REPORT OF WORK PACKAGE 3

PATIENT-ORIENTED MODELS OF GOOD PRACTICE FOR THE MANAGEMENT OF RARE DISEASES

Lead partner of Work Package	**Maastricht University**
WP n° and title	WP3. Develop EMR models of RD patient pathways in order to elaborate patient-oriented recommendations in synergy with national and European developments
Activity n° and title	A3.1, A3.2 and A3.3. Development of organisational models for the management of rare diseases in the EMR with generic and specific organisational models in border regions and with recommendations for national and European developments
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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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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**.

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LEGAL ISSUES

EXECUTIVE SUMMARY

During the course of the EMRaDi project, we established that the numbers of rare disease patients in the Euregio Meuse-Rhine (EMR) is sufficiently large to warrant a systematic approach. This conclusion is also supported by patient experience. Two issues were highlighted in particular in the WP2 field study with the patient interviews: the delays in receiving a diagnosis, as well as the burden the patients and their informal caregivers experience for some RDs due to having to manage the multidisciplinary care rare diseases require themselves. The aim of this Work Package was to identify potential improvements in patient pathways for rare disease patients in the EMR that explicitly aim to reduce the time to diagnosis and reduce the care coordination burden of patients and informal caregivers.

The usual approach to patient care pathway optimisation involves methods from the discipline of logistics, in particular microsimulation. These methods have previously been used to optimise various aspects of care provision, including reducing waiting times and deciding whether opening additional wards or hiring additional staff is cost-effective. However, microsimulations normally require a substantial amount of data describing the system, including information on the number of patients and providers, the referral patterns and their probabilities, and the characteristics of interactions between patients and providers. The data available on rare diseases in the EMR was not sufficient.

We therefore used an alternative approach called participatory dynamic simulation modelling. We collected qualitative information on the RD patient pathways from providers and patients and identified a number of innovations in patient care pathways they considered interesting. We then explored these innovations using a simulated environment to identify the most promising ideas. Where this was not possible, we collected the relevant experience from other chronic diseases such as dementia and heart failure. The results were then presented to patients and rare disease specialists to verify the acceptability and the identified, most promising innovations.

The two innovations that were identified as most promising are:

- *Supporting primary care providers (e.g., GPs) in suspecting and referring potential rare disease patients to a specialised centre for diagnostics; and*
- *Introducing case managers that assist rare disease patients and their informal caregivers with coordinating multidisciplinary care.*

We recommend that these two pathway innovations are tested as pilot projects in the EMR in the context of well-designed clinical trials. We also call on the European Union and national governments to improve the infrastructure for health services research relevant to rare diseases, and health insurance funds to consider developing funding mechanisms for cross-border consultations for rare disease patients.

1 INTRODUCTION

Work Package 3 aimed to develop organisational models for the management of rare diseases (RD) in the Euregio Meuse-Rhine (EMR), and in particular provide a **generic organizational model for the management of rare diseases in border regions, specific EMR organizational models for the management of selected rare diseases**, and identify recommendations for national and European Union developments. It relies on insights gathered in Work Package 1 on the epidemiology of rare diseases in the EMR, and Work Package 2 on the field analysis of existing RD patient pathways, as well as the participation of stakeholders in Work Packages 4 and 5. This Report will tackle the question of optimising care pathways for patients with rare diseases in the EMR and the European Union.

In our report on the demands and needs of rare disease patients[1], we emphasised the fact that rare diseases are often associated with a long waiting time between onset of symptoms and a definitive diagnosis – the so-called diagnostic odyssey, which is likely the consequence of a lack of widespread awareness of rare diseases and the limited availability of the relevant diagnostic procedures (e.g. exome sequencing). The Global Commission to End the Diagnostic Odyssey for Children with a Rare Disease – a collaboration of rare disease patient groups, healthcare providers, research institutions, and industry – states that the average time to diagnosis of rare diseases in children is 4.8 years and warns that delays in diagnosis may lead to inappropriate care and disease progression.[2] A EURORDIS survey of eight rare diseases in Europe found that a quarter of patients experienced diagnostic delays between five and 30 years, and almost half (40%) received an incorrect diagnosis during this time.[3]

Rare diseases, along with other more common chronic conditions, share the need for complex interdisciplinary care involving several medical specialties and allied health professionals.[4] This creates an additional burden for rare disease patients and their informal caregivers, a burden which primary care physicians are often not in the position to share. Results from 62 interviews of patients and informal caregivers carried out as part of WP2 bear this out for the EMR as well. The patients and relatives reported that they needed to consult and coordinate with between six (polycythaemia vera) and 25 (Rett syndrome) different specialists and healthcare professionals for the comprehensive care of the RD. They also expressed the need for a central contact person throughout treatment to assist them with the coordination of care.

