Together4RD
RARE DISEASES

Together for Rare Diseases
Activity Report

ASSESSMENT AND IMPACT OVER THREE YEARS
OF THE MULTISTAKEHOLDER COALITION

Created in 2022, Together4RD was formed by leading representatives of Europe's rare disease community, with a multistakeholder Steering Group composed of ERN coordinators and representatives, patient organisations, research infrastructures and the pharmaceutical industry with the purpose of harnessing collaboration between European Reference Networks (ERNs) and industry in rare disease research.

Together4RD has positioned itself among a growing number of organisations and initiatives calling for, and demonstrating the value of public-private partnerships (PPPs) between ERNs and industry, moving the needle in rare disease research by demonstrating through three pilot projects how PPPs can work and be scaled up in the future. These pilots have provided valuable learnings for collaboration in rare disease research, and the key lessons were published in a 2025 Toolkit on fostering ERN-industry collaboration.

In advocacy, Together4RD has actively sought more political action on rare diseases, working closely with a number of Members of the European Parliament, officials at the European Commission's Directorates-General for Health and Food Safety (SANTE) and Research and Innovation (RTD), EU Council Presidencies, the European Economic and Social Committee and the ERN Board of Member States.

The initiative's pausing in 2025 owes to its success in demonstrating the potential of PPPs in rare diseases research to a wide range of stakeholders, culminating in a successful conference in the European Parliament in September 2025 and the development of concrete recommendations on what all stakeholders in rare disease research can do to **overcome barriers to public-private partnerships between ERNs and industry in rare disease research**.

This report weaves together 4 years of work to **advocate for cohesive, ambitious policy** to boost ERNs' research activities to address unmet medical needs, as well as **comprehensive activities to foster ERN-industry collaboration** and demonstrate the effect of transparent, patient-centred pilot projects, and develop **a toolkit for stakeholders to emulate and take forward these collaborative projects**.

Together4RD
RARE DISEASES

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RARE DISEASES

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Together For Rare Disease has made tangible contributions to European rare disease research activities and policy.

1

Pilot research projects between European Reference Networks and industry

Three pilot projects were devised between European Reference Networks and pharmaceutical companies to make inroads on different diseases, with Together4RD facilitating the launch of each pilot which was then taken on by the ERN-industry partners.

To find more information about our pilot projects, head directly to page 34.

2

Toolkit to foster ERN-Industry collaboration

The **Together4RD Toolkit** is intended to support a broad range of collaborative activities in which ERNs and industry might partner. It is Together4RD's most comprehensive effort to date to strengthen research collaboration between ERNs and industry. ERNs, established to improve the diagnosis and care of people living with rare diseases, are recognised as key enablers of rare disease research due to their pan-European networks, data infrastructure, and deep disease-specific expertise. Yet, many of these networks operate in fields with limited prior R&D and lack experience in engaging with private sector partners. ERNs and industry may have different needs, and see value in different components of this resource, but the Toolkit provides added-value for both sets of stakeholders.

To find more information about our Toolkit projects, head directly to page 36.

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Continuous and impactful engagement with key policy stakeholders

Together4RD has contributed to shaping the environment for rare disease research in Europe by consistently highlighting the role of public-private partnerships between ERNs and industry. Through ongoing engagement with Members of the European Parliament, the European Commission, the ERN Board of Member States and rotating Council Presidencies, the coalition has helped keep rare diseases, and the research mission of ERNs, on the EU agenda, including by engaging with the ERN Board of Member States to adapt its 2019's statement on ERN-industry collaboration. Its position statement, policy asks and targeted events in the European Parliament have translated advocacy messages into concrete proposals to enable ERN-industry collaboration.

To read our key recommendations for policymakers, head directly to page 73.

Supporting ERN–industry rare disease research collaboration through advocacy

Together4RD's Position Statement on collaboration between European Reference Networks and industry

Hedley *et al.*
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Orphanet Journal of Rare Diseases

POSITION STATEMENT Open Access

Together4RD position statement on collaboration between European reference networks and industry

Victoria Hedley[1*], Matt Bolz-Johnson[2], Ines Hernando[2], Rosalind Kenward[3], Rima Nabbout[4], Clara Romero[3], Franz Schaefer[5], Sheela Upadhyaya[3] and Together4RD Steering Group

Abstract

Notwithstanding two decades of policy and legislation in Europe, aimed to foster research and development in rare conditions, only 5–6% of rare diseases have dedicated treatments. Given with the huge number of conditions classed as rare (which is increasing all the time), this equates to major unmet need for patients (over 30 million in the EU alone). Worryingly, the pace of Research and Innovation in Europe is lagging behind other regions of the world, and a seismic shift in the way in which research is planned and delivered is required, in order to remain competitive and—most importantly—bring meaningful, disease-altering treatments to those who desperately need them. The European Reference Networks (ERNs), launched in 2017, hold major potential to alleviate many of these challenges, and more, but only if adequately supported (financially, technically, and via robust policies and infrastructure) to *realise* that potential: and even then, only if able to forge robust collaborations harnessing the expertise, resources, knowledge and data of all stakeholders involved in rare disease, including Industry. To-date, however, ERN-Industry interactions have been largely limited, for a range of reasons (concerning barriers both tangible and perceived). This Position Statement analyses these barriers, and explains how Together4RD is seeking to move the needle here, by learning from case studies, exploring frameworks for collaboration, and launching pilots to explore how best to plan and deliver multistakeholder interactions addressing real research needs.

Keywords Rare disease, European reference network, Public–private-partnership, Rare diseases, ERNs, Networking, Research

Read the full Position Statement in Annex I.

Our MEP Champions in the European Parliament

Together4RD's journey bears witness to two European Parliamentary terms under which rare diseases have gained increased prominence in policy and discourse.

The European Parliament has emerged as a leading voice for greater EU coordination and investment in rare diseases, recognising the efforts of the rare disease community, industry and patient organisations alike, in harnessing support from MEPs.

Capitalising on the formation of a fully-fledged Public Health (SANT) committee in the European Parliament in 2025, Together4RD has created highly productive relationships with several MEPs, with regular exchanges, collaborations and meetings. For example, Together4RD worked with several MEPs to **inform a plenary debate on an EU Rare Disease Action Plan** with EU Health Commissioner Olivér Várhelyi in April 2025.

A number of Members of the European Union have gone above and beyond in championing the initiative, campaigning for a more cohesive and ambitious European rare disease ecosystem which stimulates public-private partnerships in rare disease research.

"ERNs have transformed rare diseases - they are the most important innovation in this area in Europe, if not also in the world. A future plan has to coordinate and harmonise national strategies and facilitate cross-border healthcare."

MEP TOMISLAV SOKOL
EUROPEAN PEOPLE'S PARTY, CROATIA

"Europe is about unity, solidarity and about being stronger together where it matters. And we matter! The EU would not be the EU without the rare disease community."

MEP FRÉDÉRIQUE RIES
BELGIUM, RENEW EUROPE; TOGETHER4RD MEP CHAMPION, NOVEMBER 2022

At a plenary debate on the need for an EU Action Plan on Rare Diseases in the European Parliament in April 2025, EU Health Commissioner Olivér Várhelyi underlined the Commission's dedication to pan-European approaches to rare disease policy and infrastructures, notably the European Reference Networks.

