Addressing challenges to European multi-country collaboration models for rare diseases
Addressing challenges to European multi-country collaboration models for rare diseases

| Rare diseases – defined as diseases that affect no more than one person in 2,000 – currently impact between 30 and 35 million EU citizens. Limited patient volume hinders research on these diseases, to the detriment of understanding of their biology, recruitment to clinical trials and survival rates. Real-time sharing of primary health data within and between rare disease healthcare centres and across Member States is feasible but there are obstacles.  
This report focuses on childhood cancer as a rare disease prototype, addressing volume challenges by reviewing cooperative structures, exploring attitudes towards data sharing, and presenting policy options for multi-country collaboration. Interviews show support for collaboration among rare disease healthcare centres, and for sharing medical files and expertise. The policy options proposed seek to promote research and expertise-building for the benefit of rare disease patients. |
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Executive summary

Introduction

A rare disease (RD) is a life-threatening or chronic debilitating condition that occurs in fewer than one in 2,000 citizens. Combined, RDs affect 30-35 million people in EU Member States. They are responsible for more than half of all childhood deaths, among which childhood cancer is the most common cause, but survival rates vary significantly among Member States, with eastern EU Member States facing worse outcomes.

Due to their low prevalence, there is a backlog in mapping their biology, low recruitment to clinical trials, and uneven distribution of relevant expertise in diagnostics, clinical care, and/or research. Accordingly, RD healthcare, including survival rates, in general lag behind more common medical disorders. As an example, childhood cancer today accounts for 20% of all childhood deaths after infancy, compared to only 11% in the 1960s, as death from more common diseases, such as infections, has become rarer.

Building expertise to drive innovation based on large patient volume, which is obviously lacking for RDs, is as critical as providing access to existing expertise. Importantly, developing intimate multi-country RD ecosystems has been challenged by heterogenous national legal frameworks for health data security and data sharing across EU Member States.

Focusing on childhood cancer as a prototype for life-threatening RDs, this report addresses the RD volume challenges and presents six policy options conducive to more in-depth multi-country cooperation between centres responsible for treating RDs, thus creating the critical mass that can generate expertise and hence improve diagnostics and treatment.

Methods and results

The study (i) reviewed existing collaboration models, medical literature, and current legal frameworks for multi-country RD data collaboration, (ii) performed interviews with patients/parents and health professionals on their attitudes towards collaboration models, (iii) highlighted legal and practical challenges to integrated multi-country collaboration between centres responsible for treating RD, and (iv) presented the policy options to a total of 11 national competent authorities on healthcare (including members of the Board of Member States (BoMS)), chairs of European Reference Networks (ERNs), or key people in EURORDIS (Rare Diseases Europe) for comments and inputs.

Semi-structured qualitative interviews were performed with patients/parents and health professionals to clarify their viewpoints, including illustrating and qualifying the other parts of the study, such as their views on current organisational structures and potential future collaboration model options. A balanced geographical distribution was ensured between northern, southern, eastern and western EU Member States, as well as a balanced distribution across countries above or below the median population size of EU Member States (i.e. 9.1 million inhabitants). In total, we interviewed a total of 19 patients/families, 15 senior health professionals, all playing a key role in European or national pediatric oncology organisations, and five pediatric oncology trainees.

1 Multi-country ‘ecosystems’ is used to define a network of RD experts that interact intimately to provide RD patients with the needed diagnostic and medical care. In the most extensive ecosystem, the involved healthcare centres work as if being one unit.
All interviewed were in principle in favour of intimate multi-country collaboration between a limited number of specialised childhood cancer centres to promote building of and access to expertise to benefit the individual patients’ healthcare and to facilitate innovation.

Policy options

ERNs and the multi-country collaborative RD ecosystem models described in this report are not competing but rather complementary models. The policies can be regarded as add-ons to the existing ERNs, including their review services, as this will remain available as needed.

Policy options 1-4 could be regarded as extensions to the existing status, and they could potentially be embedded into ERNs and the EHDS once fully implemented, although neither ERNs nor EHDS are specifically structured to encompass deeply integrated multi-country RD healthcare ecosystems. Multi-country RD collaboration models described in policy options 1-4 will in themselves face critical common challenges, which each require specific actions (detailed in the report) relating to legal aspects, language barriers, level of patient involvement and consent processes, cultural barriers, and resources to fund such ecosystems.

Policy option 1 – pseudonymised data sharing with selected experts to improve clinical practice

This option could potentially be covered by ERNs and the EHDS once fully implemented. It promotes sharing RD patients’ pseudonymised healthcare data and would allow named health professionals within a RD ecosystem to routinely access the data. Each update of patients’ pseudonymised health data would require consent that describes the data and purpose of the RD ecosystem, including who would have access to the data, and the purpose of data sharing. For chronic RDs that are not life-threatening, option 1 would cover most of the ecosystem needs. Option 1 differs from the current ERN organisation, since the RD ecosystem models would predefine standards for what type of data will be shared, with whom, and when. The current individual ERNs could be expanded to encompass well-defined RD ecosystems that fall within the disease target of the ERNs. Health professionals within each ecosystem could increase their expertise due to their access to a larger volume of patient data.

Policy option 2 – sharing the complete medical files within a RD data ecosystem to improve clinical practice

This policy is a moderate expansion of policy option 1, but patients/legal guardians give consent to the sharing of their full medical file, albeit pseudonymised, to improve clinical care. Each update of patients’ pseudonymised health data would require consent. This option could potentially be covered by ERNs and the EHDS, once fully implemented, if the consent process included specifications on the involved centres and health professionals.

Policy option 3 – sharing the complete medical file in real-time to improve clinical practice and for individual case discussion

With this option the pseudonymised file is continuously updated in real-time, and patients provides consent only once, typically at the time of diagnosis. Health professionals within an ecosystem would have continued access to the health data and this could improve their experience-based expertise. The attending health professionals could discuss in real-time with other experts within the ecosystem the patients’ acute healthcare issues.
Policy option 4 - sharing real-time medical data with direct access to patients for delivery of care

This is similar to option 3, but the medical data are not pseudonymised. The RD experts within the ecosystem would have access to the full (in practice a secondary) medical file in real-time, and the external experts would be able to interact directly online with patients in a common language or facilitated by a machine translation interface. With respect to machine translation of medical data, the ownership of these data could be contractual and transparently regulated by the EU or national legislation, similar to the structure currently implemented in many Member States that provide their citizens with real-time access to a secondary medical file. The attending physician could participate in such conversations between patients and external experts to ensure transparency of the advice and therapeutic options. Considering the sensitivity of data and the GDPR provisions, there is a special need to safeguard data privacy and security.

Policy option 5 – EU organisation of RD data ecosystems

A central EU body for multi-country RD data ecosystems could function as a facilitating and coordinating structure to the four policy options above. The body’s main tasks would be to develop, guide and supervise infrastructure and standards for RD ecosystems.

Policy option 6 – Funding opportunities for RD data ecosystems

These novel policy options call for joint actions between the EU Commission and Member States to provide resources and funding needed to support five main areas:

- Legal description and EU standards for inter-centre contracts, consent procedures and clarification of ownership of machine translation of medical data
- Standards for data capture, data hosting, data security and data access
- Organisational standards for multi-country RD healthcare ecosystems
- Building, sustaining, and governing of multi-country RD healthcare ecosystems
- Supporting the day-to-day coordinating activities and monitoring of patient outcomes within a RD ecosystem.

The costs associated with the first three are not addressed in this report. With respect to the last two items, funding opportunities will be needed for childhood cancer and other RD healthcare centres to pilot and evaluate multi-country RD healthcare ecosystems. Importantly, the building of such ecosystems may not only reduce health inequalities, including childhood cancer survival rates, within and across Member States, but may actually save both lives and costs by improving the quality of healthcare and reducing the risk of treatment failures, e.g. for childhood cancer, where treatment of relapses is far more costly than first-line therapy.
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<td>AI</td>
<td>Artificial intelligence</td>
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<td>ALL</td>
<td>Acute lymphoblastic leukemia</td>
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<td>BoMS</td>
<td>Board of Member States</td>
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<tr>
<td>CA</td>
<td>Caesarian delivery (C-section)</td>
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<td>CCI</td>
<td>Childhood Cancer International</td>
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<td>CI</td>
<td>Confidence interval</td>
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<td>COST</td>
<td>European Cooperation in Science &amp; Technology</td>
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<td>ECIS</td>
<td>European Cancer Information System</td>
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<td>EDA</td>
<td>European Data Act</td>
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<td>EHDS</td>
<td>European Health Data Space</td>
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<td>EJP RD</td>
<td>European Joint Programme on Rare Diseases</td>
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<td>ENCCA</td>
<td>European Network for Cancer research in Children and Adolescents</td>
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<td>ERA-NET</td>
<td>Research Programme on Rare Diseases (E-RARE)</td>
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<td>ERC</td>
<td>European Research Council</td>
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<td>ERN</td>
<td>European Reference Network</td>
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<td>ERN PaedCan</td>
<td>ERN on paediatric cancer (haemato-oncology)</td>
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<td>EU</td>
<td>European Union</td>
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<td>EUROCAT</td>
<td>European network of population-based registries for the epidemiological surveillance of congenital anomalies</td>
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<td>EUROPLAN</td>
<td>The EU Project for Rare Diseases National Plans Development</td>
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<td>EUORDIS</td>
<td>Rare Diseases Europe</td>
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<td>GDPR</td>
<td>General Data Protection Regulation</td>
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<tr>
<td>GP</td>
<td>General Practitioner</td>
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<tr>
<td>IARC</td>
<td>International Agency for Research in Cancer</td>
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<tr>
<td>OMPR</td>
<td>Orphan Medicinal Products Regulation</td>
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<tr>
<td>RD</td>
<td>Rare Disease</td>
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<tr>
<td>REGI</td>
<td>The EU Committee on Regional Development</td>
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<tr>
<td>SIOP</td>
<td>International Society for Paediatric Oncology</td>
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<tr>
<td>SIOPE</td>
<td>European Branch of the International Society for Paediatric Oncology</td>
</tr>
<tr>
<td>THCS</td>
<td>Transforming health and care system</td>
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1. Introduction

1.1. Rare diseases

By EU definition, a rare disease or condition (RD) occurs in fewer than one in 2,000 citizens. RDs are life-threatening or chronically debilitating diseases with such low prevalence that special combined efforts are needed to address them. Although more than 80% have point prevalence of less than one in a million (Nguengang Wakap, Lambert et al. 2020), a total of 30-35 million people in the EU have a RD, i.e. 6% of the population, and half a million new cases are diagnosed every year (www.eurordis.org).\(^2\) Due to their rarity, there is a backlog in our understanding of RDs’ biology and natural course, including genotype-phenotype variation, a slow recruitment to clinical trials, and uneven distribution of relevant expertise and knowledge, all of which make research scarce and scattered, which slows healthcare improvements. Although mortality rates for RDs in general are falling (Baldovino, Moliner et al. 2016, Gorini, Coi et al. 2021, Botta, Gatta et al. 2022), combined RDs are responsible for 35% of deaths in the first year of life, 20-30% of RD patients do not live past five years of age and, overall, RDs cause more than half of all childhood deaths (Ferreira 2019, Gunne, McGarvey et al. 2020, Botta, Gatta et al. 2022, Santoro, Coi et al. 2022).

Of the 7,000 known RDs, 70-80% are classified as genetic (Ferreira 2019, Nguengang Wakap, Lambert et al. 2020); (Rahit and Tarailo-Graovac 2020, Editorial 2022, Sikonja, Groselj et al. 2022), of which at least two thirds manifest themselves clinically already in childhood, e.g., cystic fibrosis, hemophilia, most inborn errors of metabolism, and childhood cancers. Other RDs are autoimmune diseases, endocrine disorders, and various organ system dysfunctions. RDs differ with respect to their degree of morbidity, mortality, and the psychosocial burden they impose on patients and families (Ferreira 2019, Borrescio-Higa and Valdes 2022, Delaye, Cacciatore et al. 2022, Tsutsui, Ando et al. 2023). Important RD characteristics include whether the disease is:

- present at birth (e.g., most inborn errors of metabolism) versus occurs later in a previously healthy individual (e.g., cancer);
- transient (e.g., a congenital malformation correctable by surgery) versus chronic (e.g., short bowel syndrome);
- stable (e.g., endocrinological disorders requiring life-long hormone replacement) versus progressive (e.g., the premature ageing in Hutchinson-Gilford progeria syndrome);
- associated with moderate to severely reduced or progressive deterioration of cognitive function (e.g., lysosomal storage disease) versus normal cognition (most RDs);
- life-threatening (e.g., cancer or severe organ dysfunction) or not.

Beyond supportive care, only 10% of all RDs are clinically actionable, i.e. established preventive or therapeutic interventions can change the clinical course of the disease. Despite this, the nation-wide neonatal blood spot screening programmes for RDs across Member States vary considerably. Currently only a small fraction of these actionable RDs are included, since only a few have detectable aberrant biomarker levels in neonatal blood spots and the cost of extensive genetic screening has so far been too high (Loeber, Platis et al. 2021, Woerner, Gallagher et al. 2021, Sikonja, Groselj et al. 2022, Lombardo, Seedat et al. 2023). With the advent of next generation sequencing options, it is likely that genomic newborn screening in the near future will be able to identify far more patients.

\(^2\) EURORDIS – Rare Diseases Europe is a non-profit alliance of over 1000 rare disease patient organisations from 74 countries that work together to improve the lives of over 300 million people living with a rare disease globally.
with genetic RDs, and this in turn will call for improved EU healthcare strategies (Ferlini, Gross et al. 2023, Spiekerkoetter, Bick et al. 2023, Stoltze, Hagen et al. 2023).

Figure 1: Trends in mortality in children aged 0-14 years in 11 European Union countries, 1980-2010

Source: WHO Mortality Database, 2012 (taken from Wolfe, Thompson et al. 2013)

Improved socioeconomic conditions, preventive measures such as vaccinations, and better healthcare have led to a marked reduction in overall childhood mortality (please see Figure 1). Although these measures have impacted the quality of diagnostics and treatment, RD survival rates overall lag behind more common medical disorders. As a striking example, outcomes of childhood cancers have changed from being almost universally fatal in the 1960s to current 5-year survival rates above 80% (Botta, Gatta et al. 2022). However, cancer today accounts for 20% of all childhood deaths after infancy, compared to only 11% in the 1960s. This does not reflect an increasing incidence, but merely that the improvement in survival rates has been surpassed by more common medical causes of death, such as infections (Wolfe, Thompson et al. 2013, Gatta, Botta et al. 2014, Botta, Gatta et al. 2022). This has resulted in childhood cancer being the most common medical cause of childhood death after infancy (please see Figure 2).
To tackle these challenges, the EU Commission has initiated multiple legislative and non-legislative initiatives to ease patients' access to expertise in diagnostics and therapy nationally as well as multi-country. These include (i) the EU Project for Rare Diseases National Plans Development, EURPLAN, which has facilitated development of national RD policies across the EU, not least through the EURPLAN National Conferences and a common set of recommendations and indicators for these plans (Taruscio, Gentile et al. 2013); (ii) Directive 2011/24/EU on patients' rights in cross-border healthcare (please see Section 4.2.4), and (iii) the EU Reference Networks (ERNs) (please see Section 4.2.5).

However, building expertise is as important as providing access to existing expertise, and clinical experience is a driving force behind experience-based expertise (Gatta, Botta et al. 2019). Centralising the healthcare of RDs has been a national or regional driver for building expertise at highly specialised, tertiary healthcare facilities. The recent centralisation of all children with cancer in the Netherlands to a single national centre in Utrecht, the Princess Maxima Centrum, is a prototype example of this strategy, now being the largest childhood cancer centre within the EU (van Goudoever 2015). This has clear advantages with respect to building expertise, providing better diagnostics, improving cure rates, and promoting staff recruitment, research and funding opportunities. Yet, given the median size of EU Member States (less than 10 million citizens), centralisation to even one centre per country will, for most RDs, not be sufficient to generate the necessary critical patient volume. Furthermore, political, structural, practical and attitudinal factors, including the travel burden for affected patients and families, makes centralisation challenging within a Member State and virtually impossible across Member States and is generally not regarded as a sustainable solution (Adachi, El-Hattab et al. 2023). The main exceptions are certain complex point interventions, such as proton-beam therapy and early-phase medical trials.

When patient volume is sufficiently high, clinical expertise can be built within a single RD department, since real-time health data are shared openly among the involved health professionals.

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3 ‘When addressing rare diseases, the smaller the evidence base, the greater the opportunity for both patients and professionals to share their expertise based on their collective experience, because experience is the driving force behind new knowledge.’ Citation from Bolz-Johnson, M., T. Kenny, Y. Le Cam and I. Hernando (2021). "Our greatest untapped resource: our patients." J Community Genet 12(2): 241-246.
In contrast, real-time access to patients and health data between RD centres, including transnationally within the EU, is currently impossible due to the absence of the necessary organisational, structural, and legal frameworks, including secure real-time data transfer, data storage, and legal standards for authentication and authorisation for access (please see Section 4.3).