It is important to note that these two challenges arise directly from the way care is provided to rare disease patients and can be met by improving the care pathways that patients experience. Therefore, we focused our work in this Work Package on identifying innovations in the care pathway that would directly and positively impact the time to diagnosis and support patients in coordinating care, both in the EMR and the European Union more broadly.

The remainder of this Report is structured as follows: The methods describe our approach to simulating the rare disease care pathways in the EMR and identifying promising improvements. The results section provides an in-depth description of the two improvements, referral to centralised rare disease diagnostic centres and case managers. In the final section, we provide our reflections on the research process and offer recommendations for next steps in improving care pathways for rare diseases in the EMR and the European Union.

2 METHODS

2.1 RESEARCH DESIGN

Care pathway optimisation consists of various techniques and approaches, commonly inspired by other disciplines, including business, manufacturing, and logistics. The common initial step to all care pathway redesigns is constructing a pathway map, which describes the physical patient journey, the flows of information, and staff responsibilities.[5] Pathway mapping, however, requires a large amount of data from a well-defined organisational context. In rare diseases, both of these elements are missing. One reason is that the health information systems in the EMR are not well developed to support health services research relevant to rare diseases[6]. The second reason is that the current RD care pathways tend to be *ad hoc* in most healthcare organisations in the EMR due to the (perceived) low number of patients. Finally, we aim to provide recommendations for care pathway innovations that span several RD groups, which necessitates an approach abstracted from a specific organisational context.

We utilise an alternative approach that generates a generic virtual care pathway based on the experiences of patients and care providers. The inspiration is participatory dynamic simulation modelling – a systems science method that recreates a complex system in a virtual world and which has been used to support public health policy in Australia[7]. The approach engages the stakeholders in the modelling process, relying on their tacit expertise to both construct the simulation and validate its results. The method relies on the identification of, *a priori,* ideas for interventions or scenarios in our case innovations in the care pathway, the effects of which are then modelled in the simulation. For more information on using participatory dynamic simulation modelling and case studies of its use to design interventions that prevent alcohol related harm, reduce childhood overweight and obesity, and improve service provision for diabetes in pregnancy, we refer the interested reader to the publication by Freebairn *et al*.[7]

Our implementation of participatory dynamic simulation modelling included three steps:

1. Elicitation of a generic RD care pathway from stakeholders
2. Generation of a simulated generic RD care pathway and its analysis
3. Validation of the simulation results and recommendations

Steps 1 and 3 took the form of focus groups with patients and care providers affiliated with the EMRaDi Project Work Packages 4 and 5, respectively. Step 2 involved the creating of a multistate microsimulation of a cohort of homogenous patients interacting with the generic RD care pathway under various scenarios, and a rapid literature review. The next two sections provide further details on both.

2.2 DATA COLLECTION AND ANALYSIS

2.2.1 FOCUS GROUPS

For steps 1 and 3 of our study, we organised two separate focus groups with patients and care providers. Table 1 summarises the sessions, the participants, and the topics of discussion.

Table 1 Summary of focus group sessions

Session	Date	Participants	Topics
Patients 1	8 November 2018	Four rare disease patients from the EMR	Purpose of activity Simulation as a tool for care pathway optimisation Initial RD care pathway architecture and key outcomes Proposed scenarios to investigate, in particular innovations that could reduce time to diagnosis and reduce the care coordination burden on patients and informal caregivers.
Providers 1	17 December 2018	Three rare disease specialists from the EMR	
Patients 2	23 May 2019	Four rare disease patients from the EMR	Preliminary simulation results Recommendations
Providers 2*	1 June – 1 September 2019	Two rare disease specialists from the EMR	
*** This session was conducted virtually via phone and email due to the unavailability of participants.**			

The focus group sessions were embedded in other EMRaDi project activities, namely the Patient Sounding Board (Work Package 5) and university hospital networking (Work Package 4).

