REPORT OF WORK PACKAGE 4

NETWORKING

Lead partner of Work Package	**UK Aachen**
WP n° and title	WP4 Networking, training and exchanges of expertise of health professionals
Contents of the report	- General info on RD situation - Organizational project framework - Improving knowledge and increasing cooperation between the EMR Centres of Expertise - Increasing awareness and knowledge - Translational aspects - Kabuki syndrome as a model project - Input to other work packages - Presentation
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lead partner

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The Interreg V-A Euregio Meuse-Rhine (EMR) programme invested almost EUR 100 million in the development of the Interreg-region until 2020. This area stretches out from Leuven in the west to the borders of Cologne in the east, and runs from Eindhoven in the north all the way down to the border of Luxemburg. Over 5.5 million people live in this cross-border region, where the best of three countries merges into a truly European culture.

With the investment of EU funds in Interreg projects, the European Union directly invests in the economic development, innovation, territorial development and social inclusion and education of this region.

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2 PROJECT DESCRIPTION

"EMRaDi" stands for **Euregio Meuse-Rhine Rare Diseases**.
The project started on 1st October 2016 and ended on 31st March 2020

This project involved a **cross-border cooperation** between health insurers, university hospitals, patient associations and a university in the Euregio Meuse-Rhine. It was part of the European Union INTERREG V-A Euregio Meuse-Rhine programme.

Thanks to their long experience in cross-border healthcare, the project partners have decided to join forces in the specific field of rare diseases. This EMRaDi project was innovative in the sense that it was a patient-oriented and cross-sectoral project. The consortium of partners included the major health players who support rare disease patients and their relatives in their day-to-day rare disease patient pathway.

Through **the project activities**, the EMRaDi project aimed to:

- increase the transparency of needs and availability of services in the field of rare diseases in the Euregio Meuse-Rhine (EMR);
- develop EMR models for *rare disease patient pathways* in order to draw up patient-oriented recommendations in synergy with national and European developments;
- improve the network of healthcare providers, health insurance providers and patient organisations and raise (public) awareness of rare diseases.

The general long-term aim was to **improve the quality of life of these patients**.

www.emradi.eu

3 DISCLAIMER

This report was produced within the framework of the EMRaDi project. The facts and views expressed in this publication are the sole responsibility of the authors and do not necessarily reflect the position of the EMRaDi partner organizations. All the personal data gathered during the EMRaDi project were processed in accordance with the European Regulation 2016/679 (EU) on the Protection of Personal Data (GDPR).

4 EXECUTIVE SUMMARY

Through the INTERREG and co-funding of the regional authorities, a lot of progress could be made in the field of Rare Diseases in the EUREGIO Meuse-Rhine. In several work packages, work has been carried out in the EMRaDi project.

This Report focuses on WP4 – the networking between the university hospitals and beyond. The development of RD structures in all three countries that was triggered through the respective National Rare Disease plans was accelerated. The exchange and cooperation between the university hospitals themselves and with other project partners increased – also with scope for after the end of the funding. In the field of increasing awareness and knowledge, the ties to the other health care providers, health insurance funds and patient organizations – all three crucial partners in the field of RDs were intensified. Kabuki syndrome - a rare genetic condition with intellectual disability – was set up as a model project.

The partners of WP4 regret the end of the funding but are very convinced that a perfect basis has been created which will lead to continued activities and successful applications for more third-party funding.

5 INTRODUCTION

WP4 is entitled “Networking, training and exchanges of expertise of health professionals”, and the work done in this Work Package focused not only on its networking objective (c), but also on the other two objectives of increasing transparency (a) and modelling (b) (see Chapter 2). Major contributions were made by the university hospital (UH) partners, but input from other partners should not be neglected – first and foremost from the project leader in the field of management and communication, and secondly from University Maastricht, the health insurance funds and the patient organizations.

In October 2016 at the time the project started, the basic Rare Disease structures already existed at the three UHs, but without any doubt the INTERREG project led to a boost in the development also in this field of international cooperation. This constitutes an interesting parallel development as 2016 was the year of the first call for applications for European Reference Networks (ERN). The regional Cross-Border Health Care (CBHC) cooperation increased at the same pace as the European-wide one with fruitful mutual exchange. It is no surprise that the call for applications of new partners for existing ERNs that were launched in 2019 led to an increased interest of the EMRaDi Project UH partners.

The starting point for the cooperation between the three UHs was diverse – apart from individual contacts between different scientists and clinicians in the field of Rare Diseases, no special or extensive exchanges existed in this area. From the point of view of the whole institution and widespread diseases, UKA and MUMC+ have held a Cooperation Agreement since 2004 with common professorships, research projects, intense exchanges and joint patient care. The lab experts from the Human Genetics Departments of CHU and MUMC+ had a valuable collaboration for metabolic sample analyses. However, generally speaking, the cooperation “Aachen – Liège”, “Maastricht – Liège” and “Aachen-Liège-Maastricht” was not generally so well developed. Nevertheless, the knowledge sharing, existing cooperation and multiple innovations at the start of the project left us wanting more. Therefore, the three UHs decided to join forces and work together to improve their healthcare services and the high quality of the patient journey by focusing on Patients with a Rare Disease (RD) in the Euregion (300,000 patients).