1.2. Inequality in access to RD expertise

Due to uneven health resources, including limited access to the relevant expertise and the newest, high-quality treatment, eastern Europe lags behind other EU Member States, leading to inferior survival rates in RDs (Garne, Stoll et al. 2001, Kole and Faurisson 2010, Botta, Gatta et al. 2022, Sikonja, Groselj et al. 2022). Furthermore, it is challenging for patients to seek healthcare in another Member State due to (i) insufficient information from health professionals on treatment options in another Member State; (ii) diverse government practices, including implementation of a formalised system for prior authorisation of requests for cross-border healthcare; (iii) difficulties faced by health professionals regarding access to the necessary legal expertise on cross-country health-data sharing and patient transfer; and (iv) family burdens, such as language barriers, costs associated with travel, accommodation and the treatment itself, and the obvious lack of relatives or friends to rely on, receive support from, or stay with in cases of cross-border healthcare.

These shortcomings have significant impact on RD morbidity and mortality. For example, in a 2021 publication covering 17 congenital anomalies registries, with data linkage on 115 219 live births with CA, members of EUROCAT demonstrated that 5-year mortality rates varied from less than 3% to almost 13% across European countries (Santoro, Coi et al. 2022). Similarily, an analysis of 135 847 childhood cancer patients (age: 0-14 years) diagnosed between 2000 and 2013 demonstrated significant inequalities among European countries with age-adjusted 5-year survival rates ranging from 71% [95% confidence intervals (CI) 60-79] to 87% [CI 77-93]) (Botta, Gatta et al. 2022).

As highlighted in the WHO CureALL framework for childhood cancer, uneven distribution of health involves unequal quality of diagnostics and professionals’ skills as well as lack of collaboration among healthcare institutions. Likewise, reports from the European Commission and WHO point out that survival data for childhood cancer reveals significant disparities in 5-year survival rates between high-income, middle and low-income countries, with survival differences between countries of 20% or more (Bosetti, Bertuccio et al. 2010, Gatta, Peris-Bonet et al. 2017, Botta, Gatta et al. 2022).

1.3. EU joint actions with Member States

Over time, several stakeholder groups have been brought together by the EU Commission to provide expert advice on actions on RDs across Member States. Since 2018, issues related to RDs have been addressed at EU level by the Steering Group on Health Promotion, Disease Prevention and Management of Non-Communicable Diseases, whilst questions related to ERNs are dealt with by the Board of Member States of the ERNs (BoMS). The multiple EU joint actions that specifically address RD health improvements include the European Joint Programme on Rare Diseases (EJP RD); the Rare2030 foresight study; EURORDIS (Rare Diseases Europe), a non-profit alliance of over 1 000 RD patient organisations; the RD-code project to improve Member States’ gathering of information on RDs; the Orphan medicinal products regulation (please see Section 4.2.6); various RD research

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4 The European network of population-based registries for the epidemiological surveillance of congenital anomalies.
5 This WHO framework document is a ‘how-to’ guide for policy-makers and programme managers to effectively implement the CureAll pillars and enablers with justification for action, priority interventions and a monitoring framework.
activities and programmes: Directive 2011/24/EU that enables patients to be reimbursed for treatment in another EU Member State (please see Section 4.2.4); the European Union (EU) e-Health Action Plan of 2004 to facilitate information-sharing through interoperability in national health IT systems; the EU Health Data Space legislative proposal (please see Section 4.2.3); the EU Genomic Data Infrastructure project building on the Beyond 1 Million Genomes (B1MG) project; setting up and supporting the 24 ERNs (please see Section 4.2.5); the European Cooperation in Science & Technology (COST) networks; and the EU Interreg programme supporting cooperation across borders through project funding to find shared solutions, including in health. However, none of these joint actions specifically aim to facilitate multi-country real-time online access to patients and sharing of health data between RD healthcare centres to provide better healthcare and build expertise within multi-country RD data ecosystems. Similarly the EU Committee on Regional Development (REGI)’s 2021 report on ‘Cross-border cooperation in healthcare’ that recognises the need for multi-country collaboration, but does not address or even mention potential benefits of, or challenges associated with, improving RD healthcare through multi-country collaborative ecosystems.
2. Objectives

The aim of the study is to explore current conditions and propose policy options to facilitate more integrated cooperation between healthcare institutions responsible for treating childhood cancer and other RDs. The study explores the necessary novel organisational collaborative models needed to address the volume issue that challenges building of expertise on RDs. The study also explores the extent to which the current legal framework allows such organisational models within the EU. The study reviews medical and legal literature relevant for the study objectives, conducts interviews with patients/parents and health professionals, and explores health authorities and RD organisations’ and networks’ (including ERNs’) attitudes towards various collaboration models. This includes attitudes to real-time online access to patients and sharing of real-time health data, knowledge and resources between RD healthcare centres as well as potential challenges to such collaboration models.

Representing the most common medical cause of childhood death and being a highly specialised and well organised RD with European guidelines for diagnostics and treatment, childhood cancer is used as a prototype for RDs. The project’s objectives are threefold:

- To review existing cooperation on childhood cancer: Formal and informal cooperation, particularly relevant for subsets with high mortality rates or significantly reduced quality of life;
- To identify barriers to integrated clinical cooperation: Organisational, legal, attitudinal, and financial barriers that impede integrated real-time clinical cooperation and data exchange, as well as staff mobility among childhood cancer centres across multiple EU Member States;
- To propose policy measures for EU cooperation models: Based on the findings in the first two objectives, the study presents options for ongoing and future policy work to facilitate new EU cooperation models that can promote innovative patient-related diagnostics, treatment and follow-up for childhood cancer as a RD prototype.
3. Study methodology

3.1. Medical literature review

In identifying relevant literature concerning in-depth multi-country and/or transregional cooperation to generate volume in childhood cancer, a list of relevant keywords (‘Rare Disease’/‘Childhood OR Paediatric Cancer OR Oncology’/‘Volume’/Collaboration OR Cooperation OR Centralisation’ OR ‘Ecosystem’) was applied to search both scientific and grey literature, including studies and other content made available by both national and international bodies such as the European Parliament and EU Commission (e.g., CORDIS (N=31 reports) as well as its deliverables and publications), and websites linked to ENCCA, ERA-NET, ERN, EURORDIS, Horizon Europe, SIOPE, and WHO. The scientific literature search was subsequently further refined through an iterative process, including limitation to English documents, time period 2003-2023, and primarily targeting cancer in children (please see details of search in Annex III), where references and notes in the identified literature were used to include additional references. In the literature review process, focus was on medical challenges for RDs and the EU legal framework for Member State collaboration on RDs, including both documented and anticipated benefits and drawbacks of centralisation that aims at generating novel expertise through increment in patient volume as well as barriers to accomplishing this. Additional references were identified through advice from medical experts, health authorities and representatives from ERNs and EURORDIS who had participated in interviews. Subsequently we summarized in the study benefits, drawbacks and challenges to in-depth real-time multi-country collaboration models.

Importantly, since multi-country RD primary healthcare ecosystems across EU Member States is currently non-existing, we wrote a narrative review rather than a formal systematic review or meta-analysis, relating to current limitations and potential future collaboration options. Using childhood cancer as the RD prototype, the review focused on diagnostic efficacy; treatment efficiency; toxicities and supportive care.

3.2. Review of existing EU regulatory frameworks

A section reviews the existing regulatory frameworks related to health data sharing, health data protection, online access to patients, including the consent process, and other relevant legal aspects that can impact cross-border cooperation in RD ecosystems, with emphasis on sharing of patients’ health data for primary rather than secondary use, including for research. The study focuses on EU directives and regulations. A thorough and comparative review of national legal frameworks, including interpretation and implementation of EU legislation within and across Member States, is outside the scope of this report. The study addresses the challenges faced by multi-country collaboration on RDs, and necessary adaptations or clarifications of current directives and regulations to facilitate future close multi-country collaboration.

3.3. Interviews with stakeholders

Semi-structured qualitative interviews were performed with patients/parents and health professionals to clarify their viewpoints, including illustrating and qualifying the other parts of the study, such as their views on current organisational collaborative models and potential future collaborative options.
The interviews were all qualitative in their nature. Obtaining the full quantitative picture on how current as well as future more integrated collaboration models across multiple RDs are or would be perceived is beyond the scope of the present study.

The recruitment for semi-strutured qualitative interviews took place in two rounds. In exploring experiences, viewpoints and perceptions among health professionals through the semi-structured interviews, a balanced geographical distribution was ensured between northern, southern, eastern and western EU Member States, as well as a balanced distribution across countries above or below the median population size of EU Member States (i.e. 9.1 million inhabitants).

The preliminary questionnaires were sent to a total of five health professionals or patients/families for comments and subsequently discussed by the study team. Subsequently patient/family questionnaire was tested and discussed with one family to ensure clarity in all questions. In the final round a total number of 39 interviews were conducted according to the criteria listed above following interview guides, which were sent to the participants beforehand (please see Annex I and Annex II). All participants were interviewed online one at a time.

### 3.3.1. Interviews with patients/parents

A total number of 19 patients/parents were interviewed. The interviewed patients/parents were qualified by having or having had a child with the RD in question. The interviewees were unbalanced regarding education, since interviewees predominately held an academic education (parents) or were in the process of attaining one (patients), and English skills were a prerequisite for participating in the interview. The main purpose of the interviews was to gain insight into interviewees’ experiences in cross-country collaboration, their view on structural barriers to sharing real-time healthcare data, as well as their ideas on how to address current challenges, including access to RD expertise and cross-border healthcare.

The patients/parents were recruited by through their attending physician, who was known through already-established contacts.

### 3.3.2. Interviews with health professionals

The senior health professionals were chosen among heads of pediatric oncology units that in addition play a key role in European childhood cancer organisations. The centres were contacted consecutively to ensure a broad representation across EU Member States (north/south/east/west; large/small country size). In total of 18 health care professionals were contacted, of who 15 were interviewed based on (i) their availability and (ii) that their EU region and country size were not already covered. Among those 15 participating, we asked them to identify at least one pediatric oncologists in training from their centre, and a total of five of these were interviewed (again covering north/south/east/west; large/small country size).

A total number of 20 health professionals were interviewed of which five were trainees. The majority of interviewed health professionals were heads of departments within their medical specialty (e.g. childhood cancer). The interviewees were recruited via existing European networks in paediatric oncology (SIOPE and I-BFM) or through relevant ERN networks. The health professionals who were still in clinical training and thus early in their career as paediatric oncologists were identified by the interviewed senior paediatric oncologists. As with the patients/parents interviews, the main purpose of the health professional interviews was to gain insight into their experiences in cross-country collaboration and their view on structural barriers for sharing real-time healthcare data, as well as their ideas on how to address current challenges in these areas.
While the senior health professionals were recruited through already established contacts, trainees were recruited with the assistance of their seniors.

Subsequent to the content analyses of the interviews, identification of current challenges, and potential future avenues, the policy options were presented to a total of 11 national competent authorities on healthcare (including members of the Board of Member States (BoMS)), chairs of individual ERNs and key people in EURORDIS (Rare Diseases Europe) for comments and inputs.

3.3.3. Analyses of interviews

Notwithstanding the premise that qualitative data gathered by semi-structured interviews may neither be fully reproducible nor representative, the study attempted to cover EU Member States broadly, taking into consideration that each interviewee’s country represents specific geopolitical, socioeconomic, and healthcare characteristics.

The analyses of the interviews were performed along the lines of the study’s strategic focus on RD collaboration models addressing the volume challenge and access to expertise within a RD ecosystem. Each recorded interview was transcribed into a word document using an approved transcription tool developed by Viceron and made available by the Capital Region of Denmark (https://transcription.regionh.dk/). Data were then imported in the qualitative research software program NVivo version 14.23.1.38. The subsequent analyses delved into personal experiences and attitudes towards close cross-country collaboration and real-time access to patient files. Special attention was given to the interviewees’ perspectives on the dilemmas concerning data security and patient privacy versus direct access to expertise and the advancement of science, including research, diagnosis and treatment, which was reflected in the questionnaire. The sub-themes offer diverse perspectives and approaches within the main themes. Consequently, the identification of themes followed a deductive approach adhering to the pre-established focus while at the same time allowing novel insights to shape the analytical direction.

Qualitative content analysis was used to identify meaning units, condense meaning units, develop categories, and analyse and compare subthemes and themes (Graneheim and Lundman 2004, Graneheim, Lindgren et al. 2017). This includes four steps in an iterative process moving back and forth between, as well as within, each step, i.e. (i) reading the interviews to obtain overall understanding of content, (ii) identifying meaning units as sentences or paragraphs containing information of interest for the study’s objectives, and (iii) condensing all meaning units and labelling them with categorisation codes. In this process the meaning units were compared for similarities and differences, and then categorised, whereafter each category was re-evaluated and organised into subthemes. Finally, (iv) subthemes were merged into main themes. Coding was primarily on a de facto level, i.e. the study focuses on describing, rather than interpreting, the interviewees’ experiences.
4. Synthesis of the research work and findings

4.1. Medical literature review

As a response to the volume issue, i.e. low numbers of patients regarding RDs, attempts have been made to reduce the number of national childhood cancer centres. Centralisation of all patients with a specific RD to a single healthcare centre has taken place within healthcare regions or full Member States (e.g. Ireland and Holland (van Goudoever 2015)) to improve diagnostics, quality of healthcare, and survival for children with cancer, not least the rarest ones, with retrospective analyses supporting that such centralisations improves survival (Smith, Butler et al. 2004, Ford, Almond et al. 2017, Gatta, Capocaccia et al. 2017, Gatta, Botta et al. 2019, Roy, van Peer et al. 2022, Wijnen and Hulscher 2022). In contrast, the literature on in-depth multi-country collaboration across EU Member States, and even worldwide, is virtually non-existent. Thus, existing literature mainly focuses on patients’ access to specific healthcare services not available in their own country, but made feasible within the EU through Directive 2011/24/EU, including ERNs, rather than building RD, including childhood cancer, ecosystems (Eggermont, Apolone et al. 2019). However, the directive aims at individual patients’ access to existing expertise and healthcare services, rather than reviewing collaborative efforts to build expertise and provide RD patients with access to experts within a multi-country RD ecosystem.

Theoretical drawbacks of regional or national centralisation efforts include those that are known from industrial monopolies such as production inefficiency and insufficient drive for innovation due to lack of competitors. However, since RD healthcare improvements for childhood cancer have mainly been driven by international collaboration and competitiveness, these potential negative aspects of centralisation will not be addressed further in this report.

An obvious drawback of centralisation is the need for patients to travel long distances, away from their home, school, work, family, and friends (Pelletier and Bona 2015, Helms, Schmiegelow et al. 2016, Borrescio-Higa and Valdes 2022, Fujiwara, Ogura et al. 2022, Tsutsui, Andoet al. 2023). Instead, large European or even wider international networks have been established to promote research and run clinical trials (Bolling, Braun-Munzinger et al. 2015, Dome, Graf et al. 2015, Gaspar, Hawkins et al. 2015, Isakoff, Bielack et al. 2015, Olson, Murray et al. 2015, Pui, Yang et al. 2015, Rodriguez-Galindo, Friedrich et al. 2015, Zwaan, Kolb et al. 2015).

However, since the multi-country collaborative options presented in this report do not require centralisation, but rather to build and provide expertise to where the patients primary healthcare centre is located, this aspect will also not be addressed further.

4.1.1. Diagnostic efficacy

‘When you hear hoof beats, think horses, not zebras’ is what medical students and doctors are taught, i.e. focus on the most likely diagnoses, rather than the least likely. However, patients with a RD are the ‘zebras’ in healthcare. Accordingly, the ‘zebras’ often experience diagnostic delays (Foldvari, Szy et al. 2012, Gainotti, Mascalzoni et al. 2018, Benito-Lozano, Arias-Merino et al. 2022).

Nearly all childhood cancers are localised in the inner organs, and their main symptoms are often uncharacteristic, like poor wellbeing, fatigue, nausea, and fever, causing diagnostic delays that vary across Member States (Raab and Gartner 2009, Ahrensberg, Schroder et al. 2012, Verma and Bhattacharya 2020, Pedersen, Erdmann et al. 2021). This may be especially profound when a patient has symptoms easily linked to another disease, such as children with seizures or behavioural
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Although multi-country large-volume RD healthcare ecosystems could potentially be relevant for diagnosing certain RDs that either lack a clear genetic cause or a patognomonic clinical or biochemical markers, the diagnostic delay challenge will in such cases more effectively be addressed through conventional search engines and future use of artificial intelligence (AI) diagnostic platforms, e.g., for facial feature patterns (Qiang, Wu et al. 2022).