The focus group sessions were chaired by UM researchers and lasted approximately 30 minutes. For each of the sessions, the chairs prepared a protocol of the session that included the topics to be explored and questions to be answered. The contents of the sessions were recorded in the form of minutes, which were verified by all participants.

The results of the sessions were then used when building the simulation and performing the rapid literature review (first two sessions) and preparing the final conclusions and recommendations (second two sessions).

2.2.2 MICROSIMULATION

For step 2 of the study, we constructed a simple microsimulation[8]. Each simulated individual could be present in one of two states, non-diagnosed and correctly diagnosed, while there were no further differences between the simulated individuals (for example age, sex, health status, etc.). We simulated a cohort of ten thousand patients interacting within a care pathway outlined in Figure 1 (standard model). The cohort was followed for 36 cycles, each representing a month. The outcomes simulated were the proportion of the cohort that received a diagnosis in 12 months and 36 months, and the average cost per individual accumulated over 36 months. The model was implemented using R[9].

Each of the locations on the care pathway was associated with a probability of transition from non-diagnosed to correctly diagnosed, as well as with a probability of being referred to a different part of the system (arrows in Figure 1). The transition and referral probabilities were estimated from the literature and the inputs from the focus groups (Annex 1). Costs were extracted for the Dutch healthcare system using estimated 2019 reference prices from the Dutch Healthcare Authority (NZa). Note, however, that the purpose of the model was not to conduct a full cost-utility analysis, but rather explore potential innovations in the care pathway with the participants of the focus groups and identify those most promising for further research.

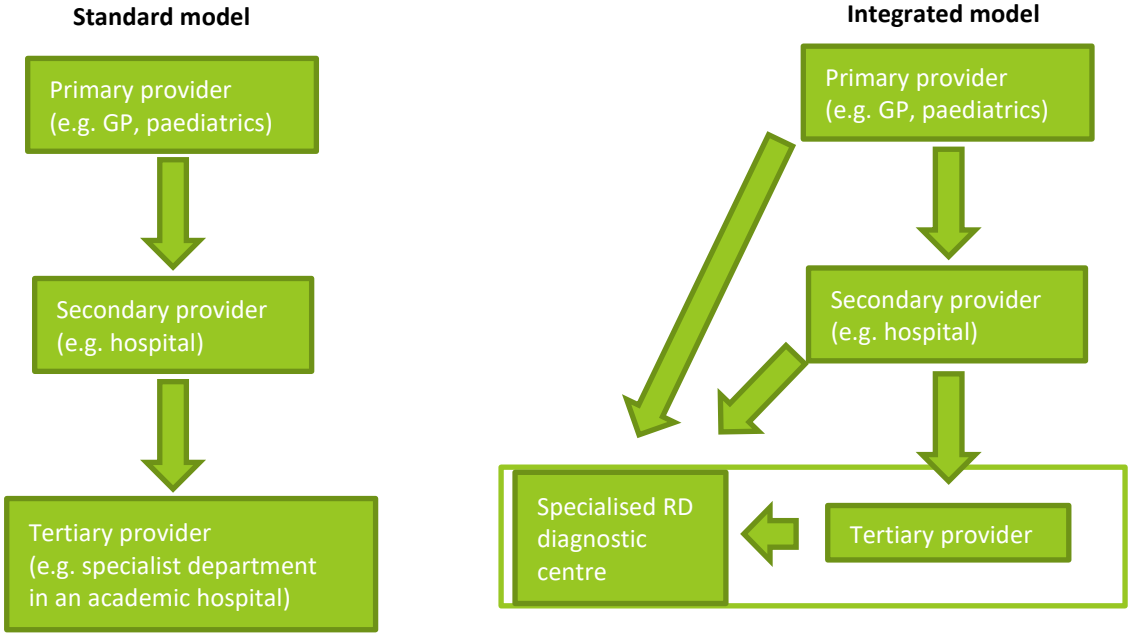

Figure 1 Rare disease patient care pathways used in the microsimulation.

Based on the input from the focus groups, we concentrated on comparing the standard model with a scenario in which a specialised rare disease diagnostic centre exists and, where awareness-raising efforts among primary care providers were made to enhance the probability of referral to such a centre. The results of the microsimulation were presented to the focus group during the second two sessions (step 3 of the study).

2.2.3 RAPID LITERATURE REVIEW

We performed a Rapid Literature Review of the scientific publication on case managers[10]. This was done in lieu of building a microsimulation of this innovation because of insufficient quantitative data.