We extend our sincere thanks and gratitude to:

9TH PARLIAMENTARY TERM (2019-2024)

MEP Sara Cerdas
S&D, Portugal

MEP Ondrej Knotek
Renew, Czechia

MEP Stelios Kympouropoulos
EPP, Greece

MEP Frédérique Ries
Renew, Belgium
(Vice-President of the European Parliament)

10TH PARLIAMENTARY TERM (2024-2029)

MEP Vytenis Andriukaitis
S&D, Lithuania
(former EU Health Commissioner)

MEP Stine Bosse
Renew, Denmark
(Vice-Chair of the SANT Committee)

MEP Romana Jerković
S&D, Croatia
(Vice-Chair of the SANT Committee)

MEP András Kulja
EPP, Hungary

MEP Tomislav Sokol
EPP, Croatia

Launch of the Together4RD Policy Asks

On 10 November 2022, Together for Rare Diseases (Together4RD) launched its recommendations to unlock ERN and industry collaboration for the benefit of people living with a rare disease, convening a high-level discussion on shaping the rare disease/ERN ecosystem, connecting ERN registries, and calling for an EU Rare Disease Action Plan.

2022 was seen as a pivotal moment to shape the rare disease and ERN ecosystem, driven by legislative revisions, Council Presidencies' interest, and the forthcoming Commission review of ERNs' first five years. Participants emphasised the urgency of an EU Rare Diseases Action Plan, placing ERNs at the heart of the ecosystem and recognising public-private collaboration as a key tool and underlined the need for **long-term funding** and **clear governance structures of ERNs**, the willingness and potential for collaboration with industry, centred on patient needs and supported by robust data and connectivity. Several other obstacles ERN growth were pointed out, such as their lack of integration into national systems, complications and privacy concerns about pooling and anonymising patient registry data for secondary use, and streamlining EMA approval processes for orphan drugs designed to treat rare diseases.

The panellists welcomed the Together4RD pilot projects, noting their ability to make collaboration transparent and accessible, and combine the strengths of ERNs (clinical expertise and data pooling) and industry (research and regulatory know-how).

"Only together can we find a solution to break the radio silence and overcome an outdated approach regarding collaboration between ERNs and industry."

YANN LE CAM
CEO, EURORDIS-RARE DISEASES EUROPE

Speakers included (list non exhaustive):

- **Vittoria Carraro**
  European Confederation of Pharmaceutical Entrepreneurs, EUCOPE
- **Hélène Dollfus**
  Coordinator, the European Reference Network for rare eye diseases, ERN-EYE
- **Victoria Hedley**
  Researcher, Newcastle University
- **Dimitrios Athanasiou**
  Board Member, World Duchenne Organisation
- **Alexis Arzimanoglou**
  Coordinator, the European Reference Network for rare and complex epilepsies, ERN EpiCARE
- **Yann Le Cam**
  CEO, EURORDIS-Rare Diseases Europe
- **Jakub Dvořáček**
  Former Deputy Minister for Health, Czech Republic
- **MEP Ondrej Knotek**
  Renew Europe, Czech Republic; Together4RD MEP Champion
- **MEP Stelios Kympouropoulos**
  European People's Party, Greece; Together4RD MEP Champion
- **Andrzej Rys**
  Former Policy Officer, European Commission

← Scan to watch the event recording

Public-private partnerships within the proposed European Action Plan on Rare Diseases

A March 2023 webinar on public-private partnerships within the proposed European Action Plan on Rare Diseases brought together a diverse panel of stakeholders to discuss how collaboration could transform the rare disease landscape in Europe.

The webinar demonstrated **broad consensus that public-private partnerships, with strong patient involvement and transparent governance, are vital for advancing research and care in rare diseases**.

Key points raised during the event included:

- A European Action Plan on Rare Diseases would set out an overarching strategy, shaping European policy in the field of rare diseases. While progress has certainly been made through legislation (e.g., the Orphan Medicines Regulation supporting innovation in new therapies), a rare disease strategy would help define a common direction and practical guidance for all stakeholders involved.
- The strategy should establish a clear framework that supports partnerships in the rare disease ecosystem and define a clear role for ERNs in the future.
- PPPs are essential for a dynamic and innovative rare disease space in Europe, which can deliver the best possible care for people living with a rare disease. These partnerships could help maintain sustainable registries in the longer term, leading to improved natural history and continuous data, essential for the development of new therapies.
- Smaller-scale collaboration between industry and (individual) hospitals exists, but engagement with ERNs at the network level is currently challenging, for several reasons. Given enough resources and support, ERNs could function as a central and coordinating entity for data collection and coordination with other stakeholders such as industry.
- Patient organisations should be involved in these partnerships from the start, to ensure an appropriate ethical governance framework that addresses patients' needs.
- Infrastructure to support larger scale cooperation already exists in other diseases areas, such as for cancer research via the European Organisation for Research and Treatment of Cancer (EORTC).

Speakers included (list non exhaustive):

- **Victoria Hedley** Researcher, Newcastle University
- **Sheela Upadhyaya** Chair of the Together For Rare Diseases Steering Group
- **Alexis Arzimanoglou** Coordinator, the European Reference Network for rare and complex epilepsies, ERN EpiCARE
- **Matt Bolz-Johnson** Former Healthcare and Research Director, EURORDIS-Rare Disease Europe
- **MEP Stelios Kympouropoulos** European People's Party, Greece; Together4RD MEP Champion
- **Victor Maertens** Government Affairs Director, EUCOPE

Capturing patient representative insights on the BoMS Statement – Joint workshop with EURORDIS and European Patient Advocacy Group (ePAG) Taskforce

The ERN Board of Member States statement from 2019 has been a focal point for Together4RD, and of the initiative's key policy asks has been the revision of the statement to allow, if not encourage, ERNs to work alongside industry in rare disease research.

Together4RD and EURORDIS-Rare Disease Europe held a workshop in August 2023 to capture patient representatives' views and insights on the statement to ensure that the putative revision reflects the patients' perspectives. The representatives disagreed with a key aspect of the statement banning directly allocated industry funding for an ERN. While there is a need for safeguards to maintain transparency and independence,

the patient advocacy groups advanced that multiple funding models, including from industry, should be permitted to finance the management of the network, events and raising awareness of the ERN and its activities. They also stated that industry funding could be used to support centres which establish and maintain patient registries, to improve data and quality assurance. They also called for a conflict-of-interest registry to advance transparency in how funding is allocated by industry to ERNs.

Tackling Challenges to Improve ERN Collaboration with Industry: workshop with the ERN Board of Member States

This policy workshop with the ERN Board of Member States, European Commission and 40 other participants, held on 17 September 2024, focused on tackling challenges to improve collaboration between ERNs and industry.

It examined policy-related barriers (both real and perceived) that had previously hindered ERN-industry interactions, notably the ERN Board of Member States 2019 statement on ERN-industry collaboration, as well as other obstacles such as the absence of guiding principles, best practices and legal templates to formalise cooperation.

The workshop served as a springboard for future advocacy, outlining the pressing challenges and setting a clear path forward. Participants reaffirmed their commitment to strengthening ERN-industry partnerships and improving the research landscape for rare diseases. With growing political attention and advocacy efforts, the call for an EU Rare Disease Action Plan gained renewed urgency, underscoring the importance of sustained engagement with European institutions.

