they are an important partner for the patients and health professionals.
- According to the projects objectives, the potential of improvement of RD patient's situation in the EMR and cross border aspects of health treatment were also important to consider.
- One well-known model RD, where a lot has already been done - where lessons can be drawn for other RD on a higher level – should also been selected.

Information collected were basic data (name, code, prevalence, …), info on the health complaints and medical treatment, possible potential for improvement in the EMR, expertise within the EMR and/or Project Group, representation in one of the European Reference Networks and last but surely not least existence of patient organizations within and outside the EMR.

We should emphasize the point that not each criterion had to be fulfilled by each candidate to 100%. As usual, compromises had to be found. The discussion process which took several months resulted in the diseases listed in table 1.

OVERVIEW OF THE EIGHT RARE DISEASES

Rare Disease Groups	Specific rare diseases
Neurological diseases	**Huntington disease**
	Duchenne muscular dystrophy
Hematological diseases	**Chronic myeloid leukaemia (CML)**
	Polycythemia vera (PV)
Syndromal diseases	**Silver-Russell syndrome**
	Rett syndrome
Metabolic diseases	**Galactosemia type 1**
	Phenylketonuria (PKU)

Tab. 1: Overview of selected rare diseases in the EMRaDi-Project

WHAT HAS TO BE EXPECTED ?

The situation of patients with one of these eight diseases will be analyzed in more detail in the EMRaDi-Project – e.g. interviews will be organized – and on this basis, information papers will be revised or established, model pathways be developed, information sessions be organized and the networking between the different stakeholders increased.

Furthermore, the patient pathways within the three health systems can be compared to each other not only from the medical point of view, but also from the care, advice, financing and other sides. This project is a chance to describe the ideal (cross-border) health care process and its organization.

The core concept of a rare disease patient pathway encompasses all the steps from the first symptoms experienced by the patient, along his or her path through the health system towards (hopefully) a fast, successful diagnosis and including every aspect of the care – whether organizational, medical, social, psychological, legal and/or vocational – to finally ensure the patient the best possible quality of life.

A tight interlinkage with other projects and institutions for Rare Diseases is also foreseen, e.g. an exchange with the European Reference Networks.

This project is to be expected to improve the quality of life and quality of care of RD patients within the EMR and beyond.

ARGUMENTS FOR EACH OF THE EIGHT RARE DISEASES

HUNTINGTON DISEASE (HD) – NEUROLOGICAL RD

HD is a well-known hereditary rare disease and a neurodegenerative disorder leading to psychiatric, cognitive and motor complaints. The average onset of the disease is between 30-50 years and the patients suffer from an increasing loss of independency and quality of life, during 15 to 20 years of illness course. This disease finally leads to death, primarily by pneumonia, secondly by suicide.

Therefore, interdisciplinary efforts are needed as this disease is not only complicated from the point of medicine ,but also from psycho-social, vocational, care and many other aspects.

All three participating University Hospitals have expertise in this disease – UKA Euregional Huntington's diseases center Aachen (EHZA) – MUMC+ an (official) designated Dutch centre of expertise – in Liège, a HD center of expertise is at ISoSL "le Pèri" (Intercommunale de Soins Spécialisés de Liège, Hôpital Pèrî) which is tightly interconnected with CHU. There is furthermore a big patient organization community opening the door for excellent EMR networking. Moreover, as in the different countries a lot has been done already, the project work can start at a higher level than for other rare diseases (well-known model RD).

DUCHENNE MUSCULAR DYSTROPHY (DMD) – NEUROLOGICAL RD

DMD is a neuromuscular hereditary disease and therefore representing another group of rare neurological diseases. The onset of the disease which primarily affects males usually starts in childhood. Usually the ability to move normally decreases rapidly leading to death in youth and young adulthood.

So far, no medical cure is available and the care is multidisciplinary and very complex – encompassing amongst others physiotherapy, cardiology, surgery as well as treatment with corticosteroids and other drugs. Comparable to HD, coordination of different types of health care professionals and others is important.

In all three countries, patients associations exist, the University Hospitals of Aachen and Maastricht showed interest with MUMC+ having a Neuromuscular Centre as (official) designated centre of expertise.