Inclusion criteria

We aimed to include systematic reviews and meta-analyses of experimental and observational studies on the effects of introducing case managers in the context of chronic disease. All general somatic chronic disease patient groups were included. Substance abuse and marginalised social groups were excluded. All effectiveness and efficiency-related outcomes were of interest, including mortality, quality of life, healthcare utilisation, and costs. We limited our search to the last 10 years (publications since 2010) and the English language.

Search strategy

We searched MEDLINE and the Cochrane Library for mesh keywords related to case management, using the systematic review and meta-analysis filters, as well as the date of publication filter.

Selection and synthesis

All results from the above-mentioned sources were extracted into an Endnote database. The relevant records were selected based on their titles, their abstracts, and finally their full text. All included publications were summarised in terms of setting, intervention, and a summary of results (Appendix 2).

The results of the Rapid Literature Review were presented to the participants of the focus groups during the second two sessions (Step 3 of the study).

3 RESULTS

The two innovations that were identified as most promising during the focus group sessions are:

1. Supporting primary care providers (e.g. GPs) in suspecting and referring potential rare disease patients to a specialised centre for diagnostics; and
2. Introducing case managers that assist rare disease patients and their informal caregivers with coordinating multidisciplinary care.

The first innovation was also evaluated using a microsimulation model described above. There was insufficient data available to construct a microsimulation model for the second innovation, so we provided insight into its effects using a rapid review of the scientific literature.

The rest of this section provides a description of each of the patient pathway innovations and summarises the evidence of their effects.

3.1 IMPROVED AWARENESS OF RARE DISEASES AT PRIMARY LEVEL AND INTEGRATED RARE DISEASE DIAGNOSTIC SERVICE

The discussion during the first sessions of the focus group produced two innovations for improving the challenge of the diagnostic odyssey. The first was to improve awareness among primary care providers of rare diseases, including providing them with a red flag list of signs and symptoms that are commonly associated with rare diseases (more information on this in Work Package 4's Report). However, even if a primary care provider suspects a rare disease, diagnostic expertise and facilities remain fragmented in the EMR and the European Union. Awareness-raising would therefore work best if primary care providers could be given a single destination (or only a few destinations) to refer all suspected rare disease cases to. The patients consulted were also of the opinion that such a solution would prevent the back-and-forth movements between various specialist services that patients currently experience.

We therefore implemented the two scenarios, higher awareness among primary care providers and a specialised rare disease diagnostic centre (attached to a tertiary care provider in the region), in our microsimulation and compared the results with the baseline scenario. The first was simulated as a non-zero probability of a primary provider referring a yet undiagnosed rare disease patient to a specialised diagnostic service. We simulated both a 5% and 10% probability of referral as a way of testing the sensitivity of the results to our assumptions.

The second was simulated by enhancing the probability of correctly diagnosing a rare disease at a tertiary care provider from 20% to 50%. The latter assumes various practical improvements. Such as a low threshold to exome sequencing, a multidisciplinary team of RD experts, and a low threshold to presenting the case to a European Reference Network Panel. The value of 50% (more than double the rate of successful diagnosis compared to the baseline) was suggested by participants of the focus groups.

Table 2 Microsimulation results

Model	Cost (36m)	Diagnosed (12m)	Diagnosed (36m)
Standard care	12,198 EUR	26%	63%
5% probability of GP referral to specialized diagnostic service	12,158 EUR	33%	72%
5% probability of all referral to specialized diagnostic service	12,326 EUR	35%	75%
10% probability of GP referral to specialized diagnostic service	12,166 EUR	38%	79%
10% probability of all referral to specialized diagnostic service	12,335 EUR	41%	83%

The results (Table 2) suggest two key conclusions. The first is that focusing awareness-raising campaigns on primary care providers – and thereby improving their referral rates to rare disease diagnostic services – has the most added effect in terms of percentage diagnosed compared to improving referral rates at all levels of the system. This can be explained by the fact that primary care providers in our model (as well as in reality) have the highest frequency of contact with undiagnosed rare disease patients, so improvements at this level have the most effect.

The second conclusion is that introducing an expensive specialised diagnostic service (see Annex 1 for cost estimate) does not produce higher costs, but does lead to a higher percentage of successful diagnoses. This is also not an unexpected finding, since a higher likelihood of success reduced the back-and-forth of patients within the system, thus stopping the accumulation of healthcare costs associated with the diagnostic odyssey. The overall costs will in reality depend on the cost of treatment, which varies vastly between different rare diseases and was therefore not included in our simulation.