← *Scan to read the report*

NEXT STEPS

The workshop identified important next steps to take together:

- Continue work on a T4RD **toolkit** to support ERN-industry collaborations.
- Explore development of **Generic collaboration contract guiding principles** based on the Sanofi-ERN BOND pilot (and if possible, the other two) to standardize future partnerships.
- Gather examples of existing public-private collaboration agreements and consortia models to provide a reference point for new collaborations.
- Explore developing **a "sandbox" framework to facilitate innovative ERN-industry collaborations**, allowing for flexible experimentation in partnerships.
- Continue and potentially expand pilot projects that demonstrate successful ERN-industry collaboration.
- Propose a revised statement on ERN-industry collaboration for potential uptake by the ERN Board of Member States (BoMS) to reflect a more supportive view on research collaboration.
- **Share experiences and best practices regarding industry collaboration** from more 'research mature' and experienced ERNs with other ERNs, to showcase how partnerships can be set-up in the absence of ERNs being legal entities and foster collective learning.
- Explore **opportunities for pre-competitive collaborations**, leveraging industry assets and expertise to drive innovation and research.

Boosting EU competitiveness through public-private partnerships in rare disease research: the role of ERNs – Conference in the European Parliament

On the 24th of September 2025, Members of the European Parliament Stine Bosse (Renew, Denmark) and András Kulja (EPP, Hungary), Together for Rare Diseases' MEP Champions, co-hosted a high-level conference with over 100 people, including 40 in person, on the urgent need for EU policy to enable ERN-industry collaboration on rare disease research.

The main objective was to demonstrate how public-private partnerships (PPPs) between European Reference Networks (ERNs) and industry can boost the European Union's competitiveness by accelerating rare disease research as well as identifying the barriers and needed solutions.

Read the full report in Annex II.

Executive Summary

On the 24th of September 2025, Members of the European Parliament **Stine Bosse** (Renew, Denmark) and **András Kulja** (EPP, Hungary), Together for Rare Diseases' MEP Champions, co-hosted a high-level conference on the urgent need for EU policy to enable ERN-industry collaboration on rare disease research.

The event was organised by Together For Rare Diseases (T4RD) and joined in-person by 40 representatives from ERNs, research infrastructures, patient representatives, the European Parliament, the European Commission's DG Research and Innovation, the pharmaceutical industry and trade associations, with 89 more registered online.

The main objective was to demonstrate how public-private partnerships (PPPs) between European Reference Networks (ERNs) and industry can boost the European Union's competitiveness by accelerating rare disease research as well as identifying the barriers and needed solutions. Public-private partnerships are delivering value and should be acknowledged as essential drivers of societal progress. They have already delivered well beyond immediate market returns whilst creating long-term value for patients, healthcare systems and society as (for example) clearly demonstrated by the many Innovative Medicine/Health Initiative funded projects.[1]

> *From the first time I heard about ERNs, I knew we had a system worth investing in.*
>
> - MEP Stine Bosse

ERNs are Europe's flagship rare disease infrastructure, and operate at the heart of diagnosis, patient care, registry development and clinical trials. However, while ERNs have excelled in clinical care, education, and guideline development, their research contributions have been limited or less visible (without "ERN branding"), partly because research may not have been seen as a central part of their mission as ERNs received research funding through Horizon 2020, its successor Horizon Europe and co-funds from Member States through the European Joint Programme on Rare Diseases (EJP RD) and ERDERA. For ERNs to contribute directly to European competitiveness, they must move from being the backbone of rare disease care to becoming engines of research and innovation.

[1] https://www.ihi.europa.eu/about-ihi/impact

A change of perspective is needed to embrace public-private partnerships between ERNs and industry as flexible, well-resourced and highly productive forms of collaboration which can unlock rare disease research in Europe.

They need to be encouraged by public and private research funders. A clear signal about the expectation that some objectives are addressed by public-private consortia would be important to promote and demystify these types of collaborations. Industry are key partners for researchers, as **highlighted by ERN coordinators and industry partners in a joint T4RD and ERICA webinar** as well as by a representative of a patient organisation who shared it was easier work with industry than with ERNs.

Although several ERN-industry public-private partnerships such as Conect4Children have been highly successful, these types of collaborations are still limited by the **2019 statement by the ERN Board of Member States (BoMS)** discouraging ERN-industry data collaboration.

To fully harness the potential of PPPs, they should be allowed and promoted as effective conduits for rare disease research, notably in the ERDERA (European Rare Diseases Research Alliance) ecosystem, which already provides a coordinated EU-level framework and support for RD collaboration. Greater legal flexibility as the absence of an ERN legal entity remains an administrative hurdle, with researchers advocating for more centralised and transparent governance for ERNs.

> *Together For Rare Diseases' three ERN-industry pilot projects have demonstrated the willingness of both parties to enter partnerships to better understand rare disease burdens on quality of life, develop innovative endpoints or advance the consolidation of data registries.*
>
> *As a result, the ERN Board of Member States will look into the learnings of the pilot projects to assess the possible revision of the 2019 Statement.*
>
> **- ERN Board of Member States (BoMS)**

Europe now has a critical policy window to boost rare disease research. The Multiannual Financial Framework (MFF) for 2028-2034, unveiled by the European Commission in July 2025, **provides an opportunity to better exploit ERNs' potential by placing strategic emphasis on biotechnology**. This allows rare diseases to be woven into flagship EU funding instruments such as the proposed European Competitiveness Fund (a €409 billion initiative targeting strategic sectors including biotech) and Horizon Europe's successor programme **FP10** (with €175 billion allocated for 2028-2034). This includes ensuring that the **Life Sciences Strategy** (adopted July 2025), the forthcoming **Biotech Act**, the **European Innovation Act** (expected Q1 2026), implementation of the **EHDS** Regulation (which entered into force in March 2025), the **EU Startup** and **Scaleup**

> *An EU Action Plan on Rare Diseases would be a way of attracting investment from global pharmaceutical companies and incentivise them to develop technologies here in Europe.*
>
> - MEP András Kulja

Strategy (launched May 2025), and the **European Strategy on Research and Technology Infrastructures** (adopted September 2025) are all opportunities for unlocking rare disease research and translation. The Life Sciences Strategy is one of the main strategies under the competitiveness agenda and aims to strengthen the rare disease ecosystem by improving access to data, tools, actors and partners for collaboration. An **EU Action Plan on Rare Diseases**, strongly supported by MEPs in an April 2025 plenary debate, would ensure funding and policies are efficiently directed towards boosting rare disease innovation.

Participants called for the proposed **MFF 2028-2034 to ringfence funding for health infrastructures such as ERNs** to anchor rare diseases as a strategic, competitive investment. Suggestions for the MFF included earmarking part of the ERN core budget for clinical trial readiness and public-private partnerships, as well as establishing a network of ERN centres qualified for early human trials to accelerate patient access to advanced therapies. On the other hand, the envisaged **MFF Single Rulebook for Financial Rules,** while positive for some aspects of simplification, could impose a one-size-fits-all approach to research which will make it harder and less flexible for public-private collaborations to occur and thrive.

> *It is very hard to keep health on the top of the European agenda. As much as you need me, I need you to **speak up** and continue to talk into this obvious fact that when we work together we can do more and we can do it cheaper.*
>
> - MEP Stine Bosse

The momentum created by the European rare disease community has succeeded in placing rare diseases on the policy agenda as rarely before.

Together For Rare Diseases calls upon its MEP Champions and members to carry forward the optimism and suggestions surrounding public-private partnerships between ERNs and industry, and to disseminate them in key discussions such as the MEP Interest Group on Cancer and Rare Diseases[2] and the High-Level Meeting on European Research and Innovation for Rare Diseases.[3]

[2] https://www.europarl.europa.eu/meps/en/intergroup/details/7898/Intergroup%20on%20Cancer%20and%20Rare%20Diseases

[3] https://www.brains4brain.eu/category/meeting/

Detailed learnings

Public-Private Partnerships (PPPs) as drivers of Rare Disease innovation

PPPs must be recognised as a policy tool rather than an optional add-on. Stronger political mandates and targeted funding are essential to make PPPs routine in EU health and research policy. Clear political signals must be established in upcoming legislative packages (Life Sciences Strategy, Biotech Act and the next MFF) to earmark resources and explicitly promote PPPs as a strategic instrument for Europe's health and industrial policy.