With the other full partners of the project, institutional cooperation existed in part only: MUMC+ and the Dutch Umbrella Patient Organization for Rare and Genetic Diseases, VSOP, have a long-lasting cooperation in Rare Diseases – indeed, VSOP is an important institution for the nationwide accreditation of Dutch healthcare providers. The Maastricht University and RWTH University Hospital Aachen (UKA) have had several projects in the field of health economics.

Through the project, the cooperation between all the partners intensified; examples will follow in the subsequent chapters.

6 GENERAL INFORMATION ON THE RD SITUATION IN THE THREE PARTNER COUNTRIES

In Belgium, the Rare Diseases Plan saw the light of day in 2013, based on the recommendations and proposal for the Belgian Plan for Rare Diseases, written in 2010 by groups of medical, scientific, political and patient representatives. It provides rare disease functions, CoEs (by group of RD) and networks involving functions and other healthcare providers. Functions are conditions that the hospital must fulfil and which are defined by a Royal Decree. It is a "set of activities that support the treatment and care of patients and are accessible to all disciplines of the hospital". The aims of the Belgian Plan for Rare Diseases are to reduce the delay of diagnosis and decrease the number of misdiagnosis, increase the quality of care and the quality of life for patients and relatives, stimulate the development of and access to new treatments, and increase the knowledge and the awareness surrounding rare diseases. Seven RD functions linked to university hospitals were created. It was decided to give priority to the start of networks containing the four conditions identified by the Minister as priority: LUNG for idiopathic pulmonary fibrosis, RITA for primary immunodeficiency, SKIN for epidermolysis bullosa and RND for multisystem atrophy. The networks are defined and structured according to the European Reference Networks (ERN). The country's seven rare diseases functions provide the names of experts involved in these networks.

In the Netherlands, the National Rare Diseases Plan (NPZZ) was also introduced in 2013 in response to the regulation of the European Commission to place patients with a rare disease in the so-called Centres of Expertise (CoEs). Detailed information about the criteria to become an official registered CoE in the Netherlands can be found on the Netherlands Federation of University Medical Centres (Nederlandse Federatie van Universitair Medische Centra (NFU)) website. In summary, these CoEs have been officially recognized after assessment by an independent committee and the associated patient association by the Minister of Health, Welfare and Sport. The CoEs are then expected to cooperate with similar CoEs on an (inter)national level. In the Netherlands, there are a total of 350 official registered CoEs. At Maastricht University Medical Center (MUMC+), there are 24 official registered CoEs. In 2016, eight of them participated in the ERN and by the end of 2019, nine of the 24 Dutch CoEs were participating in the ERN.

In Germany, the National Action League for People with Rare Diseases (NAMSE) was founded in 2010. This league brings together all key bodies and organizations of the German healthcare system, which enables collaborative action (28 partners, see https://www.namse.de/english). In 2013, the (German) National Plan of Action for People with Rare Diseases was published, which recommends 52 measures to improve the situation of patients with a Rare Disease (see www.namse.de/fileadmin/user_upload/downloads/National_Plan_of_Action.pdf). There is one point to be suggested here: the three-tiered centre model that was the basis for the foundation of the Aachen Centre for Rare Diseases in 2014. Although RDs are focused on more and more – e.g. there is an increasing number of national and international calls for applications – an assessment of the German RD CoEs has not yet been carried out. The INTERREG participation also widened the scope of the Aachen experts for international participation. The second call for applications to participate in ERNs lead to eight applications in 2019 after having only two in 2016 (when EMRaDi started) for the first call.

7 ORGANIZATIONAL PROJECT FRAMEWORK: FORTNIGHTLY VIDEOCONFERENCES, TASK FORCE AND MORE

Videoconferences were regularly organized for the core team from the three institutions – depending on workload and season, between every two to four weeks normally. These calls – where representatives of all three university hospitals and sometimes other members such as central project coordinators took part – constituted the backbone of the WP4 cooperation. As such, a direct and fast exchange was possible. Members included the central RD coordinators and speakers of the three UHs. It was an excellent way to receive an overview of the project's progress and to communicate the work to be planned. At the beginning, Meetgreen was used as a conference tool; Skype for Business (now Microsoft Teams) was used later on, which opened more possibilities exchange (https://meetgreen.de/ and https://www.skype.com/en/business/).

A Task Force of RD experts from the different university hospitals (UH) was founded, which convened several times throughout the project at all three locations (between 5-10 experts from each UH). They represented the eight RDs that were the focus of the project and the bridge to OncoCare – another INTERREG Project with the participation of all three UHs. In the Task Force, not only the basic strategic lines, but also concrete questions were presented and discussed. The expert opinion of the members was integrated into the planning, detailing their daily problems, and guiding the project. Hence, adjustments were made. It was also a very good occasion to meet each other and to increase the collaboration between the medical experts of the EMR UHs.

Members of the core team also participated regularly in the Steering meetings and the project's other meetings, showing their immense interest in the overall project.