Even when a childhood cancer has been diagnosed, the precise genetic, molecular and/or histopathological diagnosis is highly relevant for delivering the correct therapy (Trubicka, Grajkowska et al. 2022). Cancer subtypes differ in their response to therapy, and the precise subgrouping is thus of prognostic significance. This is why nearly all childhood cancer clinical trials have detailed diagnostic standards, including analytical methods, and some even require centralised review of diagnostic biospecimens. Local expertise plays a role in recognising unusual cases that may require additional diagnostic workup. Accordingly, large-volume RD centres may be more likely to recognise patients with unusual cancer subtypes.

4.1.2. Treatment efficacy

In recent reviews exploring the impact of patient volume on survival rates and quality of and radiotherapy for childhood cancer, larger patient volume seems to be associated with better outcomes for brain tumours, acute lymphoblastic leukaemia, osteosarcoma, Ewing’s sarcoma, and children receiving treatment with allogenic bone marrow transplantation (Bakhsheshian, Jin et al. 2016, Bekelis, Connolly et al. 2016, Rolle 2017, Janssens, Timmermann et al. 2019, Shinjo, Matsumoto et al. 2019, Roy, van Peer et al. 2022, Van Schaik, Schouten-van Meeteren et al. 2023, Colori, Ackwerh et al. 2024). Larger patient volume may furthermore accelerate research and promote training of future specialists (Knops, van Dalen et al. 2013, Pritchard-Jones, Pieters et al. 2013, Gatta, Botta et al. 2019, Sikonja, Groselj et al. 2022). However, the reviewed studies were quite heterogeneous regarding design, population sizes and quality. Furthermore, there is a lack of literature directly and quantitatively exploring the effect of centralisation (i.e. pre-/post-centralisation outcome data), and since the impact of centralisation can only be measured after a period of time, such comparative analyses should be adjusted for the general improvement in childhood cancer healthcare and treatment options.

4.1.3. Treatment efficiency

Paediatric oncology is a highly specialised RD undertaking. The majority of patients/parents are offered and consent to inclusion in clinical trials with standardised diagnostic procedures, anticancer therapy, response monitoring, timeline and duration of treatment phases, and, to a certain degree, also supportive care. Accordingly, all children that participate in such a trial should experience the same treatment efficiency. However, inferior survival in low-volume centres has been associated with delays in certain critical treatment components, such as local radiotherapy (Lin, Ludmir et al. 2019). Furthermore, children with side effects may require treatment adaptation, and the ability to ensure high treatment intensity can reduce the risk of relapse (Schmiegelow, Nersting et al. 2016, Albertsen, Grell et al. 2019, Gupta, Wang et al. 2020).

4.1.4. Toxicities and supportive care

While anticancer treatment for the most part is standardised, this is almost never the case for supportive care nor acute toxicities and decisions on re-exposure, if a specific anticancer agent or
surgical procedure is suspected to have caused the toxicity. This reflects in part that each of the acute treatment-related toxicities, except opportunistic infections, are rare, and this compromises the building of experience and research on individual toxicities. This is critical since 20% of all childhood cancer death are due to treatment-related toxicities (Loeffen, Knops et al. 2019). In a recent analysis of 14 serious, treatment-related toxic effects across 15 international study groups dealing with childhood acute lymphoblastic leukaemia (ALL; 25% of all childhood cancers), no two protocols shared identical definitions of all toxic effects, and no definition of a toxic effect was shared by all protocols (Schmiegelow, Attarbaschi et al. 2016). Since 50% of all deaths among children with ALL are caused by toxicities, rather than progressive leukemia, international standards and exchange of expertise on supportive care and handling of acute toxicity could contribute to increased survival of childhood cancer.

4.2. Existing EU regulatory frameworks

4.2.1. Introduction

Each EU Member State is responsible for organising and delivering healthcare services to its citizens, while the EU provides complementary health policies to improve efficacy and efficiency in healthcare. In addition, the EU promotes preparedness, response and research for cross-border health threats, as highlighted during the COVID pandemic. These coordinating activities and the facilitation of cross-border healthcare are direct consequences of the free movement of people and goods in the internal market.

This review addresses the legal requirements and obligations arising from data protection laws and regulations, most notably the GDPR, the EU Health Data Space (EHDS), and Directive 2011/24/EU on patients’ rights in cross-border healthcare. The Orphan Medicinal Products Regulation (OMPR) will be discussed only briefly, since it is not directly relevant for the multi-country collaboration models that are the objective of this study.

The overview relates to:

- involvement of EU experts in the treatment of a patient with a RD (primary use of patient data);
- health professionals’ access to data from patients with a RD at another centre (in the form of reading health data and/or direct patient contact) to optimise healthcare for those patients;
- health professionals’ access to data from patients with a RD (in the form of reading health data), even when not directly involved in treatment of those patients, in order to optimise healthcare for their own patients, i.e. building of expertise;
- access to patient data for research purposes.

Currently, no piece of EU directives or regulations specifically aims to facilitate close, real-time multi-country cooperation between RD centre to increase patient volume and thus build clinical expertise. Such collaborative efforts have so far been restricted by the lack of an EU-wide secure technical platform that facilitates sharing of sensitive health data and by each Member State having their own unique regulatory framework for healthcare and sharing of health data.

4.2.2. General Data Protection Regulation (GDPR)

The GDPR directive has provided clear requirements for health data sharing within the EU, but GDPR has been implemented very heterogeneously across Member States, which has restricted the extent of sharing of health data. Importantly, publications on its consequences has almost exclusively
addressed its influence on secondary use of data for research purposes rather than primary use for improvements in healthcare (Williams 2018, Eiss 2020, Molnar-Gabor, Sellner et al. 2022, Vassal, Lazarov et al. 2022, Lawlor 2023)

Closer, multi-country cooperation between hospitals treating RDs within the EU could generate larger volume of patient data accessible to the individual RD centres and their health professionals to facilitate building of expertise, provide patients with access to a wider group of RD professionals, and promote health research and innovation. The objective for such cooperation would be that a requesting and receiving health centre in country/region A can access data from a providing health centre in country/region B.

Since the patient data exchanged within such a cooperation is extremely sensitive, sharing must be in line with the GDPR’s notion of processing. According to Article 4 GDPR, processing involves: ‘any operation or set of operations which is performed on personal data or on sets of personal data, whether or not by automated means, such as collection, recording, organisation, structuring, storage, adaptation or alteration, retrieval, consultation, use, disclosure by transmission, dissemination or otherwise making available, alignment or combination, restriction, erasure or destruction’.

For a RD healthcare centre to access patient data from another healthcare centre, it is necessary for the providing hospital to transmit the patient data. The GDPR should always be applied, even if the requesting hospital only reads the data.

According to Article 5 GDPR, personal data must be:
- processed lawfully, fairly and in a transparent manner in relation to the data subject (‘lawfulness, fairness and transparency’);
- collected for specified, explicit and legitimate purposes and not further processed in a manner that is incompatible with those purposes;
- adequate, relevant and limited to what is necessary in relation to the purposes for which they are processed (‘data minimisation’);
- accurate and, when necessary, kept up to date; every reasonable step must be taken to ensure that personal data that are inaccurate, are processed, are erased or rectified without delay (‘accuracy’);
- kept in a form which permits identification of data subjects for no longer than necessary for processing personal data; personal data can be stored for longer periods insofar as it is of public interest, scientific or historical, research or statistical purposes in accordance with Article 89(1) GDPR (‘storage limitation’);
- processed in a manner that ensures appropriate security of the personal data, including protection against unauthorised or unlawful processing and against accidental loss, destruction or damage, using appropriate technical or organisational measures (‘integrity and confidentiality’).

Such multi-country collaboration could include a general EU legal standard, including a contract between the involved RD centres, as well as a technical structure that ensures data security.

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8 Article 5, Regulation (EU) 2016/679 of the European Parliament and of the of the 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation).
The rights of patients and the obligations of data processors do not, in principle, preclude cooperation between hospitals, even transnationally, but place specific requirements on the data processing.

According to Article 4(15) GDPR, health data includes all ‘personal data related to the physical or mental health of a natural person, including the provision of healthcare services, which reveal information about his or her health status’. When health centres work together, a wide variety of data are processed, such as anamnesis, clinical examinations, biochemical tests and images, all of which are defined as health data according to GDPR. This is critical because health data, as a special category of personal data under Article 9 GDPR, is subject to particularly high requirements for protection and lawfulness.

In a multi-country/regional RD ecosystem data are processed by both the providing and the requesting hospital, and both are subject to lawfulness standards.

**Lawfulness of the processing by the providing (primary) hospital**

In principle, the providing hospital should be authorised to process patient data based on various authorisations (e.g., patient consent). If arrangements have been made for an external health professional to be involved in the treatment of a particular patient, whether in the form of an advisory consultation or a virtual visit, the patient must be informed of this as part of the consent process. In accordance with data protection law, it is relatively unproblematic for health professionals from other EU countries to provide advice based on the provision of patient data or even become part of the treatment team, provided the patient consent and the data transfer are secure. However, since the external health professional can be regarded as indirectly participating in the treatment, the issue of liability must be addressed in the contract between the collaborating RD healthcare centres.

**Lawfulness of processing by the requesting hospital**

The requesting hospital, as the secondary processor of the data, is also required to obtain authorisation to process the data. Even reading patient data constitutes a processing operation and consent would be required according to Article 9(2)a GDPR.

The GDPR imposes several obligations on data processors to protect personal data. Such obligations cannot always be fulfilled within a RD ecosystem models. As an example, patients have the right to withdraw consent at any time. The consequence of withdrawal should, in principle, be that data processing cannot continue. However, data may already have been used at the time of withdrawal and may have found their way into other data sets. Thus, it would be necessary to introduce a provision in the contract between the RD centres, where it is clarified that if the requesting healthcare centre no longer has access to the primary data in the event of consent withdrawal, that data can continue to be processed in an anonymised form.

It is worth noting that all centres in a RD ecosystem should comply with Member State legislation for every country involved in that ecosystem. Obtaining consent is only possible for the health centre providing the data, but the requesting hospital, which also processes the data, is not subject

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*Article 4 No. 15, Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation)*
to this standard of lawfulness. Importantly, the building of such ecosystems would not require an amendment of the GDPR.

Article 9 GDPR generally prohibits the processing of health data, unless there is an exceptional reason, such as:

- Consent, Article 9(2)a
- Processing for labour law reasons, Article 9(2)b
- Protection of vital interests, Article 9(2)c
- Processing by a foundation, association or non-profit organisation, Article 9(2)d
- Publicly accessible data, Article 9(2)e
- Assertion/defence of legal claims, Article 9(2)f
- Processing for reasons of substantial public interest, Article 9(2)g
- Processing for the purposes of healthcare and preventive healthcare, Article 9(2)h
- Processing for reasons of public interest in the area of public health, Article 9(2)i
- Archiving purposes, scientific or historical research purposes, statistical purposes, Article 9(2)j.

In accordance with the objectives of this study, the following four exceptions from Article 9 GDPR can be considered:

- Consent, Article 9(2)a
- Processing for the purposes of healthcare, including preventive healthcare, Article 9(2)h
- Processing based on public interest in the area of public health, Article 9(2)i
- Archiving purposes, scientific or historical research purposes, statistical purposes, Article 9(2)j.

**Consent** according to Article 9(2)a GDPR is 'any freely given, specific, informed and unambiguous indication of patients' wishes by which he or she, by a statement or by a clear affirmative action, signifies agreement to the processing of personal data relating to him or her'. Consent can be obtained if patients are informed about the purpose for which the data is processed, who is responsible for the data processing, and consent has been given voluntarily (requirements arise from Article 7 and Article 4(11) GDPR). Thus, patients are free to decide whom their data is passed on to. In the case of multi-country collaborative RD ecosystems, the providing healthcare centre must specify exactly to whom the data is transmitted, who has access to it, and what the purpose of the data transmission is. When clarified, access may be given to groups of health professionals at the receiving healthcare institution(s), with the purpose of comparing similar patients’ data as well as to optimise, build expertise, train and research within specific RDs.

According to Article 7(3) GDPR, consent can withdraw it at any time. Up to the point of withdrawal, completed data processing remains unaffected but further processing is no longer permitted from the time of withdrawal.

**Processing with the purpose of healthcare** is permitted according to Article 9(2)h GDPR if ‘processing is necessary for the purposes of preventive or occupational medicine, for the assessment of the working capacity of the employee, medical diagnosis, the provision of health or social care or treatment or the management of health or social care systems and services on the basis of Union or public interest in the area of public health, or for archiving purposes, scientific or historical research purposes, statistical purposes’.
Member State law or pursuant to contract with a health professional and subject to the conditions and safeguards referred to in paragraph 3.\textsuperscript{11}

This notion of necessity is only a valid justification if the processing operation (optimal diagnostics or treatment) cannot otherwise be fulfilled. However, since some standard of diagnostics and/or treatment will be available, processing of health data with the sole purpose of promoting healthcare or training in broad terms cannot justify health data sharing without informed consent from the patients (or parents or legal guardians). Thus, this exception from Article 9 GDPR cannot be considered in the building of multi-country RD ecosystems.

\textbf{Processing based on public interest} according to Article 9(2)i GDPR is justified ‘for reasons of public interest in the areas of public health without consent of the data subject.’\textsuperscript{12} Taking into account the number of EU healthcare centres involved, it can be argued that the balancing of interests must be in favour of the patient and that public interest must be subordinated. Thus, this exception from Article 9 GDPR cannot be considered in the building of multi-country RD ecosystems.

\textbf{Research purposes}, as defined in Article 9(2)j GDPR, can only be applied as a legitimate purpose for health data sharing within a RD ecosystem, when such research is specified, has been approved by national competent authorities, and is based on consent, although some Member States allow data without consent if the data are fully anonymised. Thus, the treating hospital cannot obtain a general consent to share health data from patients in favour of the requesting and receiving hospital for the purpose of unspecified potential future research. Obtaining such consent for potential future research purposes is also problematic, since at the time consent is obtained, it is not definitively known whether the hospital will ever collect the data of the consenting patient for the purpose of potential future research. The declaration of consent would therefore be too vague and excessive. In addition, centres belonging to the RD ecosystem, that were not yet part of the study at the time consent was given, would be excluded from access. Thus, this exception from Article 9 GDPR cannot be considered in the building of multi-country RD ecosystems.

\subsection*{4.2.3. EU Health Data Space}

On 3 May 2022, the EU Commission published a proposal for a new regulation on the \textit{EU Health Data Space} (EHDS), promoting healthcare interoperability and patient empowerment. The regulation was needed, since existing legislation and voluntary measures had proven ineffective in providing a functioning infrastructure for health data storage and sharing at EU level. On March 2024, political agreement was reached on EHDS between the European Parliament and the Council.

To overcome legal, interoperability and data quality obstacles, the EHDS contains rules for both primary use of health data (to provide health services to an individual) and secondary use of health data (for health research and product development). The proposal also establishes common rules, including obligations on standards, such as electronic health records systems, to ensure interoperability.

The Explanatory Memorandum accompanying the EHDS proposal states that ‘the EHDS will help to improve understanding, prevention, early detection, diagnosis, treatment and monitoring of cancer, through the EU cross-border secure access and sharing between healthcare providers, including

\begin{footnotesize}
\textsuperscript{11} Article 9 (2) (h), Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation).

\textsuperscript{12} Recital 54 of the GDPR.
\end{footnotesize}
cancer related data of natural persons. Therefore, by providing secure access to a wide range of electronic health data, the EHDS will open new opportunities for diseases prevention and treatment of natural persons.’

Importantly, with respect to the present study, the EHDS would be without prejudice to other Union legal acts, in particular Article 1 GDPR regarding electronic health data.

The focus of the EHDS has been on (i) empowering individuals to digital access to their electronic personal health data, (ii) establishing a single market for electronic health record systems, and (iii) secondary use, including for research.

The EHDS provides new rights of and standards for data portability for primary use\(^\text{13}\) of health data. Article 3(8) in the Commission’s EHDS proposal gives an individual ‘the right to give access to or request a data holder from the health or social security sector to transmit their electronic health data to a data recipient of their choice, immediately, free of charge and without hindrance from the data holder or from the manufacturer of the systems used by that holder.’\(^\text{14}\)

This new far-reaching right to data portability could be a relevant basis for health-data sharing within a multi-country RD ecosystem. The EHDS proposal stresses the need for timely access to shared data, and an absolute right to access another healthcare provider’s system to promote the treatment of RDS would be a necessity for multi-country RD health ecosystems to operate.

**Access by health professionals to personal electronic health data**

Article 4(1) in the Commission’s EHDS proposal states that health professionals shall ‘have access to the electronic health data of natural persons under their treatment, irrespective of the Member State of affiliation and the Member State of treatment.’