Overall, we can conclude that empowering primary care providers with the necessary knowledge of rare diseases and a clear pathway of referral to a diagnostic service would reduce the time to diagnosis without increasing healthcare costs associated with diagnosing the disease.

The EMRaDi Final Report and the WP4 Report mention the steps that were already implemented during the project lifetime to this end, including, amongst others, the training of GP and the provision of a factsheet for first line practitioners to raise their awareness of detecting rare diseases and to support patients and informal caregivers.

3.2 INTRODUCING A CASE MANAGER FOR RARE DISEASES

The focus group discussion also identified an innovation that could reduce the care coordination burden that rare disease patients and their informal caregivers experience. Drawing on the experience of other European projects (e.g. Innovcare, https://innovcare.eu/) and other complex treatment procedures (e.g. stem cell transplantation in the Netherlands), the participants identified case managers as a promising innovation for rare disease patients in the EMR and the European Union.

Because insufficient data were available to model this intervention as a microsimulation, a Rapid Literature Review of case managers in the context of other chronic diseases was conducted.

Out of 105 unique reviews that were uncovered, 16 are included in our summary. Annex 2 lists all the included publications. The reviews included diverse patient groups and included patients suffering from both somatic diseases (e.g., hypertension, osteoarthritis, and heart failure) and psychiatric conditions (e.g., dementia and depression). Case management was usually defined as interventions that included the five core elements outlined by the Standards of Practice for Case Management: Assessment, Planning, Facilitation, Care Coordination, Evaluation and Advocacy[11]. Case managers were most often nurse practitioners. The outcomes of introducing case management differed by condition, setting and implementation. The reviews came to conflicting results in terms of clinical outcomes and healthcare resource use, including institutionalisation, when comparing case management to standard care. However, the qualitative syntheses suggest that case management is well received by the patients and their informal caregivers, enhances trust between care providers and patients, improves the experience of care as well as access to care, and reduces the perceived burden on patients and informal caregivers by meeting their needs[12–15].

Separate from the Literature Review, we also considered the results of the INNOVCare project, the only case management study to our knowledge that focused on rare disease patients. The INNOVCare study found an improvement in patient empowerment, confidence, and information, but no significant improvement in quality of life[16].