8 IMPROVING KNOWLEDGE IN EMR CENTRES OF EXPERTISE AND INCREASING COOPERATION BETWEEN THE EMR PARTNERS

8.1 RARE DISEASE EXPERTISE AT THE THREE UNIVERSITY HOSPITALS

At the time the project started in 2016, all three university hospitals well aware of the topic of RDs and had already increased their activities in this respect. Nevertheless, a lot of expertise in different RD fields has a long-lasting tradition at all three UHs which already had a Human Genetics Departments long before 2016. The following table gives an overview of the focal RD fields of the three UHs:

UKA	MUMC+	CHU
Neurology[1]	Neurology	Neurology
Haematology	Haematology	Haematology
Liver and gastrointestinal diseases		
Skeleton	Skeleton	Skeleton
Nephrology		Nephrology
Inflammatory diseases (children)	Inflammatory diseases (adults)	Inflammatory diseases (children and adults)
Retinopathies		Rare eye diseases
Syndromic diseases and infantile breathing	Syndromic diseases	Syndromic diseases
Rare allergies and skin diseases		
Cardiomyopathies and keratinopathies (research only)	Cardiomyopathies and keratinopathies	
Cancer	Cancer	Cancer
	Genodermatoses	Genodermatoses
Metabolic disease is partly covered in the other topics.	Metabolic diseases, especially galactosaemic	Metabolic diseases
		Endocrine diseases (adults and children)[2]

Table 1:Overview of Rare Disease Groups with special expertise at the three UHs (overlap at all UHs in dark green and at two UHs in light green, as of March 2020).

[1] As 8,000 rare diseases exist, the listed groups indicate focal fields. This does not mean that, for example, all rare neurological diseases are treated at the respective hospital.

[2] This field is partly covered by the other University hospitals too.

The tables reveal that there are RD fields treated at all three UHs, but that there are also RDs that are found at only one UH. This was also taken into account when choosing the eight RDs the project would focus on. This decision process was organized by consensus and took quite a while. The starting point was a long RD list which encompassed around 70 RDs and included a lot of information: Basic data (name, code, prevalence, etc.); information regarding the health complaints and medical treatment; possible potential for improvement in the EMR; expertise within the EMR and/or Project Group, and last but surely not least, the existence of patient organizations within and outside the EMR. This was then the basis to focus on eight diseases (see the respective description document which can be found at www.emradi.eu).

Neurological diseases	UKA	MUMC+	CHU
Huntington disease	x	x	x
Duchenne muscular dystrophy		x	
Haematological diseases			
Chronic myeloid leukaemia (CML)	x	x	x
Polycythaemia vera (PV)	x	x	x
Syndromic diseases			
Silver-Russell syndrome	x		x
Rett syndrome		x	
Metabolic diseases			
Galactosemia type 1		x	x
Phenylketonuria (PKU)		x	

Table 2:Overview of selected rare diseases in the EMRaDi-Project and Expertise at the different centres

Table 2 shows that there is a balanced mixture of RDs covered by one, two or three partner UHs. In the project's final phase, the developments at the MUMC+ Expert Center for Kabuki syndrome were also taken into account as a model project. The CoE finished a clinical trial on a new therapy – growth hormone treatment for children – by the end of 2018.

Within the university hospitals, the experts expect a continuously growing interest in patient and/or cross-border knowledge mobility in order to spread the latest know-how in diagnostics and treatment, ultimately contributing to an improved patient journey (more details in Chapter 11).

8.2 RARE DISEASE STRUCTURES AT THE THREE UNIVERSITY HOSPITALS

Within the project, not only cooperation between the experts from the different hospitals was renewed or newly established, but a tight interlinkage between the RD central structures was also built up. There was an intensive exchange on how to deal with patients without diagnosis, who often contact the central RD structures. Patients, who have a diagnosis already know with which institution they should get into contact and, for the most part, go there directly. An exceptional result of the process is that the CHU Liège created a Rare Diseases Centre on the basis of ZSEA.

ZSEA consists of a central office and ten Patient Care and Research Centres covering different RD fields. The central structure is tightly embedded into the RWTH Aachen University Hospital (UKA), where the expertise of the RDs is located. The ZSEA is structured as follows: a speaker, an Executive Board (which consists of members of the UKA directorate, the ZSEA speaker and representatives of the Patient Care and Research Centres) and an Advisory Board with external experts – also representatives from patient organizations. Patients with an unknown diagnosis and are suspected of having a Rare Disease normally contact the physicians working at the central office, whereas patients with an RD diagnosis normally contact the specialists in the Hospital directly. The first group need a supporting physician to be accepted. Based on a questionnaire, information from the supporting doctor, and more material such as doctors' letters, images, lab values, etc., an epicrisis is formulated and new strategies to come to a diagnosis are elaborated. These are then followed by the ZSEA patient guides, who are medical doctors in cooperation with experts in and outside the UKA. If this process is not successful and a RD is still suspected, an interdisciplinary case conference is another way to come to a diagnosis.