If a patient with a RD is considered ‘under their treatment’ by a health professional participating in the clinical cooperation, that professional has a right to access the medical file. Combined with the patient’s right to portability described in the previous section, this article provides an avenue for extensive clinical cooperation.

The European Parliament’s amendment 128 to the EHDS regulatory proposal states that health professionals may ‘a) have access, based on the data minimisation and purpose limitation principles, to the electronic health data of natural persons under their treatment and exclusively for the purpose of that treatment’.

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\(^{13}\) Primary use of electronic health data means ‘the processing of personal electronic health data for the provision of health services to assess, maintain or restore the state of health of the natural person to whom that data relates, including the prescription, dispensation and provision of medicinal products and medical devices, as well as for relevant social security, administrative or reimbursement services’ (Article 2.2 d).

\(^{14}\) Recital 12 states: ‘Natural persons should be able to exercise control over the transmission of personal electronic health data to other healthcare providers. Healthcare providers and other organisations providing EHRs should facilitate the exercise of this right. Stakeholders such as healthcare providers, digital health service providers, manufacturers of EHR systems or medical devices should not limit or block the exercise of the right of portability because of the use of proprietary standards or other measures taken to limit the portability.’
Directive 2011/24/EU defines ‘Member State of treatment’ as the Member State on whose territory healthcare is provided. In the case of telemedicine, this relates to where the health professionals are affiliated.\(^{15}\)

Being ‘under their treatment’ implies a legal responsibility of the health professionals. However, given development of multi-country collaboration models for RDs, such liability is unrealistic. Health professionals taking part in a cooperation to assess patients with RDs in another Member State would have the right to access the medical file for that purpose. However, in terms of the liability issue, providing expert guidance in real-time is not specifically addressed in the EHDS regulation. Furthermore, the proposal does not provide any right to access transferred health data to treat other patients for the purpose of building expertise. Although some Member States already give health professionals such a right to health data access for treating other patients, there is currently no plan for harmonising this across Member States.

### Secondary use of health data

According to Article 33 of the EHDS, the notion of secondary use\(^{16}\) refers to a minimum category of electronic data that shall be made available, e.g., for research purposes as well as for assessing, maintaining or restoring the state of health of individuals based on the health data of other individuals (Article 34(1)h EHDS).

Moreover, Chapter IV of the EHDS reads that Member States shall establish bodies responsible for making health data available for secondary use, deciding on applications for secondary use of health data as well as processing such data in secure environments and facilitating cross-border data sharing.

In conclusion, the proposed system for secondary use provides an avenue forward for some parts of the data sharing necessary for multi-country integrated RD ecosystems. However, this will require establishment of national data-sharing bodies and structures that facilitate such access to medical files based on EU standards.

#### 4.2.4. Directive on patients’ rights in cross-border healthcare

The 2011/24/EU Directive aims to secure that personal data can flow from one Member State to another: ‘Ensuring continuity of cross-border healthcare depends on transfer of personal data concerning patients’ health. These personal data should be able to flow from one Member State to another, but at the same time the fundamental rights of the individuals should be safeguarded.’

The Directive has also framed the data sharing taking place within the ERNs (please see Section 4.2.5). In addition to the hurdles arising when dealing with different national and/or regional data systems and approaches, the external treatment provider is unable to directly access the patient’s medical file in real-time. Consequently, the provider will neither be able to (i) observe and directly

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\(^{15}\) The European Parliament has added an obligation for Member States to establish rules providing for the categories of personal electronic health data required by different categories of health professions or different healthcare tasks. Such rules shall not be based on the source of electronic health data (Article 4.2). The Parliament’s version of the proposal also states: ‘In the case of treatment in a Member State other than the Member State of affiliation, the rules referred to in paragraphs 1a and 2 of the Member States of treatment shall apply’ (Article 4.2 a). However, these proposed changes do not address the ‘under their treatment’ concept discussed here.

\(^{16}\) Secondary use of electronic health data means ‘the processing of electronic health data for purposes set out in Chapter IV of this Regulation. The data used may include personal electronic health data initially collected in the context of primary use, but also electronic health data collected for the purpose of the secondary use.’
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influence the treatment, nor (ii) monitor the efficacy and toxicity of the treatment after the patient has returned to the country of origin.

EHDS facilitates cross-border access to healthcare for the individual patient but does not directly address integrated multi-country centre collaboration. It remains uncertain whether the 2011/24/EU Directive on the application of patients’ rights in cross border healthcare fully covers this avenue or whether a positive obligation for such specific purpose should be added.

Transfer of health data would continue to follow all EU regulation safeguarding data protection. This includes Article 8 of the European Convention on Human Rights, which secures patients’ right to informed consent in relation to data-processing and sharing.

The EHDS specifically mentions RDs in several Articles, particularly supporting diagnosis and treatment. Article 12 Directive 2011/24 highlights the importance of the Commission’s support to Member States for the development of centres of expertise, in particular within the area of RDs. However, even though the directive is applicable for RD ecosystems, the directive is too general with regard to developing novel organisational collaborative models for multi-country RD ecosystems.

4.2.5. European Reference Networks

The ERNs, such as the paediatric oncology reference network ERN PaedCan, have been a significant step forward in addressing RD challenges and promoting high-quality, cost-effective care across the EU Member States for complex and rare diseases. So far, 24 ERNs are working on a range of medical disorders and more can be added based on specific criteria and procedures.

ERNs are virtual networks connecting healthcare providers, health professionals and patients across the EU. They tackle complex or rare diseases and conditions which require highly specialised treatment and a pooling of knowledge and resources. ERNs enable patients and doctors across the EU to access the best expertise and timely exchange life-saving knowledge without having to travel to another country. The networks facilitate sharing the latest knowledge and experience to member hospitals, researchers, and patient groups. They offer healthcare providers throughout the EU the possibility to request, review and seek advice on an individual patient’s diagnosis and treatment through virtual advisory panels of medical specialists using a dedicated IT platform and telemedicine tools.

In addition to the provision of second opinions on specific individual patients’ diagnostics and therapeutic options, the ERNs facilitate data sharing and collaborative research (Zurek, Ellwanger et al. 2021), and build RD registries, provide educational activities, including webinars and training courses, and outreach programmes. ERNs also develop and disseminate European standards of clinical practice (ESCP) to contribute to more uniform and improved healthcare.

From a legal perspective, ERNs are framed by Directive 2011/24/EU on patients’ rights in cross-border healthcare as well as by the Commission’s Delegated Decision defining the criteria and conditions to be fulfilled and the Commission’s Implementing Decision defining criteria for establishing and evaluating ERNs. The BoMS, composed by representatives from EU Members plus Norway, is in charge of overseeing the activities of the ERNs.

Although the ERN platform has proven to be a major step forward to address healthcare inequality across and within Member States, it also faces several challenges, including insufficient participation and funding as well as unequal regulatory harmonisation across Member States, all of which influence governance, sustainability and quality (Tumiene, Graessner et al. 2021, White,
Wagner et al. 2022). These factors also limit the wider application of ERN structures to close multi-country RD healthcare ecosystem models as presented in this report (please see Section 6).

4.2.6. Other EU regulations relevant for RDs

Other EU regulations are relevant for improving healthcare for RDs, but as they do not directly relate to the objectives of this study, i.e. integrated real-time collaboration in day-to-day clinical care, we do not address them in detail. Amongst others they include:

- **Pharmaceutical legislation**: On November 25, 2020, the EU adopted a new pharmaceutical strategy. On April 26, 2023, the European Commission submitted two proposals for new legislation regarding pharmaceuticals; a new directive and a new regulation set to repeal the current EU general pharmaceutical legislation, including the The Orphan Medicinal Products Regulation (OMPR).\(^{17}\) The OMPR, as it currently stands, provides incentives to the pharmaceutical industry to promote research and production of orphan medicinal products in accordance with the OMPR. It does not explicitly deal with cross-border cooperation in relation to RDs, and it is unclear whether multi-country collaborative models for RDs may be regarded by the pharmaceutical industry as beneficial in their development and clinical testing of orphan medicinal products, including basic research investment. Parts of the new proposed legislation deal specifically with medicines for RDs, which has previously been addressed in the OMPR. With the new legislation, the duration of market exclusivity for RDs is proposed to be nine years, which is longer than the proposed exclusivity for other medicinal products. Manufacturers of medicines for RDs will also have access to a longer duration of exclusivity, if they meet certain criteria, such as launching the medicine in all Member States. With the proposed merging of the legislation, medicines for RDs will continue to adhere to specific requirements to support their development.\(^ {17} \) Whether and how the proposed amendments to the EU Pharmaceutical legislation will affect multi-country collaboration models as described in this report is currently unclear.

- **The European Data Act** (EDA) sets up rules on who can use and access what data for which purposes across sectors in the EU. The scope of the EDA is currently focused on industrial data collected through connected products, such as data generated through smart objects, machines, and devices. Health data and medical data are currently only collected through digital devices (like phones and smart watches) to a very limited extent, and the EDA fails to address sharing of health data generated at hospitals and other healthcare institutions, including for research purposes.

4.3. Analysis of interviews with stakeholders

4.3.1. Interviews with families/patients

All of the interviewed parents had higher levels of education, most of them holding a university degree. This can be attributed in part to the interview criteria, as English skills were a prerequisite for inclusion. There is diversity in the interviewees’ or their children’s current medical statuses, ranging from a majority having been cured by first line anticancer therapy to some still receiving treatment or having had a relapse, and a few having experienced the loss of a child. However, no obvious correlation was identified between specific attitudes and the current medical condition of the child with cancer.

All interviewees were parents of patients with childhood cancer or patients themselves, except for a parent to a child with an inborn *de novo* genetic bone disorder that leads to short limb dwarfism and non-progressive moderate muscle weakness, who received therapy outside the home country. In contrast to the concern for full recovery among the cancer group, this parent was primarily preoccupied with the long-term quality of life.

The analytical themes are categorised into two sections:

- A segment delving into individual experiences with physicians both before and after receiving the diagnosis, seeking second opinion, engaging external expertise and participating in organisations associated with the specific disease/condition (please see Figure 3). This section aligns with the initial part of the questionnaire that explores personal matters and individual experiences (please see Annex I);
- A segment dedicated to attitudes regarding intimate cross-country collaboration (please see Figure 4), corresponding to the final section of the questionnaire that concentrates on the study's focus on such close collaboration (please see Annex I).

Participants in general were positive about close collaboration and multi-country sharing of medical files and direct patient contact. Despite a lack of substantial variation in these responses, the detailed inquiry into this aspect allowed for the emergence of nuanced perspectives and elaboration.

While the analysis centers on the pre-defined focus as outlined in the interview guide, the sub-theme *self-initiative* emerged as a recurring topic spontaneously introduced by the interviewees, warranting its inclusion although not directly relating to the main theme. The analysis draws from the analytical themes although it does not slavishly follow their chronological structure.

**Characteristics of interviewees**

Number: 19  
Sex F/M: 10/9  
Patients: 9  
Parents: 10  
Long (academic) education: 10  
Disease cancer/Short limb dwarfism: 18/1  
Medical status recovered/under treatment/chronic/deceased: 12/3/2/2  
Countries: Bulgaria; Croatia; Czechia; Denmark; Germany; Greece; Hungary; Ireland; Italy; Latvia; Lithuania; Spain; Sweden.

**ANALYSIS**

**Experiences with health professionals**

What stands out throughout the interviews is a univocal trust in the primary attending RD physician and the health professional team responsible for the treatment. The expression of confidence includes (i) recognition of the affiliated treatment centre as the best place to be treated, (ii) emphasis on the treating physician's knowledge and expertise, and (iii) stating full trust in the physician's ability to take the right decisions. As stated by some of the interviewees:

‘[We] decided to rely completely on our doctor in [name of treatment centre]’;

‘With the core team of oncologists the relationship was fantastic… I saw how they fought for my daughter, looking for new treatment’;
‘In [name of treatment city] we had perfect doctors’;

‘I adore our doctor. She did her best and is still doing it. And I believe her. She is like a second mother to my son. She helped me a lot, even with my psychological condition…my emotions’.

The confidence in the health professionals was independent of the outcome of treatment, as it was expressed equally by those who lost their child and those being or having a child alive and well. Moreover, parents were not critical towards the child’s primary RD physician, even when they were actually reporting negative situations, treatment outcomes, and experiences.

Several parents reported delays or negative outcomes while the child’s primary specialist was away from the hospital. When describing not being able to understand complex diagnostic information, a parent blamed her own anxiety rather than her child’s primary attending physician’s ability to communicate information in a manner she could understand. Other parents described negative experiences from hospital clinicians who were not part of the child’s primary care team. However, even in these cases, parents were eager to remove blame for anything from their primary specialist, underscoring that their child’s primary specialists were doing the best they could.

Figure 3: Analytical themes vis-à-vis interviewees’ characteristics and experiences

While taking into consideration that selection bias may occur as some of the interviewees were recruited directly by their/their child’s attending physician, it is worth noting that the positive attitude extended to doctors abroad specialised in the RD of the patient in question.

In comparison with attitudes towards specialised teams and doctors, such as paediatric oncologists, interviewees exhibited less trust in their general practitioner (GP). Several interviewees gave examples of diagnostic or treatment delays due to incompetence on the part of the GPs or practicing paediatricians. Examples include GPs playing down symptoms as being normal or related to diet,
age, and the like, and doctors not being able to come up with a correct diagnosis but instead providing medicine that was not helpful.

Figure 4: Analytical themes vis-à-vis collaboration

Treatment abroad/second opinion

Certain parents would team up with carefully chosen experts from abroad, forwarding their child’s medical files in anticipation of obtaining a second, potentially more positive, opinion about their child’s condition. In specific instances, these collaborative endeavours between parents and experts were structured in a way that involved volunteer parents assisting other parents.

Parents described how carefully they navigated bringing information that they found on their own to their child’s attending physician. Some would emphasise the need to address extra-medical treatment, such as physiotherapy or speech therapy. Others had gained information about a clinical trial abroad they wanted their child to participate in and explained how diplomatic persistence enabled an opening for their child.

Self-initiative

Some interviewees were active in relevant parent organisations by being directly employed, contributing financially or participating in summer retreats. Active engagement by parents was primarily motivated by a wish to help fellow parents in similar situations to navigate complex medical grounds, to share information about specific experts, and to share personal experiences about the RD in question.

A theme that stands out is self-initiative, i.e. the various ways in which parents themselves took initiative to seek alternative treatment or second opinions. Participants had themselves shared information amongst other parents but data sharing at one’s own initiative extended to doctors, e.g., providing information from fellow parents to RD specialists in the hopes of improving diagnosis and treatment of their child. Self-initiative was especially accentuated in relation to treatment for side effects. As one interviewee explained, the focus on strictly medical issues, such a blood results and the like, left little room to discuss the non-medical issues. Moreover, in cases where curative treatment was not available, parents took extreme measures to find alternative solutions. As an interviewee with a child with a rare cancer explains:

‘I was desperate. Looking for other families, something that could help my [child].’
It is worth noting that, in most cases, the attending physician was informed about the alternative solutions sought by the parents and in many cases also involved in connecting the families with experts in other countries. A parent with a child with a very rare, incurable cancer started following international research and debate, latest progress and the like, and provided the attending physician with such information.

**Pros and cons of multi-country collaboration**

Unanimous support was expressed for a collaboration model with real-time data sharing, provided it contributes to improved diagnosis or treatment. This stance is illustrated in many statements, such as:

‘It is very, very important that doctors share real-time information’;

‘I 100% agree [to such data sharing].’

Almost all participants not only favoured collaboration in a general sense but also sharing data about their own child:

‘There is no dilemma at all. I mean, I haven’t met any family who were not willing to share data from their own child in order to get the best treatment, or at least better treatment, or in order for the research to advance, not for your own child but for the future’.

Several parents expressed surprise that such cross-country real-time data sharing was not already happening and that barriers existed to such collaboration. The parent of a child who died because of a serious infection stated that she had expected that doctors were already sharing real-time information on their own. Another parent commented:

‘I never thought before this is a problem, until you asked me this question.’

Another parent, whose child died, stated that interregional data sharing was not only beneficial, but that it should be compulsory at least between EU Member States.

However, one parent specifically mentioned worries about data storage and misuse, including commercial exploitation of data.

The positive attitude towards real-time cross-country collaboration was notably influenced by the seriousness and rarity of the RD in question. While patient interviewees generally favoured multi-country collaboration, but provided limited elaboration, parents overwhelmingly expressed a strong positive stance.

On the other hand, most patients emphasised that improving treatment ought to be the paramount reason for data sharing. Thus, when asked about sharing information that was more non-medical and private, such as psychological and socio-economic issues, some concerns were expressed, and emphasis was placed on such information’s relevance to medical treatment and and the interviewees’ trust in their attending physician:

‘No, I would not. As long as it benefits treatment or diagnosis, as long as it’s for medical reasons…’

‘I’m not probably informed enough to say [...] what are the consequences of this use, because I would assume it can be used in many different ways.’