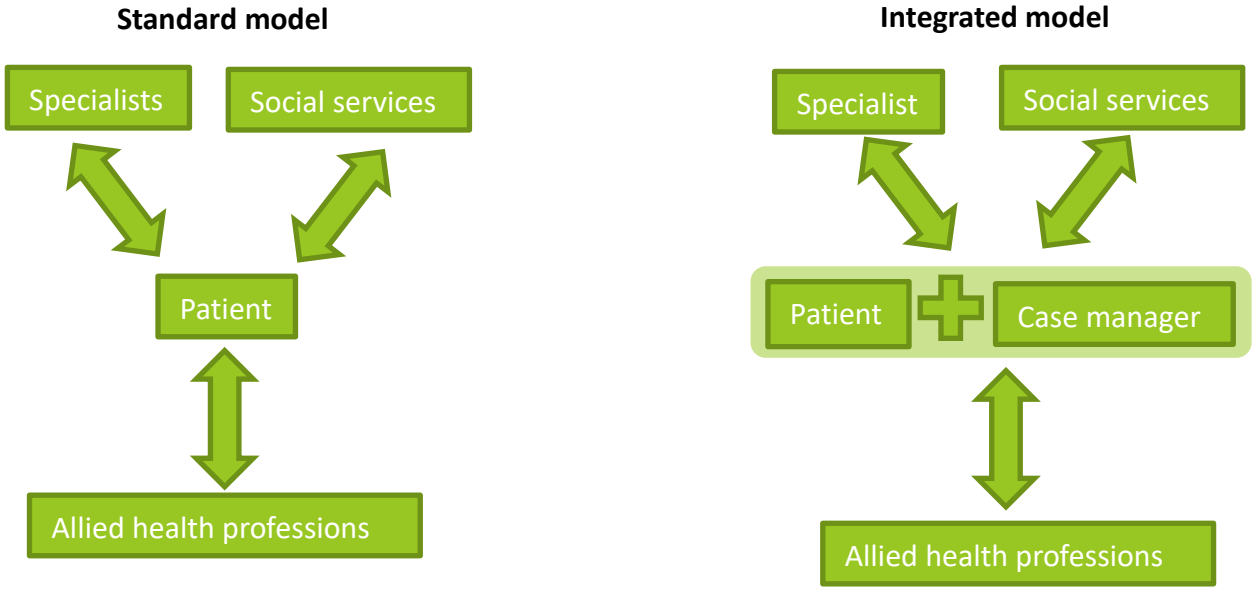

Figure 2 Rare disease case manager model

4 CONCLUSION

4.1 KEY FINDINGS

Our study found that two innovations in the patient care pathway could positively contribute to the experience of rare disease patients, particularly their experience of delayed diagnosis (diagnostic odyssey) and of the burden of care coordination.

The first innovation combines supporting primary care providers (e.g., GPs) in suspecting and referring potential rare disease patients to a specialised centre for diagnostics. Our microsimulation shows that this innovation could potentially reduce the time to diagnosis while not increasing the healthcare costs associated with the diagnostic odyssey of rare disease patients.

The second innovation introduces case managers that assist rare disease patients and their informal caregivers with coordinating multidisciplinary care. While RD-specific data relevant to this innovation is scarce, evidence from other chronic diseases indicates that patients and informal caregivers experience case management as valuable help. The clinical and healthcare utilisation outcomes associated with introducing case managers differed in the literature by disease, context, and implementation and thus necessitate further rare disease-specific research.

4.2 RECOMMENDATIONS

Based on the key findings of our study, we can make several recommendations relevant to the EMR and the European Union.

First, we recommend testing the two innovations identified as promising (awareness-raising among primary care providers combined with a specialised rare disease diagnostic service and case management) in the EMR in the context of well-designed clinical trials. As we have seen from the Rapid Literature Review, there is evidence that the effect of case management intervention is both context-specific and lacking for the field of rare diseases. This can be generalised to all patient care pathway innovations. An effort to test the proposed intervention in the EMR would bridge an important gap in our knowledge and position the EMR as a region at the forefront of rare disease health services research and innovation.

Based on our experience in the EMRaDi project, the current efforts around Kabuki syndrome at MUMC+ (online portal, expert network, health information infrastructure), combined with the networking activities derived from EMRaDi activities, represent sufficient starting infrastructure for patient recruitment and follow-up to begin developing the proposed clinical trials.

Second, with regards the report on the evaluation of the number of patients with rare diseases in the EMR (WP1), we would like to reiterate our recommendation to EU and national governments to support the health services research on rare diseases.

. This includes (1) support for projects that build up RD data infrastructure, including data cooperatives, (2) support for projects that clarify the legal status of RD healthcare utilisation data, and

(3) support for methodological standardisation and guideline development for health services research in the field of rare diseases. These are necessary conditions for future innovation in patient care pathways in rare diseases. Without them, rare disease patients will continue to experience the care provision-related challenges we outlined in the introduction to this Report.

Finally, we recommend that health insurance funds, together with the support of the EU, consider developing reimbursement procedures for cross-border consultations related to RDs. This involves (1) clearly defining inter-professional consultations regarding diagnostic or treatment plans as a distinct healthcare service that can be reimbursed, irrespective of where in the EU the consulted professional resides, and (2) providing a priority procedure for the reimbursement of such services for RD patients. This is particularly relevant in the context of developing and testing specialised rare disease diagnostic centres, which may need to function beyond national borders in order to combine the necessary expertise over a wide range of rare diseases.

4.3 STRENGHTS AND LIMITATIONS OF THE STUDY

Our study was the first to apply a participatory dynamic simulation modelling approach in the context of rare diseases and the first stakeholder-driven study of rare disease patient care models at the euregional level. Through its focus on stakeholder participation, a process of reflection began on the care provision experiences of rare disease patients in the EMR that is likely to outlive the EMRaDi project. It also identified concrete innovations that have high buy-in from patients and care providers, as well as promising empirical underpinnings. It thereby identifies a clear path for future research, which was outlined in the previous section.