At MUMC+, the "Polikliniek Klinische Genetica" has a central contact point for general practitioners and medical specialists for patients with an unknown diagnosis and are suspected of having a RD. Also, in the Netherlands, patients with an unknown disease first visit their GP. If there is a strong indication of an unknown RD, the GP makes a referral to the Department of Clinical Genetics, or directly to one of the RD CoEs if there is a strong indication of a specific disease cluster (e.g. CoE for Cardiogenetics). If needed, a peer consultation is offered to find the dedicated RD expert, enabling a seamless referral to the right expert. From April 2020 onwards, these types of peer consultations (telemedicine) will be reimbursed in the Netherlands (adapted policy from "Nationale Zorgautoriteit"). The "Polikliniek Klinische Genetica" has a team of (resident) clinical geneticists, physician assistants, and specialized genetic counsellors (40 persons altogether). They are all trained to guide the patient with an unknown diagnosis to the correct diagnostic lab request. Lab experts and clinical geneticists work side-by-side to come to a diagnosis. In the event of a rare disease in which the whole team has limited expertise, they then have access to the knowledge of the CoEs in one of the other seven Dutch University Hospitals. Should this approach fail to solve the unknown case, the case will be presented via the Clinical Patient Management System (CPMS) to an ERN, also involving the CHU and UKA.

CHU Liège is designated as having a rare disease "function" in Belgium (see Chapter 6). Following this strategy, a RD contact point with a coordinator was created in February 2018. The coordinator listed the RD expertise of all CHU departments with the name of a specific physician. This contact point was implemented to inform patients and professionals (GPs and specialists) about specific CHU experts, give information about RDs or RD treatments, and to reassure patients and families. Processes were

established for patients with or without a diagnosis. When patients and professionals are looking for an expert, the RD coordinator can give a precise answer for a specific disease. In the event of an undiagnosed disease, the RD coordinator asks different experts. The coordinator also implemented a tab in the medical file to give all the information about the rare disease for all practitioners of the hospital.

The RD centre at CHU had to cope with 75 requests since its foundation in February 2018. This is comparable to the requests the ZSEA received when founding the centre in 2014. In Aachen, an increase of requests could also be measured due to the INTERREG activities. The Aachen RD central office receives around 300 requests per year. Liège and Aachen count the requests directly by going to the central coordinator (CHU) or the central office (UKA), and do not include those going to the Human Genetics Department or other CHU or UKA institutes or clinics directly. At MUMC+, this cannot be separated as the coordinator/central office forms part of the Human Genetics Department. On a yearly basis, the Department of Clinical Genetics at MUMC+ has a yearly turnover of 450 requests to solve unknown cases.

8.3 INCREASED COOPERATION BETWEEN THE EMR PROJECT PARTNERS

As stated before, cooperation between the three university hospitals was increased not only at a RD expert level, but also between the colleagues in the RD centres themselves. Additionally, there was also a very good collaboration with the partners of the other Work Packages, resulting in a lot of recommendations from the others also being taken into account by the UHs (an overview of the main work done by the UHs for the other partners can be found in Chapter 12).

Apart from those project-specific partner exchanges, further collaboration was and is taken into account. First and foremost, a discussion to set up an EMRaDi 2.0 Project took place between all the partners and will continue after the project ends. Within WP4, two other calls outside INTERREG were already discussed for a joint application with more to follow. Also, UKA plans to cooperate with VSOP in the field of eLearning, as VSOP, together with other partners, set up an eLearning platform with a special focus on RDs (https://www.huisartsengenetica.nl/nascholing-erfocentrum) (see also Chapter 9.2). One module “Van allerdaagse klacht naar zeldzame aandoeningen” will be translated into German shortly and will give German-speaking physicians the possibility to get credit points. This development fits perfectly together with the funding from Minister Laumann from the North Rhine-Westphalian Ministry of Work, Health and Social Affairs for an NRW Training Academy for Rare Diseases for the Network of the seven NRW Centres for Rare Diseases, led by ZSEA (see www.nrw-zse.de).

Between the UHs, an easier way to exchange medical files was explored. Medical information is subject to special data protection rules and is particularly protected. At the moment, medical files are often exchanged via post or fax, which is time consuming and cumbersome. In the field of Rare Diseases in particular, with its need to work interdisciplinarily, a lot of projects to ease this situation are ongoing. For patients without a diagnosis, the key to find it often lies in the combination of different experts discussing the case in a conference. Within the OncoCare INTERREG Project, with which EMRaDi has close ties, the UHs in Liège, Aachen, and Maastricht aim to set up pathological and clinical teleconferences (teleconsulting) to facilitate knowledge-exchange between the hospitals. For this

purpose, they need to exchange patient data and hence intend to buy a software for electronic patient records. They will also set up a data security plan to ensure it meets the requirements of European and national data protection regulations and laws. The conferences are intended for oncological diseases, including a lot of RDs. Extensions to other RDs after implementation is also expected. Another possibility is already in use – the Clinical Patient Management System (CPMS) set up for the European Reference Networks, a secure web-based application. This tool can be used to share patient data not only within and across ERNs, but also with guests. A lot of experts in the three EMR UHs are already registered with a regular account, and more will follow in the next few months (the review of the current call to participate in existing ERNs as a new partner is ongoing, with results being expected at the end of 2020). For non-members, as previously stated, a guest status can be enabled (see https://cpms.ern-net.eu/login/).

Between the WP4 participants, a lot of exchanges took place, both via phone and in person, to improve the working methods in each rare disease centre, for example the CHU coordinator visited ZSEA in order to exchange information on the structures and processes in Aachen, and MUMC+ and ZSEA visited CHU to introduce a new coordinator from CHU into the project. Especially interesting was also the exchange on how to cope with patients without a diagnosis who represent a special demand to be dealt with by the RD structures. EMRaDi Members also participated in meetings to explain guidelines for patients without a diagnosis.