‘[...] that cannot be relevant for [the daughter’s] disease. Everything that is not relevant [...] to how to treat her, how a doctor could treat her [...]’

Especially intimate information about the family’s income or psychological issues was, for some, regarded as problematic to share:
‘I don’t want them to know [about] my personal life, but maybe my medical stuff. Not my family’s […] economic situation.’

‘I think [the] parents’ income is fine, but [that they have] talked to a psychologist…it shouldn’t be [shared]. Focus [needs to] be about how to help you better.’

Thus, in evaluating the balance between data security on one hand, and full access to information about selected patients’ individual medical files and history on the other, interviewees predominantly leaned towards the latter.

Four prominent themes emerged in favour of multi-country collaboration regarding real-time data:

• A volume theme that relates to the rarity of RDs and the necessity to share as much information as possible. An interviewee explained: ‘More knowledge, more people, more opinions. It is definitely better to share information.’

• A life-and-death theme that relates to personal experiences of how data sharing was crucial for one’s own or one’s child’s survival. A parent whose child suffered from an incurable cancer and who started looking into relevant research and clinical advancement, but found none, stated:
  ‘My family suffered directly due to lack of research and lack of sharing information about [name of the cancer].’

• A theme of altruism relating to the argument that helping future patients was a key reason for data sharing.

• Finally, a future advancement theme with a hope that close data-sharing may help advance research and clinical practice of relevance to future patients. As was expressed by an interviewee:
  ‘[data sharing] is very important in order to advance in research; I believe that more information from different countries will be the key to finding a solution.’

Collaboration barriers

Presented with issues relating to language or cultural barriers as well as incompatible eHealth systems among Member States, none of the interviewees were preoccupied with these matters. Some interviewees emphasised the commonality of the English language and the potential use of translation tools. None expressed concern that other countries’ health professionals would lack expertise or that specific countries would offer low quality of treatment or the necessary data security. The interviewees did not have strong opinions about how many doctors were to have access to the sensitive real-time medical data, nor how many countries were to be involved.

Concern about potential data misuse was raised by a few participants, one of whom supported sharing of medical data, but not non-medical information. Another, in favour of real-time information sharing, expressed concerns about the duration of data retention and usage:

  ‘The problem is not real-time data. The problem is how long you keep the data afterwards, at least if not anonymised.’

Data security was mentioned as a concern by some interviewees, although not as an issue regarding the interviewees’ affiliated healthcare centre but as a more general concern about whether data might be misused later once they were shared with others.

Conclusion: The survey reflects a favourable attitude among the childhood cancer families towards multi-country collaboration with access to real-time data aimed at improving RD diagnosis and treatment. Confidence in RD specialists played a pivotal role in shaping these attitudes. Nevertheless, some expressed concern about data security and misuse, as issues to be solved, while keeping the overarching goal of advancing medical knowledge and improving patient outcomes. Four sub-themes supported intimate multi-country collaborative models, namely need for patient volume, altruism, the life-and-death situation, and future advancements.
4.3.2. Interviews with RD health professionals

The analysis is divided into a descriptive part, which focuses on the interviewees’ self-evaluation of their own and other centres, and a part emphasising the interviewees’ normative stands on close collaboration and real-time access to health data.

All interviewees were physicians, most of them being seniors specialised in childhood cancer and less than one third being trainees undergoing specialisation. As with the patient/parent interviews, the aim was to gain insight into individual experiences with collaboration and data sharing and extract opinions on real-time access to data, here with an emphasis on clinical experience.

The analytical themes were categorised into two sections:

• A section delving into personal clinical experience and characteristics of the interviewees’ healthcare centre (please see Figure 5). This section corresponds with the first part of the questionnaire and questions in the second part concerning centre characteristics of the interviewees’ affiliated health centre (please see Annex I).

• A section delving into the interviewees’ personal views on close collaboration and data sharing based on clinical expertise (please see Figure 6). This section aligns primarily with the second part of the questionnaire (please see Annex I).

The analysis draws from the analytical themes, although it does not slavishly follow their chronological structure.

Interviewees characteristics

Total number: 20
Seniors/trainees: 15/5 (Austria; Czechia; Denmark; Germany; Spain)
Sex F/M: 9/11
Countries: Austria; Bulgaria; Czechia; Denmark; Finland; Germany; Greece; Hungary; Ireland; Italy; Lithuania; Netherlands; Poland; Spain.

ANALYSIS

Centre characteristics

Interviewees were affiliated to centres exhibiting diverse patient capacities, ranging from handling 15 to 20 new childhood cancer patients at one extreme to managing more than 600 new patients annually at the other extreme. The most prevalent capacity falls within the range of 50 and 200 newly diagnosed childhood cancer patients per year.

The variance in a centre’s patient capacity appeared to influence the interviewees’ perception of the centre’s level of expertise as it was argued that correlation was rooted in exposure to a wide spectrum of diagnoses, toxicities, and complex cases. Nevertheless, interviewees unanimously argued that the exposure at the local centre (regardless of size) cannot sufficiently cover the experience needed to gain specialised knowledge for all childhood cancer subtypes or treatment-related toxicities. Particularly when dealing with exceedingly rare cases and medical conditions as well as specific toxicity profiles, it was argued that close national and multi-country collaboration with fellow specialists is necessary.
Existing centre collaboration

The interviewees in general emphasised the existence of well-established collaboration among European childhood cancer specialists, with a focus on the existing clinical trials networks. They expressed familiarity with fellow experts, citing already established contacts and networks. Sometimes the collaboration had a format in which a less resourceful centre would have an informal, but preferred, collaboration with a more resourceful centre in the same country or in a neighbouring country.

One type of collaboration involved the transfer of patients with specific complications to other EU countries when the required treatment was unavailable in the home country. When patient transfers do take place, it generally encompasses various complex and less widespread interventions such as proton treatment, liver transplants, cellular immune therapy, and clinical phase 1 and phase 2 trials. On average, each centre facilitated the transfer of approximately 1 to 2 patients per year, influenced by factors such as centre size, economic resources including healthcare insurance structures, established practices, and the randomness of the occurrence of patients with specific needs. The destinations for these patients varied. While neighbouring countries were a common choice, several centres had established a dedicated contact with a receiving centre offering specific services or they became part of a trial that enabled patients to access experimental treatments.

However, transferring patients may entail a financial burden on the affected families, as therapy not formally approved by the European Medicines Agency, e.g., phase 1 and phase 2 treatment, may not be covered by their healthcare/insurance systems. Families could also be required to cover non-medical expenses, including accommodation, transportation, and related costs, thus often having to collect money through charity or crowdfunding. Furthermore, some interviewed health professionals were reluctant to refer patients to treatment abroad, and favored more resources allocated to better national and regional infrastructures that promoted collaborative efforts and a better use of existing expertise in the healthcare region or home country.
Another form of collaboration involved reaching out to other specialists for a second opinion. This was either initiated at the request of the patients themselves or by the attending physician, particularly in cases involving treatment resistance, toxicities or other complexities. Some centres had a formalised procedure that provides patients with a second opinion, especially when standard treatment options were not available. However, while patients requesting a second opinion were generally accommodated and welcomed, the process rarely resulted in a change of the established treatment.

**Data security**

Although data security was not listed as an unmanageable and prohibiting limitation for multi-country RD healthcare ecosystems, it was highlighted to be of paramount significance. Some interviewees expressed general concerns about variations in the countries’ capacity to ensure data security. While such concerns were emphasised as potential impediments to close collaboration, there was a prevailing argument that fostering close collaboration could actually mitigate such differences. This proposition ultimately hinged on confidence, as one interviewee said:

‘You trust that your fellow physicians will treat data as you yourself treat data.’

Interviewees also underscored how existing EU legislation, including the diversity across Member States, may pose challenges to clinical interactions, real-time data exchange, and scientific endeavours. The repercussions of stringent legal barriers include barriers to data sharing, fragmentation of data, and impediments to research. An interviewee articulated that the current excessive emphasis on data protection has become a problem, stating:

‘There’s a lot of emphasis on data protection, but it impedes and slows down research and knowledge sharing, especially on non-invasive research. It’s a nightmare. And I would like to see and hear all the examples of misuse of medical data. Why do we put so much attention on this issue?’

Several patients/parents and health professionals stated that they do not want to share data that are not clearly needed for medical purposes (things like economic status, religion, psychological issues), whereas others were willing to share everything in the medical file that potentially could be of value to the medical handling of the child.
The process of seeking a second opinion typically relied on tapping into an existing network of experts, but in some instances specialists were contacted based on their recognised expertise as evidenced by publications and their professional standing.

A third facet of collaboration involved engagement with well-established expert networks, nationally or internationally, such as the clinical trial committees or ERN. Additionally, all the senior health professionals participated in informal networks, be they regional, national, or transnational in nature. These networks were often the result of years of collaborative efforts and mutual cooperation.
Finally, a fourth dimension of collaboration could involve the exchange of junior physicians as an important component of their specialisation and providing a structure for strengthening the collaborative models based on an on-site acquisition of knowledge of the collaborative centre’s expertise. Most of the senior interviewees had spent months to years abroad in another RD healthcare centre to gain expertise.

Irrespective of the format, the bedrock of the existing collaboration rested on trust among colleagues, forged over years of collaboration, and recognised expertise within specific domains.

**Pros and cons of multi-country collaboration**

Interviewees consistently asserted that, with respect to the most prevalent childhood cancers, centres adhere to treatment protocols that have been developed through years or even decades of centre networks (i.e. clinical trial groups) nationally, within the EU, or in a wider international context. Nevertheless, interviewees highlighted discernible differences in technological capabilities (relevant for diagnostics), availability of multidisciplinary teams (relevant for complex diseases), and institutional practices on supportive care (relevant for preventing or mitigating toxicities).

Some centres in southern Europe had not yet embraced electronic health systems and thus relied on the manual completion of medical files for documentation. Additionally, in some eastern and southern European countries, there was a lag in updating certain hospital equipment and the ability to deal with toxicities induced by the treatment.

Furthermore, some centres in southern and eastern Europe did not provide coverage for travel expenses incurred by health professionals attending conferences and medical forums abroad.

Consensus among interviewees emphasised that promoting close multi-country collaboration through RD healthcare ecosystems would significantly improve diagnostics and treatment of childhood cancers, given the accompanying increase in data volume. The anticipated benefits included improved cure and survival rates, access to advanced technology from other countries, complementary research, expanded opportunities for collaboration with pharmaceutical industries facilitating drug testing, and more generally generating synergistic effects. As highlighted by an interviewee:

‘The more cases of toxicities one is exposed to, the more it will increase your expertise… Numbers always provide you with expertise in all cases.’

On the other hand, some interviewees emphasized the need for exchange of patients and medical data locally rather than at an EU-level.

‘I believe that we have to offer […] the best organisation regarding children in general. And […] in that case, if we, this kind of specialisation and expertise are concentrated, we […] acquired […] we’ll have more expertise day by day instead of having spread all over the region.’

Regarding attitudes towards centres being part of a RD healthcare ecosystem, some emphasised that such a construct would only be meaningful on a Europe-wide scale if small or medium-sized centres were involved in collaboration rather than only the current largest and most experienced centres. When asked to specify the number of centres to be included, most argued for a maximum of ten, expressing concerns that a too large number of centres would lead to significant management and logistical challenges.
Real-time data access

Regarding the expansion of RD healthcare ecosystems to provide health professionals with real-time access to patient files from outside centres, some interviewees expressed scepticism, arguing that such access to data only might not be necessary, given the current alternative forms of data exchange. However, several interviewees emphasised the value of patients direct engagement with the attending health professionals. As put by an interviewee:

‘Without seeing real patients and real people, this [kind of] collaboration would be of partial utility.’

Others stressed the necessity for the attending physician at least to be present alongside the outside physician during online access to a patient, underscoring that patients have developed trust explicitly with their attending physician.

While interviewees generally concurred that both the attending physician and the outside physician would derive advantages from real-time access, there were variations in opinions. Many stressed the necessity to share all data without limitation in alignment with patient attitudes. As an interviewee stated:

‘I have yet to meet a family who will not allow us to share [medical] information with other doctors.’

Other interviewees advocated partial real-time data access, and this primarily related to the question of obtaining access to strictly non-medical information. Some invoked the concept of patient protection, asserting that issues of a more sensitive nature, such as psychological or economic issues, should remain private. A distinct viewpoint centred on patient consent, proposing that access to non-medical information should be consistent with the attitudes of individual patients and parents.

Successful multi-country collaboration models

Based on the interviewees’ perspectives, several prerequisites were highlighted that must be met for a successful multi-country RD healthcare ecosystem.

Some expressed that the initial imperative would be to enable close collaboration between centres within a Member State, since this is currently lacking. Subsequently, the progression would involve establishing multi-country RD healthcare ecosystems. Others stressed the necessity for the EU, at supranational level, to develop standards for multi-country collaboration. This included harmonisation and standardisation of data storage, centralised access controlled by an EU administrative body, the integration of AI for real-time translation both of medical data and during direct online patient contacts, and the formulation of procedures to address disparities in data access and data infrastructure among centres.

Confronted with three versions of how to improve multi-country collaboration – the first in which patient consent is obtained followed by granting full access to all data by the named health professionals working in the multi-country RD ecosystem, the second in which access is restricted to certain rare cases, cases with a certain toxicological profile and other complicated cases, and the third version allowing ad-hoc access with patient consent required each time – all patients/families and all but two health professionals preferred the first and the second versions. Irrespective of the specific collaborative models of the RD healthcare ecosystem. It was emphasised that patient consent was the most important and primary prerequisite.
**Conclusion:** Regardless of centre size, interviewees argued that exposure to data outside their own centre was necessary for health professionals to gain the required clinical experience necessary to build expertise. Interviewees emphasised that a well-established collaboration among European childhood cancer specialists already exists. Trust among colleagues, cultivated through years or decades of collaboration and recognised expertise, emerged as a fundamental element.

Whilst standard treatment protocols for prevalent childhood cancers were generally followed, variations were noted in technological capabilities, access to medical subspecialities and multidisciplinary teams, and institutional practices, particularly concerning diagnostics, complex diseases, and handling toxicities as well as with regards to intensity of treatment and security. While some viewed these issues as obstacles to close collaboration, most argued that fostering close collaboration could, in fact, diminish such differences.

Regardless of geographical disparities, all interviewees believed that promoting close multi-country collaboration through RD healthcare ecosystems could significantly enhance diagnostics and treatment quality through increased data volume. Benefits include access to advanced technology and diagnostics, complementary research, collaboration with pharmaceutical industries, synergistic effects in expertise, staff recruitment, and, most importantly, improved cure rates. However, for some interviewees, emphasis was placed on the need for local health development and exchange of patients and of medical information within national boarders.

Although the issue was not addressed in all interviews, those interviewees that did address it stressed the necessity for the EU, at supranational level, to develop standards for intimate multi-country RD collaboration.
5. Conclusions

Key EU initiatives to improve healthcare for RDs across Member States, including Directive 2011/24/EU on patients’ rights in cross-border healthcare, ERNs and the EHDS legislative proposal, have provided patients with options for review of diagnosis and provision of relevant treatment. They all rely on existing expertise, diagnostics, and therapies. However, of all RDs for which the molecular cause is known, less than ten percent have an approved treatment. In pediatric oncology, prevention and treatment of relapses and serious treatment-related toxicities remain key challenges. Across the board, both RD patients and health professionals favour cross-country collaboration models providing experts within the collaboration real-time access to patients and their health data to promote clinical experience and research for deeper understanding of the underlying biology and developing better diagnostics and treatment, and thus build the expertise presently not available. Importantly, such multi-country collaborative models does not require changes to the current EU legal framework, specifically the GPDR. The real obstacles to building such cross-country RD ecosystems are of national legal nature rather than attitudinal or organisational, and the presented policy options could address several current RD healthcare shortcomings (please see Section 6 and Table 1):

• **Equity for patients:** The 2011 Directive on Patients’ Rights in Cross-border Healthcare sets out a framework that allows patients from one Member State to obtain healthcare in another Member State with or without prior authorisation. However, not all Member States have a formalised system for prior authorisation of requests for cross-border healthcare. In 2021, the total amount reimbursed for cross-border healthcare constituted less than 0.02 % of the total government expenditure on patient healthcare. What proportion of this expenditure is associated with RDs is not known. Of the more than 20 000 newly diagnosed children with cancer in the EU every year (data from Cancer Today Database, ECIS and IARC), 10-25 % die from their disease or treatment, albeit with significant differences between Member States, and two thirds of survivors live with long-term side effects, but few of these are referred to ERN PaedCan.

• **Electronic medical records:** A prerequisite for multi-country RD ecosystems is electronic medical records. Although these have not been fully and comprehensively implemented throughout the Member States, this will change due to the European Health Data Space (EHDS) regulation. To which extent and by which means sharing of medical data for primary or secondary use will actually take place in the EHDS is currently unclear.