Persistent 'perceived' obstacles remain, with the 2019 Board of Member States[4] (BoMS) statement discouraging ERN–industry data collaboration for research. There is a need for a revision to clarify conflict-of-interest rules, and build trust so that collaboration is seen as safe and legitimate.

Beyond removing barriers, stakeholders called for enablers such as robust and flexible operational frameworks, standardised contracts and data-sharing agreements, and EU-level templates that can be adapted across different disease areas to lower administrative burden and speed up project start-up.

PPPs, through the generation of real-world evidence, position ERNs as pivotal hubs for trial readiness and data-driven innovation.

> *We do not only need to remove or amend the statements that prevent us from collaboration, we also need a very clear traction from funders and decision makers saying that public-private collaboration is part of our tools to achieve objectives.*
>
> Pharmaceutical industry

> *What we are still lacking largely are PPPs that would drive therapeutics development by exploiting the unique patient and data resources available in the ERNs.*
>
> ERN coordinator

> *Agile, bespoke partnerships between ERNs and industry can move the needle in rare disease research.*
>
> Pharmaceutical industry

[4] The Board of Member States (BoMS): ERN governing board

Strengthening ERNs for research and competitiveness

ERNs' original mission was primarily clinical care, which means that research infrastructures, regulatory preparedness and systematic data integration have been limited. There is a need for **dedicated EU and national funding to build sustainable ERN research capacity**.

Participants called for a **ring-fenced share of the next Multiannual Financial Framework (MFF)** to support not only clinical-trial readiness and PPPs but also registry harmonisation, patient-reported outcomes development, early-phase trial capacity, and cross-border data platforms, so that ERNs can become true innovation accelerators.

New **governance models were explored**, including for the European Commission and member states to reconsider granting ERNs legal entity or creating shared governance/umbrella entities. These models would **simplify contracts, data use, and liability management, reduce administrative duplication across member hospitals, and create a single trusted entry point for industry and academic partners**.

Strengthening ERNs' research-capacities also requires training and resources for the academic centres teams (inc. on how to collaborate with private partners), interoperable IT systems, and incentives for hospitals to invest in research roles.

> *ERNs must not only remain the backbone of rare disease care, but also evolve to become engines of research and innovation.*
>
> MEP András Kulja

> *Creating a shared legal entity saves money and time because you harmonise and have one single entry point for the collaborations.*
>
> Researcher

> *Rare diseases are a cornerstone of the European Commission's health research, and the collaboration between ERNs and infrastructures like ERDERA and Jardin are exemplary for other health areas.*
>
> European Commission

EU policy and funding frameworks
(MFF, Life Sciences Strategy, Biotech Act)

Health must stay prominent in EU budgets, with explicit and sustained prioritisation of rare diseases. Without dedicated lines in the Multiannual Financial Framework (MFF), Europe will miss the chance to anchor rare disease research as a strategic competitiveness investment.

The competitiveness framing opens a unique opportunity to weave biotech and rare diseases into EU funding instruments such as the forthcoming European Competitiveness Fund and the next Horizon Europe work programmes. This includes ensuring that the upcoming legislative framework explicitly mention rare diseases and support translational research and advanced therapies.

These frameworks should **provide clear incentives for the co-investment from the private sector**, including risk-sharing mechanisms, tax and regulatory enablers, and predictable multi-year budgets to attract global R&D capital to Europe.

Flexibility and fitness-for-purpose are critical as concerns were raised that a proposed "single rulebook" for EU funding could unintentionally hinder diverse partnership models by imposing one-size-fits-all administrative rules. Speakers argued for **adaptable governance and regulatory sandboxes allowing different PPP formats**, lighter reporting where appropriate, and the ability to pilot innovative contracting models.

Coordination across EU directorates and member states must improve so that health, research, and industry policies reinforce each other. The group called for stronger horizontal links between DG SANTE (EU4Health) and DG RTD (Horizon) and for more structured engagement of national health ministries in EU research funding decisions.

> *What is positive about competitiveness is that it will never have been easier to talk about collaborations between industry and ERNs. There is no better time than now.*
>
> European Commission

> *Framework programmes are created based on the academic needs, not on the needs of public and private. That needs to change if we want to be competitive.*
>
> Pharmaceutical industry

> *The ERNs should no longer be denied institutional budget funding for research by the Commission, nor industry collaborations by the BoMS.*
>
> ERN coordinator

Building multi-stakeholder and political momentum to foster rare disease research in Europe

There was a call for strong(er) alignment between EU and national rare disease strategies, ensuring that European investments translate into coordinated national action plans and consistent funding across member states.

Participants highlighted the need to **integrate rare disease priorities into other EU policy areas** such as the digital health, data spaces, industrial, and education strategies so that rare diseases remain visible in broader competitiveness and innovation agendas.

Sustained communication campaigns and high-visibility events, such as regular summits and parliamentary hearings, keep **rare diseases in the public and political eye**, ensuring continued pressure on decision makers.

Stakeholders advocated for **ERN monitoring and evaluation to capture PPP outcomes**, including metrics on patient impact, research outputs, and economic returns, to demonstrate value and secure long-term political and financial support.

International collaboration beyond Europe, including transatlantic and global partnerships, such as IRDiRC[5], is vital for tackling ultra-rare conditions and for **positioning Europe as a global leader in rare disease innovation**.

> *As a parent, I want to see the EU not only talk but deliver an action plan so that families like mine know treatments will come to Europe, not leave it.*
>
> Patient organisation

> *ERNs can be the engine of change and recognising this would be a way of attracting investment from global pharmaceutical companies and incentivise them to develop technologies here in Europe.*
>
> MEP András Kulja

> *This is the moment to hard-wire rare diseases into the EU's competitiveness agenda, patients and their organisations are ready to work with MEPs and the Commission to make it happen.*
>
> Patient organisation

> **The positive aspect of this new competitiveness flag is that it has never been easier to discuss collaborations between industry and the European Reference Networks. This is an opportune moment for such partnerships**. *Biotech has been designated as a critical technology within this competitiveness framework, which represents significant progress for the rare disease ecosystem. In the current budget proposal figures provide an excellent foundation for negotiations.* **Rare diseases have frequently served as examples and catalysts for advancing other legislative initiatives**. *All the necessary instruments and tools are now available to move this agenda forward under the competitiveness framework.*
>
> European Commission