The patient guides at the three UHs support the patients without diagnosis and suspicion for a RD in finding a diagnosis. This is done in close cooperation with UH internal and external experts; if this strategy does not succeed, the RD centres offer the possibility to discuss complex cases in an interdisciplinary case conference. These conferences, where a lot of physicians of different expertise convene, often lead to new approaches. The conferences organized via the ZSEA were opened to partners from CHU and MUMC+, and this was generally perceived as a very valuable extension of the range of competences.

All three UHs organized a lot of events for RDs and for this Project; partners were informed about these events, regularly leading to an increased participation of experts from the other two UHs at those events.

9 INCREASING AWARENESS AND KNOWLEDGE

9.1 RD TRAINING OF MEDICAL STUDENTS

Another line which was further explored in the project was the medical study programmes, as all three university hospitals offer them. Here, it became clear very quickly that the objective cannot be to teach all 8,000 very diverse RDs to the students as this would not fit into the programs – a “Dr House” (very popular TV character) cannot exist in reality. In Aachen, an analysis of the study program revealed that a lot of RD information is already included, as the experts active in that field are also lecturers. This content is often woven into standard lectures and courses and this was perceived as to be very good. The definition – max. 1 out of 2000 – is a little bit artificial and it is better to teach the RDs within their

context, together with the more frequent diseases. Nevertheless, the WP4 members encourage the persons responsible for the study programmes to integrate the general tools more – such as Orphanet – and the problem-solving capacities in RD, which are very useful in daily life (see also www.orpha.net). In Aachen for example, new problem-oriented learning cases specifically dealing with RDs were therefore introduced into the programme.

9.2 IMPROVING THE KNOWLEGDE AND TRAINING OF GENERAL PRACTITIONERS AND RESIDENT SPECIALIST DOCTORS

Due to the fact that GPs and resident specialist doctors are the first and foremost medical contact partners for patients without diagnosis but suspected of having a RD – also an outcome of this project – special attention was dedicated to this group. As these groups have a high workload, ways had to be explored to be as close to the daily life in a medical practice as possible.

As physicians are used to attending training sessions, one way was to offer information sessions – at special meetings or Rare Disease Days – for these groups. Within WP4, a special concept for those training sessions was elaborated with the main purpose of presenting patient cases. This then formed the framework to introduce the CoEs, and to explain Orphanet and other relevant general contents to the attending physicians.

CHU Liège organized a special event, where not only global information about RDs, but also concrete clinical cases were presented. This session, which took place on 22/10/2019, was visited by 130 physicians. At the 2018 and 2019 Rare Diseases Days, Liège organized three presentation sessions on Rare Diseases altogether. Two sessions were dedicated to specialist doctors, where specific clinical cases were introduced by different experts. One session – which was open to everybody including patients – focused on the Belgian National Rare Diseases Plan, the Orphanet tool, and the Belgian RD Register (database with all RD diagnosis and patients with RD symptoms). In March 2020, CHU Liège also organized a RD day event with information about EMRaDi and INTERREG.

Sparked by EMRaDi, UKA started a special collaboration with the North Rhine Medical Association, as they are the most important partner for GP and resident specialist doctor training sessions, offering a lot of events in the region. Nearly 100 people participated in the event, which took place on 22/01/2020 in Vaals, Netherlands (to highlight the euregional idea). Here, clinical cases were also presented and a general discussion with an intensive exchange was organized. An assessment of the event via a participant questionnaire revealed an interest for more information in this respect. The two partner organizations plan to hold more events in the RD field in the future. Furthermore, UKA organized an RD Day event in Düsseldorf on 24/02/18 within the NRW-ZSE Network, where EMRaDi was presented at an exhibition stand, and was attended by politicians, healthcare professionals, and patient and industry representatives (150 people in total).

MUMC+ and VSOP started an intensive collaboration with a specific group of GPs, called the Witte Raven, in 2017. The constructive collaboration between the three partners resulted in the first “ZeldzameZiekte borrel (ZZB)” (50 participants; the Royal Dutch Medical Association (RDMA) sponsored the event, with the VSOP in charge of its organization) in April 2018. This was an event for

general practitioners where different unknown cases were used as educational examples in order to use different search machines – like Orphanet and FindZebra - to find a diagnosis. This concept of training general practitioners to reach a diagnosis will take place for the second time sometime in mid-2020, with RDMA again planning to support it. In addition to the ZZB, postgraduate training was provided by the coordinator of the Rare Disease Centre at the end of 2018 (50 participants). Like other postgraduate training sessions, this "lunch-referaat" was taped by UM Science Vision and uploaded to a dedicated YouTube channel, which is freely accessible for those who could not participate.

Another valuable digital platform for RD eLearning is provided via https://www.huis-artsengenetica.nl/info/over-deze-website - a tool that is planned to be accessible by German physicians too (see Chapter 8.3). Modules have been developed by the Erfocentrum with input from the VSOP, clinical genetic experts, the Department of General Practice, the Department of Educational Development & Educational Research – both from MUMC+ – and the Dutch Society of General Practitioners. The different educational modules are validated and give access to the latest relevant know-how for general practitioners and other interested medical experts. Participating in these eLearning modules is encouraged via accreditation points.