• **Extent of data sharing:** Automated real-time creation of secondary health records for patients to access their own health data is implemented in many Member States (or healthcare regions) where electronic medical records are in place. This may include notes by health professionals, biochemical results, descriptions of images, etc. The timeline for full implementation of such collaborative models throughout the EU and the timeframes for uploading medical records within the EHDS are unclear. Furthermore, standards for the secondary medical files, reflecting the needs in a specific multi-country RD ecosystem, have yet to be developed, as do the standards for consent-based updating.

• **Real-time secure data access:** Real-time data is not a prerequisite for the current ERNs, and the infrastructure allowing real-time access to health data is described in the EHDS proposal. A fully developed, multi-country RD ecosystem would require a data warehouse structure that ensures encryption, secure data transfer, authentication and authorisation for access. Moreover, it would require a data hosting facility with the necessary legal and technical measures that ensure patient data can be securely uploaded, protected, and accessed (please see policy option 4 for real-time data access). The EHDS will not be based on a single point of data collection, but rather an infrastructure which allows data access from various points. It is unclear, how the subsequent data integration, as relevant for RD ecosystems, could function. RD ecosystems will require adaptations...
of the national legal frameworks as well as manageable, local strategies for automated transfer of healthcare data to a RD ecosystem within the EHDS.

- **Duration of data storage:** In ERNs, data are shared through a secure electronic information platform, the Clinical Patient Management System, that allows health professionals to enroll patients and collaborate actively within an ERN and potentially across ERNs. Unless specific consent is given, e.g., for research, data cannot be stored within an ERN registry for potential future use. In contrast, a multi-country RD ecosystem requires medical files to be stored for as long as needed for access by the involved ecosystem professionals and for quality monitoring of the RD centres’ performance.

- **Direct patient-expert interaction:** Direct patient contact is in principle possible within the ERN system, if the patient has consented and only for the purpose of (i) the patient becoming part of a research initiative, or (ii) an ERN expert needing further information to recommend management of the patient. This could be expanded in future RD healthcare ecosystems.

- **Purpose:** The primary purpose of a multi-country RD ecosystem is to improve clinical care through (i) growth of clinical expertise and (ii) direct and transparent access to the larger network of RD experts within the ecosystem, both for health professionals and patients. If multi-country RD ecosystems are built, monitoring of quality within (and between) the ecosystem(s) will also become important. Monitoring patient outcomes across the involved ecosystem centres could include predefined quality indicators, such as survival, organ functions, quality of life etc., as well as monitoring of compliance with predefined diagnostics and treatment pathways.

- **Equality of partners in a network:** Today, there are obvious differences in the healthcare provided across and within the EU Member States, as reflected in survival rates of the most serious RDs. Furthermore, not all Member States currently participate in all the ERNs. In future RD ecosystems, involved centres would not be divided into those that provide expertise and those that request expertise (e.g. through ERN), as both health professionals and patients could interact with and have access to all the expertise available within the ecosystem. Currently, some RD centres are approved as having the necessary expertise to become ERN members, whereas others are potential users of ERN. In future multi-country RD ecosystem models, the involved centres should formally have equal opportunities to engage in and establish multi-country RD ecosystems. Potential centre inequality during the setting up of the ecosystems (as centres vary in size, expertise and specialisation) should be considered relating to what each centre can provide and some basic requirements for participation such as commitment to the collaborative efforts, expertise, and research. This could be addressed as part of EU funding strategies and procedures, including basic requirements for centre accreditation for becoming members of an ecosystem.

- **Network size:** The current requirement for building an ERN is inclusion of at least ten health professionals from at least eight different EU Member States. Although derogation from these limits may be needed in a RD ecosystem models, there will be exclusivity, since it is unrealistic and impractical to have a high number of closely collaborating centres due to the need for inter-centre contracts, transparency, knowledge of relevant staff members by professionals and patients/legal guardians, etc.

- **Consent:** Depending on the collaboration model and extent of multi-country RD ecosystems, the implications of consent could be described in far more detail than is the case in the current ERN system, since patients/legal guardians consent to participate in a network of named RD healthcare centres rather than addressing a specific healthcare issue.
<table>
<thead>
<tr>
<th></th>
<th>ERN</th>
<th>Potential multi-country RD collaborative ecosystem</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Exclusivity</strong></td>
<td>Can include &gt;50 centres and must include at least ten highly specialised healthcare units from at least eight different Member States.</td>
<td>Close collaboration would limit the number of centres. Ten healthcare centres from eight Member States may be unrealistic.</td>
<td>If a derogation is included in the 2011/24/EU Directive on patients’ rights in cross-border healthcare, exclusivity would be possible.</td>
</tr>
<tr>
<td><strong>Equity</strong></td>
<td>ERNs bring together highly specialised healthcare units to whom a complicated case can be referred by clinicians for second opinion or advice. All patients treated in any EU country plus Norway may benefit from the ERNs’ virtual expert advice in equal terms.</td>
<td>RD ecosystem centres have equal rights, and collaboration is based on exchange of expertise.</td>
<td>Some centres would have more expertise than others, reflecting capacity, experience and international networks. To avoid uneven access to the ecosystems among EU centres, funding could take into consideration requirements to ensure equal access to building ecosystems.</td>
</tr>
<tr>
<td><strong>Real-time data flow</strong></td>
<td>Less relevant, although real-time transmission is legally possible by a telephone or video call.</td>
<td>Essential for the most integrated RD ecosystems.</td>
<td>To enable real-time access, technical and security measures could be provided to ensure patient data to be uploaded and accessed in real-time.</td>
</tr>
<tr>
<td><strong>Consent</strong></td>
<td>Consent to sharing of data is given for the virtual expert panel discussions and for research purposes.</td>
<td>Consent is given to participate in a RD ecosystem, similar to current consenting to treatment in a particular healthcare facility without providing any further information.</td>
<td>Legally, there is no discrepancy, but the implications of the consent could be described in more detail than current ERN consent forms.</td>
</tr>
<tr>
<td><strong>Time-line</strong></td>
<td>Access to patient data is limited in time in order to fulfil a specific task in the healthcare system, but data can be stored longer, e.g., for research purposes.</td>
<td>Health professionals have continuous access as long as the collaboration exists, unless patients opt out.</td>
<td>According to the GDPR, it is necessary to continuously check whether data is still required to fulfil the purpose. If data is no longer required, it must be deleted in accordance with the GDPR.</td>
</tr>
<tr>
<td><strong>Purpose</strong></td>
<td>To improve healthcare, diagnostics and treatment in relation to specific diseases/subdiagnoses, e.g., through second opinions for individual patients, which can include data sharing, telephone or video calls. Data can also be shared for research purposes after obtained consent for this.</td>
<td>To improve healthcare by allowing health professionals to be exposed to more RD data without a preconceived purpose, thereby accelerating and improving diagnosis and treatment.</td>
<td>The purposes of ERNs and the RD ecosystems are in principle similar, although the depth of collaboration, the patient volume issue and the building of expertise at the individual RD healthcare centre is more specific for the ecosystems.</td>
</tr>
<tr>
<td><strong>Volume</strong></td>
<td>Volume is not the target for the ERNs’ virtual expert panels, that are meant to discuss the most complex cases. Volume is an issue for the ERN registries.</td>
<td>Volume in itself is a key target for RD ecosystems, cf. the above.</td>
<td>Legally, there is no formal difference between the two systems.</td>
</tr>
<tr>
<td><strong>Patient contact</strong></td>
<td>Patients cannot self-refer to request second opinions or advice from the ERNs’ virtual expert panels. Pseudonymisation within the ERNs poses a problem for direct contact.</td>
<td>Promotes direct patient contact or at least real-time access to the patient files, both in order to provide better healthcare and increase expertise</td>
<td>In Annex IV of Commission Implementing Decision (EU) 2019/1269 of 26 July 2019, specific requirements for consent are formulated, allowing direct contact. It could be added that a network members, based on consent, could make direct patient contact, including access to the patient health file.</td>
</tr>
</tbody>
</table>
6. Policy options

ERNs and multi-country collaboration models are not competing collaboration models but rather complementary platforms to address RD health challenges. ERNs are top-down expertise networks, whereas multi-country RD collaboration models could (i) disseminate knowledge and ensure implementation of clinical guidelines emerging from ERNs to the individual RD healthcare centres, and (ii) offer bottom-up close collaboration. The RD ecosystems could at all levels strengthen networking among RD patients/legal guardians and among healthcare providers and researchers, thus providing an innovative integrated healthcare framework that may function as an alternative to the centralisation efforts that so far have characterised RD healthcare in spite of its practical burden on patients and families, and furthermore is insufficient for many RDs as patient numbers are too low even within a whole country.

To address current barriers for multi-country RD healthcare collaboration, we suggest six policy options in addition to the current ‘baseline’ case, i.e. option 0. Policy options 1-4 represent various levels of multi-country integration in RD ecosystems and the extent of health data access, and are thus hierarchical, each having a wider mission.

Even if multi-country RD ecosystems can facilitate building of expertise, policy option 1-4 will not necessarily address and solve inequality in healthcare between Member States. Although well-established ecosystems may include more centres, the organisational requirements will put a natural limit to their size. If only the patients treated in certain centres participating in the ecosystems would benefit, this could potentially exacerbate existing inequities in health outcomes. The requirements put forward to provide funding for the RD ecosystems could mitigate the risk of such inequity (please see Policy option 6). Furthermore, the impact on equity could be part of the health outcome monitoring of ecosystems.

Finally, as the policies can be regarded as a complementary add-on to the existing ERNs, including their review services, such as case discussion and consultation, these services will still remain available to any patient who would need them.

Policy option 0 - the current status

The current baseline scenario reflects the EU’s recognition of RD health and healthcare challenges, including that expertise is scarce and scattered across Member States. A few shortcomings have been mitigated by (i) the 2011 Directive on Patients’ Rights in Cross-border Healthcare; (ii) e-Health strategies to facilitate information sharing through interoperability in national health IT systems and to provide rules for the establishment, management and functioning of a voluntary network that connects national authorities responsible for eHealth; and (iii) the EHDS regulatory proposal for hosting and sharing of health data, and the ERNs to provide RD patients with access to ERN expertise to facilitate data sharing and collaborative research, build RD registries, promote educational activities and outreach programmes as well as develop common diagnostic and treatment guidelines to contribute to more uniform and improved healthcare. However, all these joint actions to some extent (although not exclusively) address access to existing expertise but do not solve the patient volume problem, i.e. building clinical expertise in quality and efficacy of diagnostics and treatment.

Policy options 1-4 can all be regarded as extensions to the existing status. Multi-country RD collaboration models could benefit from being organised as a complementary collaboration model to the current ERN system but options 1-4 will in themselves face critical common challenges, which include:

• Legal aspects: Current Member State legislation on data protection prevents an external healthcare centre or health professional from directly accessing and reading patient data, even if
the purpose is to assist or supervise diagnostics and/or treatment. On the other hand, the Directive on the application of patients’ rights in cross-border healthcare allows for flexibility and the EHDS could enable a secure and legally feasible standard. As outlined in section 4.2, the close collaboration in a RD ecosystem will face diversities in the national regulations for healthcare and health research. Obtaining harmonisation will be complex and time-consuming, but although healthcare formally is a national responsibility, the EU plays a clear role in complementing national policies. This role could be crucial for standardisation in data collection, structure, uploading, hosting, and sharing. Other legal challenges, not addressed in detail in this report, include clarification of intellectual property rights emerging from research and novel diagnostics and treatments within the ecosystems. Finally, detailed multi-lateral contract standards, including addressing responsibilities and liability issues, are needed between RD centres involved in an ecosystem.

• Language barriers: In terms of direct communication between health professionals and patients, understanding is critical. Although machine translation is useful, subtle differences in the understanding of meaning can be critical, and data ownership needs clarification. This most likely will necessitate the presence of the attending health professionals in any contact between patients and external health professionals, which, although resource-demanding, could promote the building of expertise.

• Patient involvement: Although patients can be involved in the current ERNs, multi-country RD collaboration models will call for a much deeper engagement of patients, as the RD ecosystems are likely to develop new standards and goals in patient care and research prioritisation. Standards for efficient and secure machine translation could allow patients and professionals to interact in their native tongue; help multi-country networks of patients and families to share experiences and express needs; and provide patients with a stronger voice in relation to regulators. This could prove beneficial, not least for the very low prevalence RDs, where each RD centre today may have only one or a few patients.

• Patient consent: Due to the extent of data sharing and external health professionals’ access to medical records, the informed consent process and the detail of information on the ecosystem, the involved centres, and their staff’s expertise will call for far more transparency and clarity than the current generic ERN consent forms. The health centres providing patient data could obtain consent at the time of diagnosis or start of treatment. The treating health centre could obtain consent from the patient in favour of a central body that manages data and enables other RD centres in the ecosystem (approved by the patient in the consent process) to access the data. The generic consent could cover the usual protection information (name and contact details of the controller, contact details of the data protection officer), purposes of data processing, legal basis for data processing, recipients of the personal data etc., storage time period, and right of access (Article 15 GDPR), right to rectification (Article 16 GDPR), right to erasure (Article 17 GDPR), right to restriction of processing (Article 18 GDPR), right to data portability (Article 20 GDPR), right to object (Article 21 GDPR), consequences of revocation, detailed description of categories of data, and sources from which the data originate.

• Cultural barriers: Healthcare has developed from specific historical, cultural, socio-economic and political traditions and it reflects population sizes and resources. Accordingly, it differs between Member States. ERNs do not directly address underlying differences in healthcare systems across Member States, but this may become more of a challenge with multi-country RD collaboration models. As healthcare in RDs is less evidence-based compared to more common medical disorders, and thus can differ markedly within and between Member States, multi-country RD ecosystems might face conflicts between diverse local medical standards. Of note, the ecosystems themselves could also provide a path to address these health inequalities across Member States.

• Coordination and governance: If RD ecosystems are to become a successful alternative to RD centralisation, the coordination of data and access to expertise across Member States (including
training and educational activities, staff exchanges, transparency on research programmes, etc) will require robust governance structures with the necessary insight into centre and national healthcare diversities, experience with and structures for conflict resolution, prioritisation of activities, and harmonisation efforts. Both for the individual Member State and at EU level, local and multi-country organisational experiences emerging from the first piloted ecosystems would need to be compiled and structured. The existing BoMS could expand their activities to include the RD ecosystems.

- Resources (please see Policy option 6): The establishment and continuation of RD collaboration models would require resources to address and mitigate the challenges above, which include an extra layer of facilitators and coordinators at each centre. Initially, these resources are unlikely to be allocated by the involved centres and joint efforts between the European Commission and the Member States would be needed to provide the necessary legal, technical, and organisational structures as well as funding for the day-to-day RD ecosystem coordination and patient outcome monitoring.

**Policy option 1 – pseudonymised data sharing with selected experts to improve clinical practice**

This option could potentially be covered by ERNs and the EHDS once fully implemented, and aspects of it is currently being explored, e.g., by the Rare Kidney Disease Reference Network and others (Kodra, Weinbach et al. 2018). Policy option 1 promotes sharing RD patients’ pseudonymised healthcare data and would allow named health professionals within a RD ecosystem to routinely access the data. Data are restricted in type (text excerpt, biochemical results, images etc) and in time (selected time period). Each update of patients’ pseudonymised health data would require consent that describes the data and purpose of the RD ecosystem, including who would have access to the data, and the purpose of data sharing, since broad consent may be acceptable in the frame of GDPR when targeting research, but unapplicable for primary and broad clinical purposes (Hallinan 2020).

The main difference from the current ERN system, is that data will be shared for all patients or medical issues that fulfil preset criteria. For chronic RDs that are not life-threatening, option 1 would cover most of the ecosystem needs. Option 1 differs from the current ERN organisation, since the RD ecosystem models would predefine standards for what type of data will be shared, with whom, and when. The current individual ERNs could be expanded to encompass well-defined RD ecosystems that fall within the disease target of the ERN. Accordingly, an ERN would include not one, but rather multiple ecosystems across the EU, each with a limited number of healthcare centres. Health professionals within each ecosystem would increase their expertise due to their access to a larger volume of patient data. Other efforts for building expertise within an ecosystem, such as staff recruitment strategies, clinical training and collaborative research, could be added.

**Required action:**

- All centres in a RD healthcare ecosystem would need to comply with the regulations of every country involved in that ecosystem. Obtaining consent is only possible for the health centre providing the data, but the requesting hospital, which also processes the data, is not subject to this standard of lawfulness. Thus, there would be a need for introduction of a legal standard at national level. This would require that Member States voluntarily or through an EU obligation adjust their national legislation to multi-country ecosystems. Importantly, the building of such ecosystems would not require an amendment of the GDPR.
Policy option 2 – sharing the complete medical files within a RD data ecosystem to improve clinical practice

This policy is a moderate expansion of policy option 1, but patients/legal guardians give consent to the sharing of their full medical file, albeit pseudonymised, to improve clinical care. Each update of patients’ pseudonymised health data would require consent that describes the data and purpose of the RD ecosystem. This option could potentially be covered by ERNs and the EHDS, once fully implemented, if the consent process included specifications on the involved RD centres and named health professionals within the individual RD ecosystem that can access the health data.