[5] https://irdirc.org/

Key actions proposed by the Together For Rare Diseases initiative

Actions	Description	Stakeholders
Revise the 2019 BoMS statement to explicitly allow and encourage ERN–industry research and data collaboration	Updating this guidance would lift a major regulatory barrier to ERN–industry collaboration. By clearly allowing data sharing and joint research, it would unlock stalled partnerships and speed up clinical innovation.	Board of Member States (BoMS), European Commission (DG SANTE)
Establish an EU Rare Disease Action Plan with measurable targets and stable funding	A formal, measurable plan at EU level would provide a long-term roadmap, attract private investment, and give Member States a shared framework to align national strategies.	European Commission (DG SANTE and DG RTD), European Parliament, Member States. And all other stakeholders to continue advocating
Ring-fence part of the next Multiannual Financial Framework (MFF) for RD research, clinical-trial readiness, and PPPs	Dedicated budget lines would secure predictable financing for cross-border clinical trials, registries, and PPPs, ensuring continuity beyond short funding cycles.	European Commission (DG BUDG and DG RTD), Council, European Parliament
Create a permanent EU-level cross-sector working group to coordinate rare disease policy and monitor implementation	This forum would keep rare disease policy high on the agenda, allow stakeholders to track progress, and foster coordinated action across Commission services, Parliament, industry, and patient organisations.	European Commission (DG SANTE, DG RTD and DG GROW), European Parliament, patient organisations
Develop and deploy a standardised EU-wide contracting and data-sharing framework for ERN–industry partnerships	A coordinated and 'centralised', EU-endorsed framework would reduce legal complexity, speed up partnership formation, and ensure compliance with privacy and data-protection standards.	European Commission (DG SANTE, DG RTD and DG CONNECT), ERN coordinators, industry associations
Support ERNs in becoming legal entities or forming shared-governance structures to streamline partnerships	Legal entity or a common governance umbrella would simplify negotiations with industry, clarify liability, and enable more agile multi-country projects.	European Commission (DG SANTE), ERN coordinators, Member States
Launch a European training and mentorship programme to build collaboration skills ("collaboration muscle") among ERN leaders, patients, and industry	Dedicated capacity-building would strengthen the "collaboration muscle," helping ERN leaders, patients, and industry partners to manage complex PPPs and to innovate jointly.	European Commission (DG RTD), ERNs, patient organisations, industry
Integrate rare disease priorities into broader EU policy areas (digital health, data spaces, industrial strategy) to ensure visibility and funding	Mainstreaming rare disease considerations into digital health, industrial strategy, and education would amplify impact and guarantee sustained visibility and funding.	European Commission (DG SANTE, DG RTD, DG CONNECT, DG GROW), Member States
Establish regular high-visibility events and communication campaigns to keep rare diseases on the EU political agenda	Ongoing public engagement would maintain political pressure, demonstrate success stories, and attract new partners and investors to the field.	All stakeholders, including the European Commission (DG SANTE, DG RTD, DG GROW), European Parliament, Member States, European Economic and Social Committee, ERNs, research infrastructures, patient organisations, industry
Include PPP outcomes in the monitoring and evaluation of ERNs	Transparent indicators on patient benefits, scientific outputs, and economic returns would provide evidence of impact, helping secure future investment and public trust.	European Commission (DG SANTE), ERNs

Participants list

In-person participants (40)

Policymakers

MEP Stine Bosse, *Renew Europe, Denmark*

MEP András Kulja,
European People's Party, Hungary

MEP Vytenis Andriukaitis,
Socialists & Democrats, Lithuania

Carmen Laplaza Santos, *DG Research and Innovation, European Commission*

Christina Kyriakopoulou, *DG Research and Innovation, European Commission*

Hélène le Borgne, *DG Research and Innovation, European Commission*

Boris Ajeganoff-Nielsen,
Policy Advisor to MEP Stine Bosse

Danai Spentzou,
Head of Office to MEP András Kulja

Dana Fahoum,
Head of Office to MEP Stine Bosse

Inga Stacinské, *Policy Advisor to MEP Vytenis Andriukaitis*

Industry

Alicia Granados, *Sanofi*

Anne-Sophie Chalandon, *Sanofi*

Estelle Michael, *UCB*

Jane Cooper, *Ultragenyx*

Dr. Johanna Grames, *AOP Health*

Magda Chlebus, *European Federation of Pharmaceutical Industries and Associations (EFPIA)*

Matteo Scarebelli, *European Federation of Pharmaceutical Industries and Associations (EFPIA)*

Noel Minnis, *Takeda*

Roudie Schafie, *Ultragenyx*

Toon Digneffe, *Takeda*

Viktoria Nickel, *AOP Health*

Research

Ana Rath, *Orphanet*

Dr. Biruté Tumienė,
Chair of the ERN Board of Member States

Dr. Daria Julkowska, *ERDERA*

Johanna Schell, *ERN EURACAN*

Flaminia Macchia, *Orphanet AISBL*

Prof. Franz Schaefer, *ERN ERKNet*

Prof. Maurizio Scarpa, *MetabERN*

Dr. Mehdi Brahmi, *ERN EURACAN*

Patient representatives

Lutgarde Allard, *EuMGA*

Marius Tanasé,
European Haemophilia Consortium

Rosa Castro, *EURORDIS*

Sophie Turner, *Empowered by Us*

Regional representation

Lina Christensen,
Central Denmark EU Office

Together For Rare Diseases Secretariat

Clara Romero (moderator)