The University Hospitals offer access to dedicated information for patients and professionals on their websites, and offer weblinks to partner organizations working in the RD field as well. In addition, the latest developments within the RD Centres of the UHs are published on their websites (Link MUMC+: https://klinischegenetica.mumc.nl/). For special events, for instance the political event and the final EMRaDi event, partners used several media channels to raise awareness and give access to the latest insights.

ZSEA Aachen has its own web presentation, which is directed at both patients and physicians (www.zsea.ukaachen.de). Here, on overview of all Patient Care and Research Centres, including names, telephone numbers and e-mail addresses of experts, can be found. It describes the procedure for patients without a diagnosis, and includes a questionnaire, information leaflet and a form consisting of one page with which physicians can register patients. Also, a special page for physicians exist. On the ZSEA project's webpage, the EMRaDi Project is introduced and further information can be found via the link to the www.emradi.eu website. According to the recommendations of VSOP and of the Patient Sounding Board, a link to the national contact point was added to ZSEAs website. ZSEA is present on Orphanet and the "SE-Atlas" – an atlas for RDs – and currently focuses on German-speaking countries (www.se-atlas.de).

CHU Liège's website has a Rare Disease Centre page with contact details of the RD coordinator, including a name, telephone number and e-mail address for patients and professionals. A further website with the names of all the RD experts is currently in progress.

It is also important to mention here that VSOP has a platform for patients with an unknown diagnosis – the "ZON platform"; this platform is a clear example of how other countries could develop a search machine for unknown diagnoses as well. (see https://ziekteonbekend.nl/)

A crucial point to decrease the time to diagnosis of a RD is to increase the awareness of the primary care practitioners (GPs and paediatricians) and resident expert doctors that the patient sitting before them might have a RD. Often, some characteristics come together and this was the idea to set up eight questions which, if a lot of them can be answered with yes – should lead to a faster referral to a CoE. These questions were discussed in the WP4 Task Force, during a Patient Sounding Board Meeting and in Steering committee meetings.

The "WHEN TO THINK OF A RARE DISEASE?" questions are:

1. Does the patient show acute or chronic unexplainable, incoherent or unspecific symptoms (especially at a younger age)?
2. Does a family history exist?
3. Have there been a number of sick periods because of differing or same symptoms?
4. Is there a history of senior consultations of different medical specializations without a satisfactory result?
5. Are there pathological or borderline results, which are non-conclusive on first impression?
6. Has there ever been suspicion of psychosomatic aetiology?
7. Are there phases of illness years back?
8. Are any specific exposure scenarios known (concerning nutrition, hobbies, living situation, animals, journeys or work related)?

If you can answer most of the questions with "yes" and your intuition confirms it, it might be advisable to think about a Rare Disease.

These questions were combined with relevant websites, such as Orphanet. Also, INTERREG and EMRaDi Logos and information from CHU, MUMC+ and UKA – depending on the language version – was added.

It was then decided to design a special banner pen with this information, as it was perceived that just setting up a flyer would be unsuccessful. Primary care practitioners and resident specialists often receive flyers from pharmaceutical companies, medical associations, etc, and therefore, the banner pen format was preferred. Pens are often used because doctors have to sign a lot of documents, e.g. letters and prescriptions. UKA and CHU will send the pens to all GPs and a lot of specialist doctors in the EMR, and MUMC+ will distribute the pen at different events.

9.3 EXCHANGE OF LATEST KNOW-HOW IN CLINICAL GENETICS AND LAB DIAGNOSTICS

Due to the fact that 80% of the Rare Diseases are genetically caused, the field of Human Genetics and related fields, such as Bioinformatics (to cope with the enormous amounts of data), are of high importance. The Genetics Retreat, organized by MUMC+ and it's Department of Molecular Cell Biology and Clinical Genetics, is an annual meeting that offers a unique and exclusive podium to scientists and

currently covers a broad range of scientific aspects to fundamental exploration and experimental (epi)genetics. A meeting that was planned to be organized this year for the 30th time is currently postponed due to the corona pandemic. Besides this spring meeting, the NVHG (Nederlandse Vereniging voor Humane genetica) organizes a symposium in autumn every year. The 2019 September Meeting was organized in close collaboration with the Belgium Society for Human Genetics (BeSHG). Both meetings are frequently attended by scientists, lab experts and clinicians from Germany, Belgium, the Netherlands and far beyond. Also, the German Society of Human Genetics organizes annual conferences where RDs are the main topic.

All these meetings offer a very complete informative package, however during these meetings time is often lacking to hold in-depth discussions on how the lab experts translate the latest know-how into their analytical workflow and impact clinical diagnostics. Lab experts also appreciate the exchange of their thoughts on how to implement, for instance, automation and new omics techniques into their analytical workflow. Furthermore, challenges in quality control, which is very important in clinical analyses, are often not discussed in-depth during these meetings. Another challenging topic is the how to handle big data sets and to enable data-sharing among different expert labs.