Our study was limited in numerous ways. The number of participants in our focus groups was small, although they were broadly representative of the disease groups and geographic areas included in the EMRaDi project. The microsimulation that was built is simplistic and does not reflect differences between ages, health systems, diseases and other individual characteristics of patients. Nevertheless, it was never meant as a rigorous stand-alone analytical instrument, but rather as a starting point for a stakeholder discussion. It provides a solid starting point for future work. Finally, the data (stakeholder experience and scientific literature) that was used to identify and evaluate the care pathway innovations was limited in scope and thus provides an incomplete picture. Other innovations may prove to be more relevant or effective for rare disease patients. Nevertheless, surveying the information available using the methodology utilised for this Project allows us to draw attention to the scarcity of health services research into rare diseases, identify some of the causes of this scarcity, and recommend specific actions at European and national levels that may begin to remedy the situation.

5 LIST OF ABBREVIATION AND ACRONYMS

(in alphabetic order)

e.g.	For example
EMR	Euregio Meuse-Rhine
EU	European Union
EUR	Euro €
GP	General Practitioner
ICU	Intensive Care Unit
INNOVCare	Innovative Patient-Centred Approach for Social Care Provision to Complex Conditions
MUMC+	Maastricht University Medical Centre +
RD	Rare disease

6 BIBLIOGRAPHY

1. Hrzic R, Clemens T, Schöder-Bäck P, Brand H. Report on the demands and needs of patients. 2018. EMRaDi project, www.emradi.eu

2. Global Commission to End the Diagnostic Odyssey for Children with a Rare Disease. https://www.globalrarediseasecommission.com/AboutUs. Accessed March 16, 2020.

3. Eurordis. Survey of the delay in diagnosis for 8 rare diseases in Europe ('EurordisCare 2'). 2018. https://www.eurordis.org/sites/default/files/publications/Fact_Sheet_Eurordiscare2.pdf. Accessed March 16, 2020.

4. Coles V, Chan G, Palczewski K, Lewis K, Ho J. The Importance of Complex Care Coordination. 2018. doi:10.13140/RG.2.2.31979.44324

5. Mould G, Bowers J, Ghattas M. The evolution of the pathway and its role in improving patient care. *Qual Saf Health Care*. 2010;19(5):e14-e14. doi:10.1136/qshc.2009.032961

6. Hrzic R, Clemens T, Schöder-Bäck P, Brand H. Report evaluating the number of patients with rare diseases. 2020.

7. Freebairn L, Rychetnik L, Atkinson J-A, et al. Knowledge mobilisation for policy development: implementing systems approaches through participatory dynamic simulation modelling. *Health Res Policy Syst*. 2017;15(1). doi:10.1186/s12961-017-0245-1

8. Krijkamp EM, Alarid-Escudero F, Enns EA, Jalal HJ, Hunink MGM, Pechlivanoglou P. Microsimulation Modeling for Health Decision Sciences Using R: A Tutorial. *Med Decis Making*. 2018;38(3):400-422. doi:10.1177/0272989X18754513

9. R Core Team. *R: A Language and Environment for Statistical Computing*. Vienna, Austria; 2018. https://www.R-project.org/.

10. Tricco AC, Antony J, Zarin W, et al. A scoping review of rapid review methods. *BMC Med*. 2015;13(1):224. doi:10.1186/s12916-015-0465-6

11. Case Management Society of America. Standards of practice for case management. 2016. https://www.miccsi.org/wp-content/uploads/2017/03/CMSA-Standards-2016.pdf. Accessed March 17, 2020.

12. King AJL, Johnson R, Cramer H, Purdy S, Huntley AL. Community case management and unplanned hospital admissions in patients with heart failure: A systematic review and qualitative evidence synthesis. *J Adv Nurs*. 2018;74(7):1463-1473. doi:10.1111/jan.13559

13. Joo JY, Liu MF. Experiences of case management with chronic illnesses: a qualitative systematic review. *Int Nurs Rev*. 2018;65(1):102-113. doi:10.1111/inr.12429

14. Askerud A, Conder J. Patients' experiences of nurse case management in primary care: a meta-synthesis. *Aust J Prim Health*. 2017;23(5):420. doi:10.1071/PY17040

15. Khanassov V, Vedel I. Family Physician-Case Manager Collaboration and Needs of Patients With Dementia and Their Caregivers: A Systematic Mixed Studies Review. *Ann Fam Med*. 2016;14(2):166-177. doi:10.1370/afm.1898

16. Juliet Tschank, Katharina Handler, Nela Šalamon, Stefanie Konzett-Smoliner. The effects of a case management approach on the quality of life of rare disease patients in Salaj, Romania: a pilot randomised control trial of efficacy. 2018. https://innovcare.eu/wp-content/uploads/2018/12/INNOVCare_WP7_Evaluation-report_final-version.pdf. Accessed March 16, 2020.