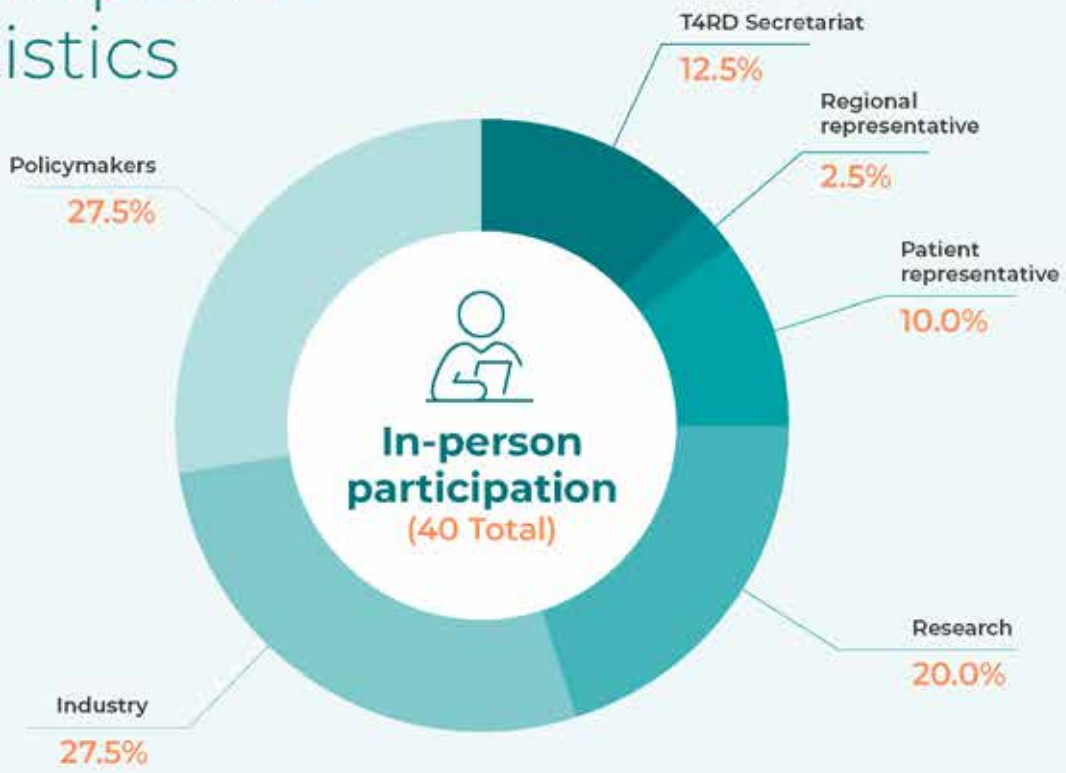
Mathieu Boudes

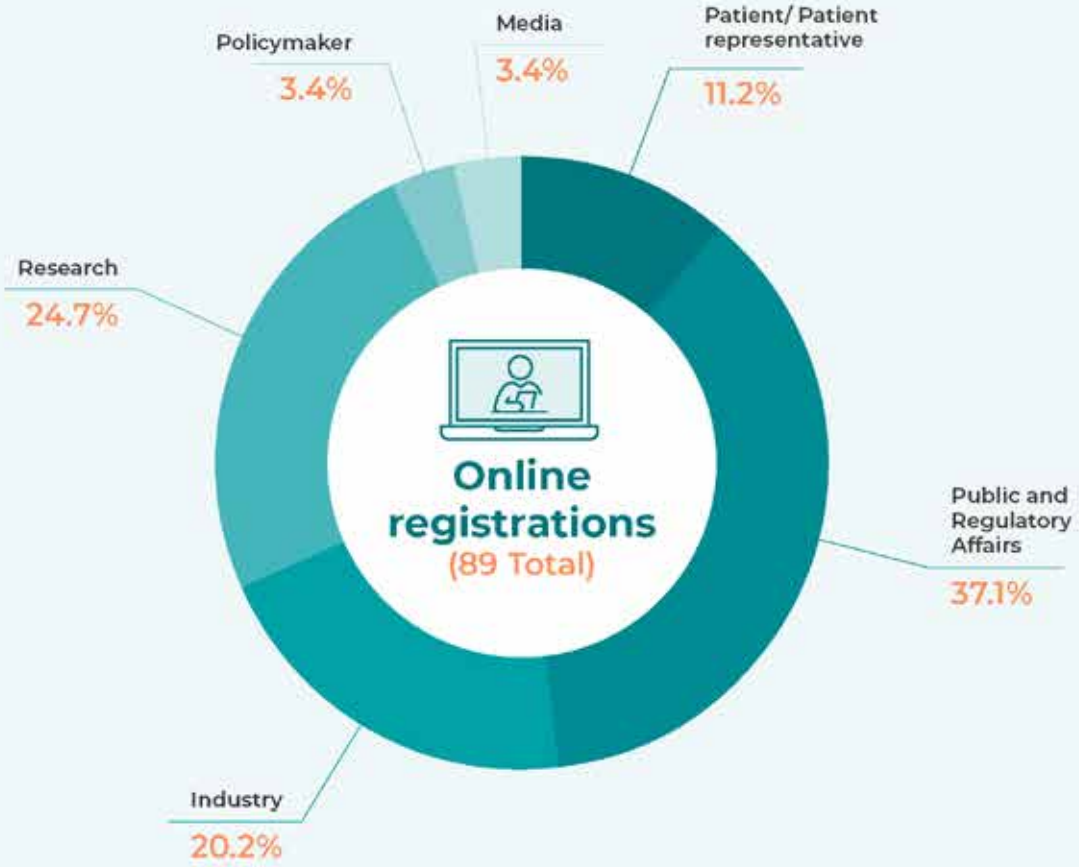
Olivier Levy

Sheela Upadhyaya

Victoria Hedley

Participation Statistics

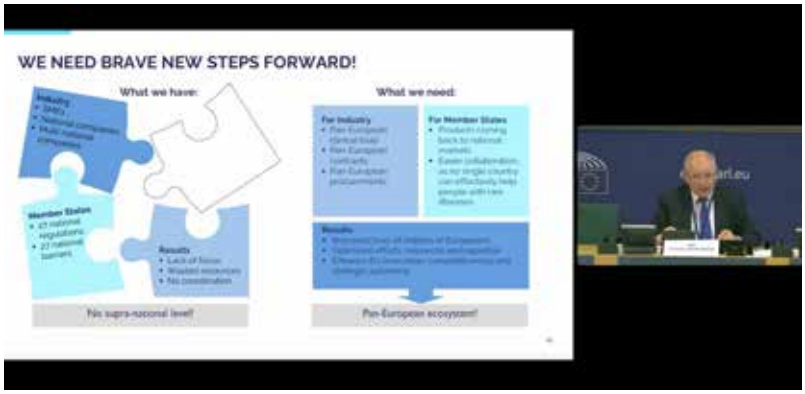




High-Level Meeting on a European research and innovation ecosystem for rare diseases

This three-day event, hosted by our Steering Group member Maurizio Scarpa (Coordinator, the European Reference Network for Hereditary Metabolic Diseases, MetabERN) and our MEP Champion (and former EU Health Commissioner) Vytenis Andriukaitis (S&D, Lithuania) gathered key stakeholders, including EU Commissioners, MEPs, member state representatives, industry leaders, patient advocacy groups, researchers, and healthcare providers.

Key discussions on policy and funding took place, creating a mandate for change and a declaration signed by several Together4RD Steering Group Members, industry leaders and even the former Italian Prime Minister **Enrico Letta**, among others. The conference hosted a wide breadth of speakers such as Commissioners **Teresa Ribera**, **Olivér Várhelyi**, **Ekaterina Zaharieva**, national ministers, the ERN Board of Member States, Members of the European Parliament, among many other key policy and opinion leaders in the European rare disease ecosystem.



Making research a pillar of the evaluation of the European Reference Networks – Joint position with Rare Disease Moonshot

In 2024, the European Commission's evaluation of ERNs highlighted significant progress in specialised care for rare diseases, particularly in cross-border consultations, clinical guidelines, training initiatives, and the development of epidemiological registries and databases.

The assessment recognised research activity as well, with 33.3% of ERNs deemed "excellent" and 66.7% "acceptable" yet also underscored that research remains uneven and under-leveraged across networks. The joint editorial with the **Rare Disease Moonshot** acknowledges these advancements but stresses the need to elevate research as a second core mission of ERNs, particularly through public-private partnerships, which remain a major untapped opportunity for accelerating scientific breakthroughs. Fully realising the research potential of ERNs requires providing the human and financial resources needed to become truly "research-ready" and capable of scaling their scientific activities. This should be paired with clear evaluation criteria, strong incentives, and a robust framework for meaningful PPPs that mobilise the scientific, regulatory and operational strengths of networks and industry, while promoting deeper integration with fundamental research institutions, pharmaceutical companies and biotech innovators.

← *Scan to read the news article*

Collaboration with ERICA

The European Rare Disease Research Coordination and Support Action Consortium (ERICA) has been a very important ally of Together4RD, and the two initiatives often worked in tandem to create synergies in rare disease research, sharing knowledge and engaging with stakeholders to capitalise on the strengths of ERNs.

2022: ERN Research Conference: ERN Data Management Strategy Multistakeholder Workshop

At ERICA's 2022 ERN Research Conference, Together4RD was presented in the context of the **funding models** for ERN registries and the short-, medium- and long-term viability of the ERN registries and the reuse of the data collected, leveraging PPPs capabilities.

2024: ERN Research Conference – Presentation of a Forum for Exchange of Information

A **Forum for Exchange of Information** was a key proposal of Together4RD and concept that could bring about informal ERN-industry meetings at ERN or scientific conferences to discuss potential areas for collaboration in therapeutic or disease-specific areas. There are major gaps in knowledge among both ERN and industry representatives about what each can offer to rare disease research, highlighted in these two reports:

> *"Many companies [...] are generally not aware of what ERNs actually offer nor what they have achieved and what priorities they are embracing for the coming years."*
>
> **TOGETHER FOR RARE DISEASES POSITION PAPER** 2023

> *"PPPs are an ecosystem. In that ecosystem or 'community of brains', every partner plays a role. In addition to financial resources, industry brings complementary skills sets, knowledge and competence. Central to success is a mutual understanding of objectives and the 'end goal', and the importance of building and sustaining trust throughout the partnership."*
>
> **IRDIRC PROJECT:** THE DIFFERENT CONTRIBUTIONS OF THE INDUSTRY IN PUBLIC-PRIVATE PARTNERSHIPS IN RARE DISEASES RESEARCH CONTINUUM, 2024

The Forum for Exchange would help both sides identify opportunities to engage, open doors for collaborations, raise commitment to co-create and pool research ideas. Sheela Upadhyaya suggested several formats and opportunities for the forum, such as:

1. Research conferences, bringing together all ERNs and industry stakeholders
2. Strategy forums, with all ERNs and industry stakeholders
3. Meetings focused on therapeutic areas, with specific ERNs and interested companies
4. ERN sub-networks and companies working on specific diseases

Sheela also identified important **success factors** for a Forum of Exchange:

At a major gathering of ERN members and coordinators in Udine, Italy, **Sheela Upadhyaya** presented Together4RD proposal for a **Forum of Exchange of Information**. Identifying the gaps in knowledge among both ERN and industry representatives about what each can offer to rare disease research, Sheela floated the idea of hosting

The Forum for Exchange would help both sides identify opportunities to engage, open doors for collaborations, raise commitment to co-create and pool research ideas.