This was exactly the reason why different information and training sessions were organized throughout the course of the EMRaDi project. The first clinical genetics & lab expert introduction meeting was in May 2019, followed by an information session (Sept. 2019) focused on different techniques of sample analyses and their subsequent bioinformatics data interpretation. At this September meeting, organized at the same date & location as the autumn meeting of NVHG & BeSHG, bioinformatics experts from Leuven, Antwerp, Brussels, and Nijmegen Academic hospitals also participated. A follow-up meeting took place in December 2019 and the next one is planned for May 2020. National data sharing working groups from Germany, France, Belgium and the Netherlands have agreed to join forces and continue to regularly exchange information on best practices in bioinformatics. One of the expressed ambitions of this Euregional Bioinformatic consortium is to explore the feasibility of cross-border data sharing, which will ultimately lead to a significant improvement in the patient's journey by tracking comparable phenotypes.

9.4 IMPROVING THE KNOWLEGDE OF RD CENTRES FOR PATIENTS AND THEIR RELATIVES

Aside from within EMRaDi in general, several WP4 meetings took place to exchange the latest know-how available on different RD clusters. Patient organizations were actively invited to the EMRaDi Events (e.g. the Closing Event in 2020) and the Rare Disease Day Events; the University Hospitals provided suggestions for invitations and used their communication channels to create awareness and to publish the invitations. UHs also contacted patients to find members of the Patient Sounding Board for WP5, and interview partners for WP2.

In order to incorporate the patient's voice, the rare disease centres involve them and their relatives in their development. Patient participation in education, research and health care is very important in order to promote qualitatively high healthcare services. At ZSEA for example, representatives of RD patient organizations are members of its advisory board. The importance and appreciation of patient

participation in optimizing the patient journey was also expressed during the Patient Sounding Board sessions organized by the VSOP, and as a need in the WP2 field study.

The MUMC+ Expert Center for Kabuki syndrome intensified its collaboration with Kabuki syndrome patient organizations in order to create an optimized integral healthcare network together, with the ultimate goal being to enable a seamless referral from the unknown to known, and from known to the first and second line medical healthcare network. Furthermore, the hope is to create a foundation in which parents of Flemish Kabuki children are also involved. Together with the Expert Center for Kabuki Syndrome they will identify solutions to enable a seamless referral to the medical network in the different provinces of the Netherlands and Belgium's Flemish region. Another hope of the (soon-to-be launched) Kabuki Syndrome Foundation is to connect to the patient network from Wallonia and Germany in order to increase critical mass, and work together with CoEs towards improved/new treatments. The first contacts with the patient organizations in Wallonia and Germany has already taken place.

In December 2019, the Dutch Kabuki syndrome patient network started a crowdfunding action to create awareness and build capital for the kick-off of their foundation. In the future, they will continue their crowdfunding actions. When the EMRaDi project ends, the collaborative activities will continue with the ultimate goal to disseminate the method of improved referral to the different medical providers.

10 TRANSLATIONAL ASPECTS

Research is a very important subject in RDs as this opens up new ways of patient care and treatment. Therefore, in contrast to the more widespread diseases, the willingness of patients to participate in clinical trials is much broader. Therefore, one overview of clinical trials of the eight focus diseases was set up and distributed. Furthermore, through the OncoCare INTERREG Project, a new database for clinical trials will be set up. The possibility of searching for relevant clinical trials via a web tool directly connected to the different Websites of the UHs is also planned. As soon as this it up and running, EMRaDi will, together with the OncoCare partners, check if an extension to more RDs and not just the oncological RDs makes sense.

11 KABUKI SYNDROME AS A MODEL PROJECT

The MUMC+ has been an accredited CoE for Kabuki syndrome since 2015.

Kabuki Syndrome has been first described by Niikawa and independently by Kuroki in Japan in 1981. The first diagnosis in the Netherlands was in 1994 by C. Stumpel and co-workers. Kabuki syndrome is a rare genetic condition with intellectual disability and facial dysmorphism, which resembles the stage makeup used in Japanese kabuki theatre, hypotonia and many other possible features. Doctors at the Maastricht University Hospital have been experienced in this syndrome since the early nineties. MUMC+ cofounded the parent support group in those years.

As with other expert centres, MUMC+ experts see children and adults from the all over the Netherlands and from abroad. At CHU and UKA, there are no expertise centres for Kabuki Syndrome.

One of the families shared their experience on L1 Television (the biggest broadcasting company in NL-Limburg) which created not only awareness for the syndrome, but also for the cross-border challenges as the partners try to tackle them in the EMRaDi project. The website "Betere zorgpaden voor patiënten met zeldzame ziekten (https://klinischegenetica.mumc.nl/content/betere-zorgpaden-voor-patienten-met-zeldzame-ziekten)" offers an impression of a selection of awareness actions to better understand the challenges UHs in CBHC face.

One of the MUMC+ clinical trials was for Growth Hormone (GH) treatment. In December 2018, the paediatric expert team's endocrinologist finished her PhD on this topic. It was proved that GH is beneficial for the children, not only in terms of height, but also for body composition in particular. Hypotonia is also improved by this treatment. In June 2019, GH treatment was recognised as a treatment for all children with the syndrome that meet the criteria. On 17th October 2019, MUMC+ held a meeting in Liege with the Belgian lay organization for Kabuki syndrome and professionals in the field. The main goal of this meeting was to exchange the best practices in the current diagnostics and treatment of Kabuki syndrome patients. As with the hope of the EMRaDi project, MUMC+ will continue the knowledge exchange following the end of the project, enabling an optimized patient journey for people living with a rare disease.