Required action:

• The consent form should include a section explaining that, by signing the form, patients/legal guardians give consent for named health professionals within the ecosystem to access their full (i.e. secondary) medical file (please see the above).

Policy option 3 – sharing the complete medical file in real-time to improve clinical practice and for individual case discussion

With this option, the pseudonymised file is continuously updated in real-time. Contrary to options 1 and 2, the patient provides consent only once (which of course can be retracted whenever the patient/legal guardians wishes to do so), typically at the time of diagnosis. The health professionals within an ecosystem would continuously have access to the health data, which could improve their clinical expertise. Additionally, this option would allow the attending health professionals to discuss in real-time with other experts within the ecosystem the patients’ acute healthcare issues that require immediate action.

Required additional action:

• Infrastructure for real-time data sharing: A secure data warehouse structure with the possibility to share real-time data. Currently, ERNs have a secure data structure network that ensures data encryption and secure transfer and hosting, authentication and authorisation for data access, but it is not built for continuous real-time data update and access, which is the main goal for option 3. Organising real-time health data update and access would include standards for pseudonymisation of data. Moreover, a section in the consent form should make the notion of ‘continuous sharing’ explicit, informing patients that sharing of their medical files involves any data additions as long as the ecosystem operates.

• Patient data should be collected and managed by a specialised central body, i.e. a legal entity, ensuring that the experience and specific solutions to consent procedures and documents, contracts between participating healthcare institutions and data hosting facilities are compiled to benefit both existing and future multi-country RD ecosystems. This could in principle be a legal healthcare entity in a Member State or an EU authority embedded in the ERN system and EHDS. This central body would be responsible for managing and complying along the lines of EU and national data protection requirements, in particular technical and organisational requirements, and it would be the central body for the collection of all information on the RD patients in question.

• In order to enable real-time access – such that the patient data managed by the central body corresponds at all times to the primary health data collected at the patients’ healthcare centre or centres – a technical option should be created to automatically update the data extract at the central body whenever changes are made to the original patient file. Such a system has already been established in several EU Member States to allow patient to access their secondary medical file in real-time.
Policy option 4 - sharing real-time medical data with direct access to patients for delivery of care

This is similar to option 3, but the medical data are not pseudonymised. The RD experts within the ecosystem would have access to the full (in practice a secondary) medical file in real-time and the external experts would be able to interact directly online with patients in a common language or facilitated by a machine translation interface, when both the patient/legal guardians and the RD institution (through the ecosystem contract) have consented to/approved this. With respect to machine translation of medical data, the ownership of these data could be contractual and transparently regulated by the EU or national legislation, similar to the structure currently implemented in many Member States that provide their citizens with real-time access to a secondary medical file. The attending physician should always participate in such conversations/interviews between patients and external experts to ensure transparency of the advice and therapeutic options, and the attending physician could then be responsible for adding the relevant summary notes in the patient’s medical file. Considering the sensitivity of data and the GDPR provisions, there is a need to safeguard data privacy and security. The ERNs’ way of establishing direct contact between patients and a larger group of physicians can stand as a basic model to be expanded.

Required additional actions:

- A contract between the ecosystem healthcare institutions would include a section highlighting that liability remains at the treating health centre. This is in line with the ERN patient consent form stating that the responsibility of the healthcare ‘will remain the responsibility of the health professionals who usually look after you’.

Policy option 5 – EU organisation of RD data ecosystems

A central EU body for multi-country RD data ecosystems could function as an add-on to the four policy options above. The body’s main tasks would be to develop and supervise the infrastructure and standards to implement RD data ecosystems.

Required actions:

- Developing regulations and guidelines for establishing the RD ecosystems, which could build on and be integrated within the existing ERN system as the two systems partly overlap and are highly complementary.
- Building, facilitating and offering RD expertise by establishing the necessary infrastructure, including technical, legal, and inter-centre contracts. Compliance with national regulations must be ensured in the development of contracts between the RD centres.
- Establishing a central health data governing structure within the EHDS with clear and transparent standards for data encryption, upload, storage, access, and deletion.
- Establishing a Governance Board, similar (or identical) to the current BoMS to supervise the RD ecosystems. The BoMS can clarify and assist in necessary adjustments of national legal regulations to allow participation in multi-country RD ecosystems. This could also include standards for quality assurance within the ecosystem, and compiling experiences from the first ecosystems to promote the development of subsequent RD ecosystems.
- Implementing standards for machine translation that allows patients and professionals to interact in their native tongue, including translation of medical records and patient-professional interviews.
- Establishing standards for the cross-country consent process, similar, albeit more detailed, to the current ERN system. This should clarify the purpose of the data sharing and the involved actors.
within the RD ecosystem, and it should include a provision that ensures that the requesting health centre no longer has access to the primary health data after cancellation but allows already used data to be processed in an anonymised form.

**Policy option 6 – Funding opportunities for RD data ecosystems**

The policy options presented above represent novel EU healthcare collaboration model that call for joint actions between the European Commission and Member States to provide resources and funding needed to support five main areas:

- Legal description and EU standards for inter-centre contracts, consent procedures and clarification of ownership of machine translation of medical data
- Standards for data capture, data hosting, data security and data access
- Organisational standards for multi-country RD healthcare ecosystems
- Building, sustaining, and governing of multi-country RD healthcare ecosystems
- Supporting the day-to-day coordinating activities and monitoring of patient outcomes within a RD ecosystem.

The actual EU and Member State costs associated with the first three are not addressed in this report. With respect to the last two items, there is a need to provide EU funding opportunities for childhood cancer and other RD healthcare centres to pilot and evaluate multi-country RD healthcare ecosystems. Importantly, the building of multi-country RD ecosystems may not only reduce health inequalities, including childhood cancer survival rates, within and across Member States, but may actually save both lives and costs by improving the quality of healthcare and reducing the risk of treatment failures, e.g., for childhood cancer, where treatment of relapses is far more costly than first-line therapy.

The EU4Health Programme highlights digital transformation of health systems and could provide calls for piloting and evaluating RD ecosystems. This could also include funding for adapting the ERN programme to ensure integrative efforts between ERNs and multi-country RD ecosystems.

The Horizon Europe programme has allocated 100 million EUR for developing diagnostics and treatment under a **new european partnership on RDs**, which would be a funding opportunity for multi-country RD ecosystem pilot projects.

For childhood cancer specifically, piloting multi-country RD ecosystems could also be embedded in the **Horizon Europe Framework Programme for Research and Innovation**, where the **Mission on Cancer** includes thirteen specific recommendations. Although none of these recommendations specifically address multi-country rare cancer healthcare ecosystems, several of the recommendations are compatible with future calls to address these:

- Recommendation 8: Create a European Cancer Patient Digital Centre where cancer patients and survivors can deposit and share their data for personalised care;
- Recommendation 9: Achieve Cancer Health Equity in the EU across the continuum of the disease;
- Recommendation 10: Set up a network of Comprehensive Cancer Infrastructures within and across all EU Member States to increase quality of research and care;
- Recommendation 11: Childhood cancers and cancers in adolescents and young adults: cure more and cure better;
- Recommendation 12: Accelerate innovation and implementation of new technologies and create Oncology-focused Living Labs to conquer cancer.

Other calls relevant for piloting and evaluating multi-country RD healthcare ecosystems include the ‘**Transforming Health and Care Systems’ (THCS) joint transnational call for proposals to ‘Healthcare of the future’**’. 
References


Ferlini, A., E. S. Gross, N. Gamier and c. Screen4Care (2023). "Rare diseases' genetic newborn screening as the gateway to future genomic medicine: the Screen4Care EU-IMI project." Orphanet J Rare Dis 18(1): 310.


Addressing challenges to European multi-country collaboration models for rare diseases


Annex I – Guide for qualitative interviews with patients/parents

The interviewer starts off briefly summarising the purpose of the study.
- May I ask you how old you are?
- What is the highest education you have completed?
- Primary school? Until what grade?
- High school or similar?
- Undergraduate degree?
- Graduate degree?
- Postgraduate degree?
- Are you OK about discussing your/your child’s disease/chronic condition and treatment?
- Can you tell me about your/your child’s diagnosis?
- Have you/your child had a relapse? How are you/your child today?
- Which country have you been treated in?
- Do you have siblings?/Do you have other children? How old are they?
- If you look back on your/your child’s illness, your/your child’s recovery (and relapse) as well as the time after your/your child’s recovery, what stands out the most?
- Generally speaking, did you feel comfortable with the doctors/the team treating you/your child?
- Did you feel comfortable about the doctors’ knowledge about your/your child’s disease/chronic condition?
- What about complications during treatment or adverse reactions? Were the doctors’ able to come up with satisfactory solutions to these problems?
- What about after treatment and long-term problems? Have the doctors been able to help you/your child?
- Have you experienced that your physician/team could not help you/your child with some of the reactions/problems/long-term effects you/your child experienced?
- What were they? (expand by follow-up Qs)
- Did you ever feel a need to look for answers outside your treatment team in your own country or abroad?
- Can you explain what you lacked?
- Did you find your physician/treatment team inexperienced? Lacked resources? Lacked time?
- How did you deal with this?
- Did you ever seek a second opinion?
- Did you find another doctor/team yourself?
- Did your doctor/team help you find another doctor/team?
- Was your doctor/team against seeking a second opinion elsewhere?
- Did you search the internet for answers to your questions?
- If your physicians were more experienced/knowledgeable, do you think that you/your child would have had a better treatment? Or a better long-term outcome?

The following questions concern your opinion on cross-country sharing of medical data on specific patients. The background for asking these questions is that many physicians specialised in rare diseases/chronic conditions, such as childhood cancer, emphasise the need to share data with physicians in other centres, and often in other countries, to better understand how to diagnose and treat patients with rare diseases/chronic conditions. However, this sharing of data from specific patients is very difficult today due to legal barriers, e.g., the GDPR. On the one hand, one may argue that sensitive data on specific patients should not be shared between centres from different countries to prevent misuse of data and protect the patients. On the other hand, professionals specialised in rare diseases/chronic conditions argue that such sharing of knowledge is necessary to offer the best possible diagnosis and treatment.
I would like to hear your opinion on this dilemma. You may consider your own/your child’s case, or you may have a position of principle on the matter (or due to your engagement in a childhood cancer organisation).

- Do you think closer international collaboration, where physicians from centres in other countries within the EU work very closely with your physicians, could make a difference in terms of establishing the right diagnosis and offering the best treatment for people with rare diseases/chronic conditions?
- If your centre worked more closely together with a few other centres in Europe, and you knew their names, affiliations, and expertise:
  - How much of your/your child’s medical file would you feel comfortable sharing with doctors from other centres in Europe so they would have access to these daily?
  - Can you pinpoint the type of data from your/your child’s medical file that you would allow access to with the purpose of improving treatment? (To the interviewer: give examples, but let the family expand on what can and cannot be shared - THIS IS THE MOST CRITICAL ASPECT AND SHOULD BE COMPREHENSIVE):
    - Non-sensitive data like age, gender, region in the country?
    - Somewhat sensitive data like cancer diagnosis, imaging and other examinations and treatment?
    - Sensitive data like psychological issues, information about your family’s economic situation or lifestyle?
  
- Regarding sharing of data, what model would in your opinion be the best? Note that the more restrictive, the less knowledge the physicians will obtain and the less it can add positive value in terms of establishing a diagnosis or offering the best treatment:
  - Any data relevant for establishing a diagnosis or for offering the best treatment, no matter how sensitive the data is, about specific patients, if the patient’s interest is in mind?
  - Only data sharing when certain complications arise. It could be that the cancer does not respond well to therapy OR a certain toxicity occurs? – if so, when should data sharing stop?
  - Only data sharing when the data shared has been approved by both parents and the patient (if an adolescent)?
  - Only data sharing among a few centres, e.g., max 2-4, 5-7 or 8-10 centres at a time?
  - If the data above were to be shared, would you approve that the pediatric oncologist from another centre:
    - directly could see and read the patient file? This would imply that the pediatric oncologist in principle has exactly the same information as your own physician; or
    - only could see a selected part of the patient file? Or
    - only could see a selected part of the patient file after your approval? If translation could be done in real time through some AI technology or professional translators, meaning that you would be able to talk your native tongue with an expert from another country, would this be of benefit? Such consultations or medical visits would in general take place with the presence of your treating physician.
  - Would you have concerns that:
    - Other EU countries (or specific countries) are not able to secure data properly?
    - The physicians sharing data do not share the same health system and thus may not understand the way the data is presented/structured and the like?
    - The physicians sharing data do not understand each other due to language barriers?
    - The physicians sharing data do not understand each other due to cultural barriers?
    - Communication between you and a physician from another country in the EU will be challenged due to language or cultural barriers?
    - That your physicians would be against such close collaboration with other countries?
  - Other concerns?
Annex II – Guide for qualitative interviews with health professionals

The interviewer starts off by briefly summarising the purpose of the study

- Is it OK that we in STOA report quotations from this interview without referral to who they came from?
- Is it OK with you that, in the appendix to the STOA report, we list your name and affiliation together with the other physicians we have interviewed?
- Current position / affiliation?
- Pts/year at your institution?
- What is your age?
- How many years have you worked in pediatric oncology?
- Which country(ies) have you primarily worked in?
- Have you trained or done research abroad for more than 6 consecutive months?
- Do you have a pediatric oncology research lab at your institution?
- How many people work at the lab?
- What is your centre’s primary clinical and research expertise?
- Do you feel comfortable about the clinical experience / knowledge junior doctors can obtain by working in your centre, or would a more extensive international collaboration with access to selected patients’ medical files on a routine basis (daily / weekly / monthly) be of benefit?
- Would this more extensive international collaboration be relevant for gaining general clinical experience?
- Would this more extensive international collaboration be particularly relevant for rare childhood cancers?
- Would this more extensive international collaboration be relevant for gaining clinical experience with complications during treatment, including treatment resistance or adverse reactions?
- Would this more extensive international collaboration be relevant for long-term toxicities / late effects?
- If you look back on some of the complicated cases you yourself have dealt with, do you think it could have made a difference, if doctors from other centres specialised in these cases or similar ones had access to your patients’ medical files?
- If so, would it make a difference in relation to establishing the diagnosis faster or more accurately?
- Would it make a difference in relation to the outcome of the treatment / cure?
- Would it make a difference in relation to dealing with toxicities, including late effects?
- Would it make a difference in relation to other problems than strictly medical ones, e.g., ethical and psychological issues, speech disabilities and the like?
- Have you / your colleagues contacted expertise outside your own centre (including international centres) to discuss complicated cases?
- If so, how often? Weekly, 1-3 month intervals, 3-12 month intervals, more rarely?
- What type of problems?
- Rare cancers / subtypes
- Toxicities
- Other
- Did you primarily reach out to international experts that you already knew? Or to others, please clarify?
- How did you identify these experts?
- Is trust in these experts based on previous interactions (i.e. you knew them already) of relevance.
- Are you aware of patients/parents of patients you’ve treated who have sought a second opinion?
- If so, how often? Weekly, 1-3 month intervals, 3-12 month intervals, more rarely?
- If so, what type of problems?
• If so, what was your role in providing / facilitating transfer of information?
• Did you agree with the need to get a second opinion?
• Do you experience that the patients/parents of patients you’ve treated search the internet for answers to clinical questions?
• If so, how often? Weekly, 1-3 month intervals, 3-12 month intervals, more rarely?
• Did some of their search findings lead to changes in your treatment or other issues?
• Are there any financial restrictions for recommended therapy from outside your centre?
• Were their internet / other search findings of clinical relevance?
• Do you regularly propose a treatment in another European country in a situation where you do not have a solution for further treatment?
• If so, how often? Weekly, 1-3 month intervals, 3-12 month intervals, more rarely?

The following questions concern your opinion on cross-country sharing of sensitive (medical) data on specific patients. The background for asking these questions is that many physicians specialised in rare diseases, such as childhood cancer, emphasise the need to share data with physicians in other centres and often in other countries to increase their expertise, including obtaining a better understanding of how to diagnose and treat patients with rare diseases. However, this sharing of data from specific patients is currently very difficult due to legal barriers, e.g., the GDPR. On the one hand, one may argue that sensitive data on specific patients should not be shared between centres from different countries to prevent misuse of data and ensure protection of the patients. On the other hand, professionals specialised in rare diseases, as well as patients themselves, may argue that such sharing of knowledge is necessary to offer the best possible diagnosis and treatment.