We firmly believe the Forum for Exchange of Information could help move the needle in promoting cooperation. Although they did not launch under Together4RD, we encourage ERN coordinators and ERDERA to take the proposal forward.

SUCCESS FACTORS

- **Focus as specific as possible (therapeutic area — disease-specific)**
- **Researchers (academia and private) focusing on the same disease(s)**
- **Clear description of "what's in it for me?"**
- **Research congresses and/or patient advocacy group-organised conferences**
- **All parties involved need to be clear on the problem statement**

Bridging the knowledge gap between ERNs and industry in rare disease research - Webinar series with ERICA on Public-Private Partnerships

Jointly with ERICA, Together4RD hosted a webinar series in 2024-2025 aimed to bridge the knowledge gaps between ERNs and the pharmaceutical and biotech industries, fostering collaborations that can accelerate research and development in rare diseases, ultimately benefiting patients and advancing medical science.

ERNS: A KEY EU INFRASTRUCTURE TO PARTNER FOR RESEARCH ACTIVITIES, THE WHY AND THE HOW

In our first instalment, ERN coordinators **Alberto Pereira** (Coordinator, the European Reference Network for rare endocrine conditions, Endo-ERN) and **Franz Schaefer** (Coordinator, the European Rare Kidney Reference Network, ERKNet), alongside **Katarzyna Mosiewicz** (Medical Affairs, Novo Nordisk) outlined **how and where ERNs can serve as research partners for industry**, presenting the resources, data repositories and clinical expertise available within ERNs.

They provided specific examples of how ERNs have developed clinical data repositories, trial networks, biobanks and tissue samples, registries, standardised protocols and guidelines, telemedicine platforms, training and education resources, and data sharing initiatives that make ERNs invaluable for research, including the RHINE Project, one of Together4RD's public-private partnerships which serves as an excellent case study of how public-private partnerships in rare disease research can develop, the capacity, skills and structures required, as well as challenges encountered in the project's development.

RARE DISEASE RESEARCH: WHAT INDUSTRY CONTRIBUTES IN KNOWLEDGE AND RESOURCES

Shifting the focus to what industry can bring to rare disease research beyond resources, **Vinciane Pirard**, **Luca Sangiorgi** (Coordinator, the European Reference Network on rare bone diseases, ERN-BOND) and **Anton Ussi** (the European infrastructure for translational medicine, EATRIS) explained that industry provides valuable insights into regulatory requirements and help guide research design to ensure research outcomes are more readily translatable. Industry participation in public-private partnership can improve the number of regulatory-grade outcomes in academic research, deploy research into real world settings, inspire collaborative leadership and innovation drive, and adopt a patient-centred approach which can result in tangible contribution to the research ecosystem.

Luca Sangiorgi dived into the PPP developed by ERN BOND and Sanofi on a pilot project aimed at better understanding the disease burden of osteogenesis imperfecta, a heritable skeletal disorder colloquially known as "brittle bone disease." The project provides a valuable example as to how to structure a PPP and advance it thanks to a milestone approach, combining tangible targets with more ambitious and mid/long-term goals.

Rare Disease Day

2023: 3rd International Conference on Rare Diseases: Greek Chapter - Session 10: Research and Clinical Trials as part of Care (March 2023)

Together4RD brought a pan-European perspective to Athens, presenting pan-European efforts, led by the European Commission, to boost research and clinical trials and reduce fragmentation, such as through the Strategic Research & Innovation Agenda of the Innovative Health Initiative (IHI), the progress of ERNs since their inception in 2017, and their ability to embed clinical trials as part of their delivery of patient care.

The discussion panel featured **Sheela Upadhyaya**, our **MEP Champion Sara Cerdas**, **Christina Kyriakopoulou** (Policy Officer, DG Research and Innovation, European Commission), **Luca Sangiorgi**, **Daria Julkowska** (Scientific Coordinator, formerly EJP RD, now ERDERA) and **Diego Ardigó** (Executive Vice-President, Global Research and Development, Chiesi). A number of pivotal topics were explored such as the conception and implementation of the European Health Data Space (EHDS), the development of international data registries which are interoperable and FAIR, and how stakeholders envision collaboration between ERNs and industry.

On a global level, **Diego Ardigó** also explained how **IRDiRC** has encouraged international collaboration and what Europe's role could be in setting a benchmark for collaboration and progress.

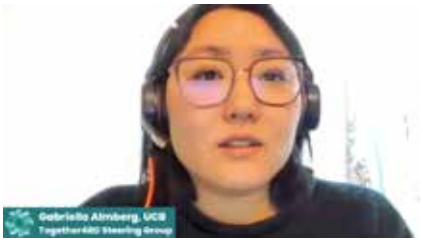
2024: Steering Group video campaign on the Together4RD position paper

In 2024 our Steering Group published a series of videos, with 7 members elaborating on the Together4RD position paper, and how Together4RDs is trying to maximise what ERNs can bring to patients by exploring opportunities for collaboration with industry.

The campaign featured clear and engaging explanations from Gabriella Almberg (Head of Health System Policy & Public Affairs, UCB), Rima Nabbout (Director, Imagine Institute), Victoria Hedley, Clara Romero (Together4RD Secretariat), Sheela Upadhyaya, Matt Bolz Johnson (formerly Healthcare and Research Director, EURORDIS-Rare Diseases Europe), Toon Digneffe (Head of Public Affairs and Public Policy, Takeda) and Maurizio Scarpa.

The series was published through January-February 2024.

← *Scan to view videos*



2025: Living with *Osteogenesis Imperfecta* / Living with *Primary Hyperoxularia*

On Rare Disease Day 2025, we published an article series explaining the symptoms, experiences and impact on quality of life living with *Osteogenesis Imperfecta* and *Primary Hyperoxularia*. We explored the daily burden of the diseases, the challenges of obtaining a diagnosis, which can be a long and difficult odysseys, and how Together4RD's pilot projects between ERNs and industry are seeking to alleviate the disease burden.

← *Scan to read "What is it to live with* Primary Hyperoxularia*?"*

← *Scan to read "What is it to live with* Osteogenesis Imperfecta*?"*

European Conference on Rare Diseases (ECRD)

2022: Thought leadership panel discussion – raising awareness about Together4RDs

MEP Ondrej Knotek led the call for EU action to address the barriers to collaboration between ERNs and industry in research.

With several Steering Group members including **Sheela Upadhyaya**, **Hélène Dollfus**, **Toon Digneffe** and **Inés Hernando** (ERN and Healthcare Director, EURORDIS-Rare Diseases Europe), Together4RD explained the role we see for ERNs in rare disease research & innovation, and what the win-win outcomes are for ERNs and industry from closer partnership. The value that the patient community sees in Together4RD's work was also outlined.