MUMC+ hopes to implement this indication for growth hormone treatment for Belgian children in 2020. The recently registered growth hormone therapy for Kabuki Syndrome patients in the Netherlands has been discussed by the Belgian Society for Paediatric Endocrinology and Diabetology. Based on its needs and demands, MUMC+ will provide them information on the stepwise approach to how they should translate a validated therapy into clinical practice. Furthermore, the plan is to also integrate the German side.

All partners hope to continue this valuable collaboration with the "Strong Together" shared motto.

12 INPUT TO OTHER WORK PACKAGES

A lot of exchange took place not only during the project meetings, but also outside via telephone between all EMRaDi partners.

One very challenging task for all project partners at the beginning of the project was the choice of the RDs to focus on. Here, the criteria had to be agreed upon, information on diverse RDs collected, and finally the decision had to be made. The process showed that all partners were able to work together to unanimously decide on the eight RDs mentioned in Chapter 8.1.

WP1 mainly depended on data delivery, and all three UHs sent summary quantitative data of the eight focus diseases to the University Maastricht partner, adhering to the Data Protection Rules

In WP2, a lot of interviews with patients, relatives and professionals had to be carried out. To do this, the three UHs needed the go-ahead from their respective ethical committees. CHU and the WP2

partners started the process and invested a lot of time in writing the application before receiving the permission from its ethical committee. For MUMC+ and UKA, it was the basis to receive their permissions easier. All three university hospitals contacted patients and professionals to invite them to participate in the study.

In WP3, the UHs gave their input to the modelling development – either directly from the partners of the core group or with the WP4 task force.

In WP5, a questionnaire to explore patient participation in the research was set up. The UHs participated in the development of the questionnaire and also in its delivery to the relevant persons. Furthermore, UKA especially strived to find German candidates for the Patient Sounding Board.

13 EMRADI PRESENTATION

The WP4 members also strived to present the EMRaDi project with reference to the funding sources whenever possible. For example, it was introduced to both of the Ministers of Health in North Rhine-Westphalia that were in charge during the project's runtime – Minister Steffens and Minister Laumann – and also to the Minister President Paasch and Health Minister Antoniadis from the East Belgian Government. Furthermore, the project was presented via posters or talks at different events, e.g. at the (German) National Conference on Rare Diseases (NAKSE) in September 2019 in Berlin (Poster), and at the meeting of IT specialists and RD experts for the Collaboration of Rare Diseases (CORD) at the Medical Informatics Initiative in Berlin, December 2019 (Talk).

14 CONCLUSIONS

In the field of RDs, major progress can often only be achieved through cooperation. The complex nature of RDs, the diverse problems patients with RDs face every day and the need for different medical disciplines to work together to find the right RD diagnosis underline this necessity.

Therefore, the WP4 partners appreciate the project – amongst others – because a very good and promising network was established with many relevant partners in the EMR: UHs, patient organizations, health insurance funds, and universities to name but a few. Cooperation between the three EMR UHs has not only increased on a daily basis, but also on a more structural level. Exchanges at interdisciplinary case conferences, for example, has started and will surely expand more in the upcoming months.

Furthermore, a lot of results were achieved which will help to develop the RD field in the EMR and beyond – the most important being to help the people living with a RD especially. Key to this are the activities to increase GP awareness, as these healthcare professionals are the first medical contact for patients with a suspicion of a RD. Here, a further reduction of the time to diagnosis can be expected. Also, the activities between the UH in different fields of RD as well as Human Genetics and Bioinformatics are very promising and shall continue beyond the end of the current funding line.

The RD structures at the University Hospitals were strengthened due to the exchanges throughout the project, and all the partners learned a lot from one another.

The clear objective is that the cooperation will continue and the plan will open up new funding sources.

15 ACKNOWLEGDEMENTS

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The WP4 partners want to thank their colleagues from the other work packages for their valuable contributions and extensive work in the project, which also helped the University Hospitals very much.

Last but not least, thanks to INTERREG and the regional authorities who funded the project.

16 LIST OF ABBREVIATIONS

CBHC	Cross-Border Health Care
CML	Chronic Myeloid Leukaemia
CoE	Centre of Expertise
CHU	University Hospital Center Liège
EMRaDi	Euregio Meuse-Rhine Rare Diseases
EMR	Euregio Meuse-Rhine
ERN	European Reference Network
GP	General Practitioner
MUMC+/AZM	Maastricht University Medical Center / Academisch Ziekenhuis Maastricht
NRW	North Rhine-Westphalia
PKU	Phenylketonuria
PSB	Patient Sounding Board
PV	Polycythaemia vera
RD	Rare Disease
RDD	Rare Disease Day
RDMA	Royal Dutch Medical Association
SC	Steering Committee
UKA	University Hospital RWTH Aachen
UH	University Hospital
UM	University of Maastricht
VSOP	Vereniging Samenwerkende Ouder- en Patiëntenorganisaties
SEA	Center for Rare Diseases at University Hospital RWTH Aachen