CHRONIC MYELOID LEUKAEMIA (CML) – HEMATOLOGICAL RD

CML is a rare hematological disease belonging to the leukaemias and is the most common myeloproliferative disorder. Patients – usually adults – may be either not affected from health complaints or suffering amongst others from fatigue, weight loss and sweats – symptoms of the disease are mostly physical. So far, predisposition and the mechanism for onset of the disease are mostly unknown, but a permanent active tyrosine kinase is the cause for the disease. Allogeneic bone marrow transplantation is the curative treatment option, but the drug imatinib mesylate – an inhibitor of the respective tyrosine kinase – improves the prognosis substantially. Nevertheless, long-term treatment and care can be very challenging.

All three participating hospitals have CML experts and also patient organizations exist. Just like HD, CML is well-known with a higher potential to raise awareness of different target groups.

POLYCYTHEMIA VERA (PV) – HEMATOLOGICAL RD

With 1-5 / 10.000 the prevalence is quite high. In PV, the red blood cell production is impaired leading to high blood hyperviscosity. Numerous complaints can be the consequences which are mostly of physical nature. There is an individual assessment necessary for treatment but generally the aim is to decrease blood viscosity. The life expectancy is close to the usual value, the disease can occur at all ages.

Within the EMRaDi Project partners University Hospitals Aachen, Liège and Maastricht, there is a broad expertise for this disease, which is an acquired myeloproliferative disorder. Also, patient organizations exist.

SILVER-RUSSELL SYNDROME (SRS) – SYNDROMAL RD

SRS is a rare congenital syndromal disorder mainly characterized by intrauterine and postnatal growth retardation, relative macrocephaly, a prominent forehead, asymmetry and feeding difficulties. SRS is primarily a clinical diagnosis, but in ~60% of patients it can be confirmed molecularly. Treatment is supportive in form of growth hormone therapy, the prognosis in case of proper treatment is good. SRS belongs to the group of imprinting disorders, and can therefore be regarded as a model for these heterogeneous disorders. Furthermore, it is a differential diagnosis for many growth retardation diseases.

Many SRS patients are diagnosed and/or treated at the University Hospitals Aachen and Liège as special expertise is located there. Furthermore, there is a close collaboration with national and international patient organizations, resulting in international consensus guidelines.

RETT SYNDROME (RTT) – SYNDROMAL RD

Rett syndrome primarily affects females - but more and more boys with a Rett-like phenotype and genotype are identified. The classic onset of Rett syndrome, a severe neurodevelopmental disorder, is between the ages of 12 and 18 months, but this can be highly variable. Patients suffer from lifelong complex medical problems with intellectual disability and much comorbidity. Treatment is therefore complex, only symptomatic and implies a lot of coordination between health, social care and others (involving physiotherapists, dieticians, occupational therapists, speech therapists and music therapists). Diagnosis can be made either on the phenotype (if classical) or by next-generation sequencing in case of less typical phenotypic features and/or at young age . Usually, the life span is (somewhat) limited and prognosis depends on the severity of comorbidity.

Maastricht is the Dutch expertise center for Rett syndrome as part of the Expertise Center for Rare Syndromes and Cognitive Disorders. This is an example for a disease which is covered only by one of the participating hospitals. Patient organizations exist in the three countries.

GALACTOSEMIA TYPE 1 – METABOLIC RD

The onset of the disease is early in life. It presents in the newborn period as a life threatening disease, whose clinical picture can be resolved by a galactose-restricted diet. The dietary treatment proves, however, insufficient in preventing severe long-term complications, such as cognitive, social and reproductive impairments. The treatment and follow-up of this hereditable disease is complex and multidisciplinary and requires a team of experts with adequate knowledge of the disease.

The University Hospital of Maastricht has an (official) designated centre of expertise, and the University Hospital of Liège has competence in this disease which belongs to the group of rare metabolic diseases and in particular to the disorders of sugar metabolism. Patient organizations exist.

PHENYLKETONURIA (PKU) – METABOLIC RD

It is a disease which can be detected via newborn screening with – provided the right medical and dietary treatment is applied – a positive course of the disease. It is a model for this type of diseases, which belong to the field of rare metabolic diseases with hereditary origin. In PKU, the metabolism of an amino acid, an important element of proteins, is severely impaired leading to a heavy mental retardation and physical complaints of un-treated patients. Patient organizations covering also this rare disease exist in the three countries.

The main driver to include PKU in the short eight RD list is the University Hospital of Liège because there, a lot of expertise is located. The University Hospital of Maastricht hospital has also extensive experience in this disease.

CONCLUDING REMARK

Sources of disease relevant information: www.orpha.net and health experts from the EMRaDi-Project, especially (in alphabetical order):

Maastricht UMC+:

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