I would like to hear your opinion on this dilemma. You may consider your own/your patients’ opinions, or it may be more a matter of principle for you.
• Do you think closer international collaboration, where physicians from centres in other countries within the EU work very closely with your physicians, could make a difference in terms of establishing the right diagnosis and offering the best treatment for people with rare diseases?
• If your centre worked more closely with a limited number of other named centres in Europe, and you knew their specialists / consultants by names and expertise:
• How much of your patients’ medical files would you feel comfortable sharing with doctors from other centres in Europe so they could have access to these daily?
• Can you pinpoint the type of data from your patients that you would allow access to with the purpose of improving treatment? (To the interviewer: give examples, but be open to the interviewee on what can be shared and what cannot - THIS IS THE MOST CRITICAL ASPECT AND SHOULD BE COMPREHENSIVE):
  • Non-sensitive data like age, gender, region in the country?
  • Somewhat sensitive data like cancer diagnosis, imaging and other examinations and treatment?
  • Sensitive, personal, data like psychological issues, information about the patient’s family’s economic situation or lifestyle?
  • Regarding sharing of data, what model would in your opinion be the best? Note that the more restrictive, the less knowledge the physicians may obtain and the less it can add positive value in terms of establishing a diagnosis or offering the best treatment:
  • Any data relevant for establishing a diagnosis or for offering the best treatment, no matter how sensitive the medical data is about specific patients, if the patient’s interest is in mind? This would imply that all medical data is shared from the time of diagnosis.
  • Only data sharing when certain complications arise. It could be that the cancer does not respond well to therapy OR certain toxicities occur? – if so, when should data sharing stop?
  • Only data sharing when the data shared has been approved by both parents and the patient (if an adolescent)?
• If intimate data sharing takes place, how many centres can be involved, e.g., max 2-4, 5-7 or 8-10 centres at a time?
• Whatever model was chosen, could this also include intimate data sharing for all patients in the EU treated according to a specific protocol, i.e. a clinical trial, allowing a central unit be able to curate all patient files for those participating.
• If the data above were to be shared, would you approve that pediatric oncologists from another centre:
  • directly could see and read the patient file? This would imply that the pediatric oncologist in principle has exactly the same medical information as your own physician; or
  • only could see a selected part of the medical patient file? or
  • only could see a selected part of the patient file after your and the child’s parents specific approval of such data?
• If translation could be done in real time through some AI technology or professional translators, meaning that a patient would be able to talk their native tongue with an expert from another country, would this be of benefit?
• Such consultations or medical visits would in general take place with the presence of yourself or a colleague – or is that not needed?
• If a patient/parent of a patient you treat does not want to share data, how would you respond to this?
  • Would you have concerns that:
    • Other EU countries (or specific countries) are not able to secure data properly?
    • The physicians sharing data do not share the same healthcare system and thus may not understand the way the data is presented/structured and the like?
    • The physicians sharing data do not understand each other sufficiently well due to language barriers?
    • The physicians sharing data do not understand each other’s medical strategies due to cultural barriers or financial constraints?
    • Communication between a patient/parent and a physician from another country in the EU will be challenged due to cultural barriers, even if translation of language was provided?
    • That your patient/the child’s parents in general would be against such close collaboration with other countries?
  • Other concerns?
• If an intimate network between a limited number of centres was established, what would you regard to be potential benefits with respect to
  • Development of clinical expertise?
  • Training of junior specialists?
  • Development of novel technology?
  • Research
  • Complementary expertise?
  • International recognition, i.e. partnerships for research?
  • Better funding opportunities?
  • Hubs for testing novel drugs or technologies (= of interest to the industry)?
Annex III – Literature search (see methods)

CORDIS

Among a total of 378 reports registered at CORDIS
https://cordis.europa.eu/search?q=%27rare%27%20AND%20%27disease%27%20AND%20%27volume%27&p=1&num=10&srt=Relevance:decreasing
the following 31 were regarded to have potential relevance to this study and were reviewed (in alphabetic order):

ASSET: Analysing and Striking the Sensitivities of Embryonal Tumours, Seventh Framework Programme, 2016
https://cordis.europa.eu/project/id/259348/reporting

Developing a Child Cohort Research Strategy for Europe, Seventh Framework Programme grant, 2010-2013
https://cordis.europa.eu/project/id/241604

ERA-NET on Rare Diseases, Seventh Framework Programme, 2010
https://cordis.europa.eu/project/id/266608/reporting

ERA-Net on Rare Diseases, Seventh Framework Programme grant, 2010-2014
https://cordis.europa.eu/project/id/266608

ERA NET rare disease research implementing IRDiRC objectives, Horizon 2020 grant

EUROlinkCAT: Establishing a linked European Cohort of Children with Congenital Anomalies, Horizon 2020 grant, 2017-2022
https://cordis.europa.eu/project/id/733001

European Clinical trials in Rare Sarcomas within an integrated translational trial network, Seventh Framework Programme, 2019.
https://cordis.europa.eu/project/id/278742/reporting

https://cordis.europa.eu/project/id/242193/reporting

EUROPEAN NETWORK for CANCER research in CHILDREN and ADOLESCENTS, Seventh Framework Programme grant, 2011-2015
https://cordis.europa.eu/project/id/261474

European Network for the Study of Adrenal Tumours – Structuring clinical research on adrenal cancers in adults, Seventh Framework Programme, 2016
https://cordis.europa.eu/project/id/259735/reporting

European Rare disease research Coordination and support Action, Horizon 2020 grant, 2021-2025
https://cordis.europa.eu/project/id/964908
Excel in Rare Diseases’ Research: Focus on LYSosomal Disorders and CILiopathies, Horizon 2020 grant 2018-24
https://cordis.europa.eu/project/id/811087

FAIR and open data sharing in support of cancer research
https://cordis.europa.eu/programme/id/HORIZON_HORIZON-INFRA-2021-EOSC-01-06

Final Report Summary - ENCCA (EUROPEAN NETWORK for CANCER research in CHILDREN and ADOLESCENTS), Seventh Framework Programme grant, 2011-2015
https://cordis.europa.eu/project/id/261474/reporting

Final Report Summary - E-RARE-2 (ERA-Net on Rare Diseases), Seventh Framework Programme grant, 2010-2014
https://cordis.europa.eu/project/id/266608/reporting

Final Report Summary - EUROSARC (European Clinical trials in Rare Sarcomas within an integrated translational trial network), Seventh Framework Programme grant, 2011-2018
https://cordis.europa.eu/project/id/278742/reporting

Final Report Summary - RICHE (RICHE – a platform and inventory for child health research in Europe), Seventh Framework Programme grant, 2010-2013
https://cordis.europa.eu/project/id/242181/reporting

https://cordis.europa.eu/project/id/305690/reporting

Final Report Summary - RD-CONNECT (RD-CONNECT: An integrated platform connecting registries, biobanks and clinical bioinformatics for rare disease research), Seventh Framework Programme grant, 2012-2018
https://cordis.europa.eu/project/id/305444/reporting

Final Report Summary - SUPPORT-IRDiRC (Support for international rare diseases research to serve the IRDiRC objectives), Seventh Framework Programme grant, 2012-2018
https://cordis.europa.eu/project/id/305207/reporting

Horizon 2020 grant: conect4children (Collaborative Network for European Clinical Trials for Children, 2023
https://cordis.europa.eu/project/id/777389

Horizon 2020 ELIXIR-EXCELERATE grant: Fast-track ELIXIR implementation and drive early user exploitation across the life-sciences, 2022
https://cordis.europa.eu/project/id/676559

Horizon 2020 EJP RD grant: European Joint Programme on Rare Diseases, 2019
https://cordis.europa.eu/project/id/825575

Horizon 2020 grant: New therapies for uveal melanoma, 2022
https://cordis.europa.eu/project/id/667787

Horizon 2020 grant: Solving the Unsolved Rare Diseases, 2017
https://cordis.europa.eu/project/id/779257
Addressing challenges to European multi-country collaboration models for rare diseases


Solving the unsolved Rare Diseases, Horizon 2020 grant 2018-24<br/>https://cordis.europa.eu/project/id/779257


PubMed

The initial crude search (trans-national[Title/Abstract] OR transnational[Title/Abstract] OR centralisation[Title/Abstract] OR multi-country[Title/Abstract] OR ecosystem[Title/Abstract]) AND (rare disease[Title/Abstract] OR childhood cancer[Title/Abstract]) gave 58 hits, of which none directly address the multi-country collaborative RD ecosystems being the target of this report, and only 13 had some relevance. Accordingly, we performed several specific and more broad PubMed searches as outlined below and scrutinized the lists to identify relevant literature.

RARE DISEASE VOLUME


A reduction to the time period 2013-2023 and limited to English literature as well as “English” and “children & adolescents” gave 626 hits among which the following six had some potential relevance to this study and search:

Hart, Ruth I, Dorothy Boyle, David A Cameron, Fiona J Cowie, Larry Hayward, Nicholas B Heaney, Angela B Jesudason, Julia Lawton, ‘Strategies for improving access to clinical trials by teenagers and young adults with cancer: A qualitative study of health professionals’ views’, *Eur J Cancer Care*, 30(3), May 2021. 


van der Zwan, Jan Maarten, Annalisa Trama, Renée Otter, Nerea Larrañaga, Andrea Tavilla, Rafael Marcos-Gragera, Angelo Paolo Dei Tos, Eric Baudin, Graeme Poston, Thera Links; RARECARE WG, ‘Rare neuroendocrine tumours: results of the surveillance of rare cancers in Europe project’, *Eur J Cancer*, 49(11): 2565-78, Jul 2013. 

Selected associated articles from these references

N=2


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**RARE DISEASE COLLABORATION OR COOPERATION**

A search on 
Addressing challenges to European multi-country collaboration models for rare diseases


van Zanten, Sophie E M Veldhuijzen … van Vuurden DG; members of the SIOPE DIPG Network, ‘Development of the SIOPE DIPG network, registry and imaging repository: a collaborative effort to optimize research into a rare and lethal disease’, J Neurooncol., 132(2): 255-66, April 2017

Selected associated articles from these references

N=51

Ali, S R, J Bryce, C Smythe, M Hytiris, A L Priego, N M Appelman-Dijkstra & S F Ahmed, ‘Supporting international networks through platforms for standardised data collection-the European Registries for Rare Endocrine Conditions (EuRECa) model’, Endocrine, 71(3): 555-560, Mar 2021


Aymé, Ségolène & Charlotte Rodwell, ‘The European Union Committee of Experts on Rare Diseases: three productive years at the service of the rare disease community’, *Orphanet J Rare Dis.*, 28(9), Feb 2014


Kinsner-Ovaskainen, Agnieszka, Monica Lanzoni, Ester Garne, Maria Loane, Joan Morris, Amanda Neville, Ciarán Nicholl, Judith Rankin, Anke Rissmann, David Tucker & Simona Martin, ‘A sustainable solution for the activities of the European network for surveillance of congenital anomalies: EUROCAT as part of the EU Platform on Rare Diseases Registration’, *Eur J Med Genet.*, 61(9): 513-17, Sep 2018


Lynn, Stephen, Victoria Hedley, Antonio Atalaia, Teresinha Evangelista, Kate Bushby; EUCERD Joint Action, ‘How the EUCERD Joint Action supported initiatives on Rare Diseases’, Eur J Med Genet., 60(3): 185-89, Mar 2017


Reincke, Martin & Anita Hokken-Koelega, ‘Perspectives of the European Society of Endocrinology (ESE) and the European Society of Paediatric Endocrinology (ESPE) on rare endocrine disease’, Endocrine, 71(3): 539-41, Mar 2021  


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Taruscio, Domenica, Amalia E Gentile, Teresinha Evangelista, Rosa G Frazzica, Kate Bushby & Antoni Moliner Montserrat, ‘Centres of Expertise and European Reference Networks: key issues in the field of rare diseases. The EUCERD Recommendations’, Blood Transfus., 12 Suppl. 3: 661-5, April 2014


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CHILDHOOD CANCER VOLUME

A search on
https://pubmed.ncbi.nlm.nih.gov/?term=childhood+cancer+volume&filter=lang.english&filter=age.allchild&filter=age.newborn&filter=age.allinfant&filter=age.infant&filter=age.preschoolchild&filter=age.child&filter=age.adolescent&filter=years.2013-2023 gave 335 hits of with the following additional two were key papers:


Selected associated articles from these references

N=6


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CHILDHOOD CANCER COLLABORATION OR COOPERATION

A search on https://pubmed.ncbi.nlm.nih.gov/?term=childhood+cancer+collaboration&filter=lang.english&filter=age.allchild&filter=age.newborn&filter=age.allinfant&filter=age.infant&filter=age.preschoolchild&filter=age.child&filter=age.adolescent&filter=years.2013-2023 gave 537 hits of which the following three were additional potentially relevant papers:


Sironi, Giovanna, Andrea Ferrari, Marta Podda, Stefano Chiaravalli, Gianni Bisogno, Giovanni Cecchetto & Maura Massimino, ‘Papillary Thyroid Carcinoma in Pediatric Age: An Example of a Rare
Addressing challenges to European multi-country collaboration models for rare diseases


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**CHILDHOOD CANCER CENTRALISATION**

https://pubmed.ncbi.nlm.nih.gov/?term=childhood+cancer+centralisation&filter=lang.english&filter=age.allchild&filter=age.newborn&filter=age.allinfant&filter=age.infant&filter=age.preschoolchild&filter=age.child&filter=age.adolescent&filter=years.2013-2023 gave 40 hits of which the following additional four were of potential relevance:


**RARE DISEASE ECOSYSTEM(S)**


The combined list below contains the references selected for thorough review. Those marked ** are directly referenced in the report:


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Aymé, Ségolène & Charlotte Rodwell, ‘The European Union Committee of Experts on Rare Diseases: three productive years at the service of the rare disease community’, *Orphanet J Rare Dis.*, 28(9), Feb 2014


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de Graaf, Johan P Friso de Vries, Anne Dirkson, Olaf Hiort, Alberto M Pereira, Mártia Korbonits & Martine Cools; Research and Science Work Package of Endo-ERN, ‘Patients with rare endocrine conditions have corresponding views on unmet needs in clinical research’, *Endocrine*, 71(3): 561-68, Mar 2021


**Ferlini, A., E. S. Gross, N. Garnier and c. Screen4Care (2023). "Rare diseases' genetic newborn screening as the gateway to future genomic medicine: the Screen4Care EU-IMI project." Orphanet J Rare Dis 18(1): 310.

Ferrari, Andrea, Dominik T Schneider, Gianni Bisogno, Yves Reguerre, Jan Godzinski, Ewa Bien, Teresa Stachowicz-Stencel, Giovanni Cecchetto, Bernadette Brennan, Jelena Roganovic, Tal Ben-Ami, Calogero Virgone, Nuno Reis Farinha, Serena Mancini, Daniel Orbach & Ines B Brecht, ‘Facing the challenges of very rare tumors of pediatric age: The European Cooperative Study Group for Pediatric Rare Tumors (EXPeRT)


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Lynn, Stephen, Victoria Hedley, Antonio Atalaia, Teresinha Evangelista, Kate Bushby; EUCERD Joint Action, ‘How the EUCERD Joint Action supported initiatives on Rare Diseases’, Eur J Med Genet., 60(3): 185-89, Mar 2017


Mora, Marina, Corrado Angelini, Fabrizia Bignami, Anne-Mary Bodin, Marco Crimi, Jeanne-Hélène Di Donato, Alex Felice, Cécile Jaeger, Veronika Karcagi, Yann LeCam, Stephen Lynn, Marija Meznaric, Maurizio Moggio, Lucia Monaco, Luisa Politano, Manuel Posada de la Paz, Safaa Saker, Peter Schneiderat, Monica Ensini, Barbara Garavaglia, David Gurwitz, Diana Johnson, Francesco Muntoni, Jack Puymirat, Mojgan Reza, Thomas


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van der Zwan, Jan Maarten, Annalisa Trama, Renée Otter, Nerea Larrañaga, Andrea Tavilla, Rafael Marcos-Gragera, Angelo Paolo Dei Tos, Eric Baudin, Graeme Poston, Thera Links; RARECARE WG, ‘Rare neuroendocrine tumours: results of the surveillance of rare cancers in Europe project’, Eur J Cancer, 49(11): 2565-78, Jul 2013.


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Rare diseases – defined as diseases that affect no more than one person in 2,000 – currently impact between 30 and 35 million EU citizens. Limited patient volume hinders research on these diseases, to the detriment of understanding of their biology, recruitment to clinical trials and survival rates. Real-time sharing of primary health data within and between rare disease healthcare centres and across Member States is feasible but there are obstacles.

This report focuses on childhood cancer as a rare disease prototype, addressing volume challenges by reviewing cooperative structures, exploring attitudes towards data sharing, and presenting policy options for multi-country collaboration. Interviews show support for collaboration among rare disease healthcare centres, and for sharing medical files and expertise. The policy options proposed seek to promote research and expertise-building for the benefit of rare disease patients.