7 APPENDICES

7.1 APPENDIX 1 – MICROSIMULATION ASSUMPTIONS

Domain	Location	Probability/cost estimate
Probability of diagnosis	At home	0.1%
	At GP	1%
	At hospital	10%
	At academic hospital	20%
	At an integrated diagnostic service	50%
Referral probability (baseline scenario)	GP to hospital	40%
	Hospital to academic hospital	25%
Costs	At GP	34 EUR
	At hospital	2,305 EUR (5-day hospitalisation is assumed)
	At academic hospital	3,340 EUR (5-day hospitalisation is assumed)
	Integrated diagnostic service	6,000 EUR (equivalent to 3 days of ICU with examinations in the Netherlands)

7.2 APPENDIX 2 – DOCUMENTS INCLUDED IN THE RAPID LITERATURE REVIEW

Joo JY, Liu MF. Case management effectiveness for managing chronic illnesses in Korea: a systematic review. Int Nurs Rev. 2019;66(1):30-42.

King AJL, Johnson R, Cramer H, Purdy S, Huntley AL. Community case management and unplanned hospital admissions in patients with heart failure: A systematic review and qualitative evidence synthesis. J Adv Nurs. 2018;74(7):1463-73.

Joo JY, Liu MF. Experiences of case management with chronic illnesses: a qualitative systematic review. Int Nurs Rev. 2018;65(1):102-13.

Joo JY, Liu MF. Case management effectiveness in reducing hospital use: a systematic review. Int Nurs Rev. 2017;64(2):296-308.

Dieterich M, Irving CB, Bergman H, Khokhar MA, Park B, Marshall M. Intensive case management for severe mental illness. Cochrane Database of Syst Rev. 2017(1).

Corvol A, Dreier A, Prudhomm J, Thyrian JR, Hoffmann W, Somme D. Consequences of clinical case management for caregivers: a systematic review. Int J Geriatr Psychiatry. 2017;32(5):473-83.

Askerud A, Conder J. Patients' experiences of nurse case management in primary care: a meta-synthesis. Aust J Prim Health. 2017;23(5):420-8.

Khanassov V, Vedel I. Family Physician-Case Manager Collaboration and Needs of Patients With Dementia and Their Caregivers: A Systematic Mixed Studies Review. Ann Fam Med. 2016;14(2):166-77.

Huntley AL, Johnson R, King A, Morris RW, Purdy S. Does case management for patients with heart failure based in the community reduce unplanned hospital admissions? A systematic review and meta-analysis. BMJ Open. 2016;6(5):e010933.

Stokes J, Panagioti M, Alam R, Checkland K, Cheraghi-Sohi S, Bower P. Effectiveness of Case Management for 'At Risk' Patients in Primary Care: A Systematic Review and Meta-Analysis. PLoS One. 2015;10(7):e0132340.

Reilly S, Miranda-Castillo C, Malouf R, Hoe J, Toot S, Challis D, et al. Case management approaches to home support for people with dementia. Cochrane Database of Syst Rev. 2015(1).

Lannin NA, Laver K, Henry K, Turnbull M, Elder M, Campisi J, et al. Effects of case management after brain injury: a systematic review. NeuroRehabilitation. 2014;35(4):635-41.

Tam-Tham H, Cepoiu-Martin M, Ronksley PE, Maxwell CJ, Hemmelgarn BR. Dementia case management and risk of long-term care placement: a systematic review and meta-analysis. Int J Geriatr Psychiatry. 2013;28(9):889-902.

Huntley AL, Thomas R, Mann M, Huws D, Elwyn G, Paranjothy S, et al. Is case management effective in reducing the risk of unplanned hospital admissions for older people? A systematic review and meta-analysis. Fam Pract. 2013;30(3):266-75.

Somme D, Trouve H, Dramé M, Gagnon D, Couturier Y, Saint-Jean O. Analysis of case management programs for patients with dementia: a systematic review. Alzheimers Dement. 2012;8(5):426-36.

Pimouguet C, Lavaud T, Dartigues JF, Helmer C. Dementia case management effectiveness on health care costs and resource utilization: a systematic review of randomized controlled trials. J Nutr Health Aging. 2010;14(8):669-76.