The panel delved into the future ambitions for Together4RD, and the collaboration pilot projects that will be used to demonstrate proof of concept to the European Commission and Board of Member States.

2024: Thought leader session, in partnership with Rare Disease Moonshot, on collaborating for change: transforming rare disease research and outcomes through public-private partnerships

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Orphanet Journal of Rare Diseases

MEETING ABSTRACTS **Open Access**

Meeting abstracts from the 12th European Conference on Rare Diseases and Orphan Products

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Meeting abstracts from the 12th European Conference on Rare Diseases and Orphan Products

COLLABORATING FOR CHANGE: TRANSFORMING RARE DISEASE RESEARCH AND OUTCOMES THROUGH PUBLIC-PRIVATE PARTNERSHIPS

Magda Chlebus[1,2], Sheela Upadhyaya[3], Danielle Dong[4], Kira Gillett[5], Roseline Favresse[6], Matt Bolz-Johnson[6], Alexandre Bétourné[7], Salah-Dine Chibout[8], Holm Graessner[9], Clara Romero[10,3], Mathieu Boudes[2,3,11*]

[1]European Federation of Pharmaceutical Industries and Associations, Brussels, Belgium. [2]Rare Disease Moonshot, Brussels, Belgium. [3]Together For Rare Disease (T4RD), Brussels, Belgium. [4]Sanofi, Cambridge, Massachusetts, USA. [5]The AMP© Bespoke Gene Therapy Consortium, Foundation for the National Institutes of Health, North Bethesda, Maryland, USA. [6]EURORDIS-Rare Diseases Europe, Paris, France. [7]Critical Path Institute (C-Path), Tucson, Arizona, USA. [8]Novartis Pharma, Basel, Switzerland. [9]Centre for Rare Diseases, University Hospital Tübingen, Tübingen, Germany. [10]FIPRA, Brussels, Belgium. [11]Montsouris Consilium, Montpellier, France.

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BACKGROUND

Despite substantial investments in rare disease research, only 5% have approved treatments. Public-Private Partnerships (PPPs) represent a promising approach to enhance innovation and accelerate therapy development. Politically, there is a growing recognition of the need for stronger partnerships to tackle the challenges in rare disease research and therapy development.

RESULTS

Public-private partnerships (PPPs) are crucial for promoting innovation into precision therapy in healthcare, with the example of the AMP© Bespoke Gene Therapy Consortium aiming to streamline the navigation of the regulatory process with the Regulatory Playbook and enhance the accessibility of adeno-associated virus (AAV) technology. The Rare Disease Cures Accelerator-Data and Analytics Platform (RDCA-DAP), developed by the Critical Path Institute, demonstrated the importance of standardizing data collection methods and creating centralized platforms to facilitate more efficient regulatory processes and therapy development. It has significant engagement from academia, industry, and regulatory agencies, with approximately 400 users accessing and analyzing the data. The Innovative Health Initiative (IHI) is another successful PPP model, promoting collaboration between industry, academia, and patient organizations to accelerate the development of innovative medicines, solutions, and research infrastructures. The importance of co-creation, transparent communication, and mutual goals for successful partnerships was emphasized, for e.g. the Sanofi-ERN BOND collaboration showed how early stakeholder engagement leads to impactful solutions and effectively addresses unmet needs in research. Pre-competitive collaboration was recognized as a significant opportunity to enhance the collaborative spirit within PPPs and eliminate competitiveness. The session also stressed the role of the human factor to foster trust and establish robust foundations to establishing a unified project scope, defining research questions, and building personal relationships among partners, particularly in the early stages of a project.

CONCLUSIONS AND NEXT STEPS

Strengthening PPPs is essential for advancing therapy development for rare diseases. Enhanced collaboration, effective co-creation, transparent communication, and standardized data collection are crucial for driving innovation. Key actions include advocating for new partnership models, removing barriers, involving patients and their representatives, focusing on incremental advancements, and sustaining pre-competitive collaborations. By implementing these steps, Europe can enhance its research capabilities and expedite treatment development for rare diseases.

Raising awareness on PPPs with ERNs to biotech companies

Together4RD has collaborated and proudly retained the support of two major European pharmaceutical trade associations: EFPIA (the European Federation of Pharmaceutical Industries and Associations) and EUCOPE (the European Confederation of Pharmaceutical Entrepreneurs).

Both are members of the Together4RD Steering Group and have shown willingness to cooperate with ERNs, experiment with new forms of collaboration and committed to exploring new avenues to advance rare disease research.

Presentation to EUCOPE Orphan Medicinal Products Working Group (November 2023)

Meeting EUCOPE's Orphan Medicinal Products (OMP) working group in late 2023, Together4RD had the opportunity to discuss ERNs with smaller biotech companies and raise awareness of the possibilities and potential opportunities in working alongside ERNs to engage in rare disease research.

Highlighting the initiative's successes in 2023 and growing momentum around rare diseases, the OMP Working Group received a thorough explanation of how Together4RD has been active in political discussions on rare diseases, and supporting ERNs to have appropriate resourcing and the enhanced ability to meet unmet needs through R&D.

Presentation to EFPIA Orphan Medicinal Products Working Group (July 2024)

In July 2024 Together4RD met with EFPIA's Orphan Medicinal Products (OMP) working group for a conversation on how Together4RD and EFPIA members can move the needle in rare disease research.

We explored the importance of gathering case studies to share understanding of where interactions already occur, displaying proof of concept to test approaches and gather learnings, engaging with patient and research communities to identify opportunities and raise awareness, gaining adequate resources to support ERNs, and considering governance and structural options for ERNs that can be established in the long-term.

The team also agreed on how to measure progress and success for the initiative in 2025, particularly gathering support from MEPs, publishing the Together4RD toolkit, and looking towards an EU Action Plan on Rare Diseases to include research and public-private partnerships between ERNs and industry.

Nordic Summit 2023

Together4RDs led a plenary session on *the role of registries in early diagnosis*, linking the importance of data registries to diagnosis and highlighting Together4RD's recommendation for independent, well-resourced and effective ERN registries.

With representatives of Horso (the Finnish Alliance of Rare Diseases and Disabilities Organizations), Alexion and EUCOPE, the panel explored how industry and multistakeholder initiatives can help build, maintain and use data registries for the benefit of patients.

NORDIC RARE DISEASE SUMMIT 2023

World Orphan Drug Congress

Together4RDs was a prominent fixture at the largest and most established orphan drug & rare disease meeting in the world, hosting important discussions about unlocking rare disease research.

2022: Putting proposals into action

In its first year at the Congress, Together4RD's Chair, Steering Group Members and MEP Stelios Kympouropoulos explained the initiative's role of exploiting the potential of ERNs to deliver progress in rare disease research.

With **Milan Majek** (Motel University Hospital), **Vicki Hedley**, **Anton Ussi**, **Matt Bolz-Johnson**, **Henrik Jarlov** (Novo Nordisk) and **Maciej Gajewski** (formerly Executive Director, Head of International Government Affairs and Policy, Alexion), **Sheela Upadhyaya** presented Together4RD's proposals to accelerate research, and position paper and findings on A new ERN-industry Framework for Collaboration (see page 41)

2023: Making headwinds in ERN-industry partnerships

An expert panel of Maurizio Scarpa, Matt Bolz-Johnson and Gabriella Almberg led a session with Sheela Upadhyaya on how ERNs can identify opportunities improve diagnosis and new therapies.

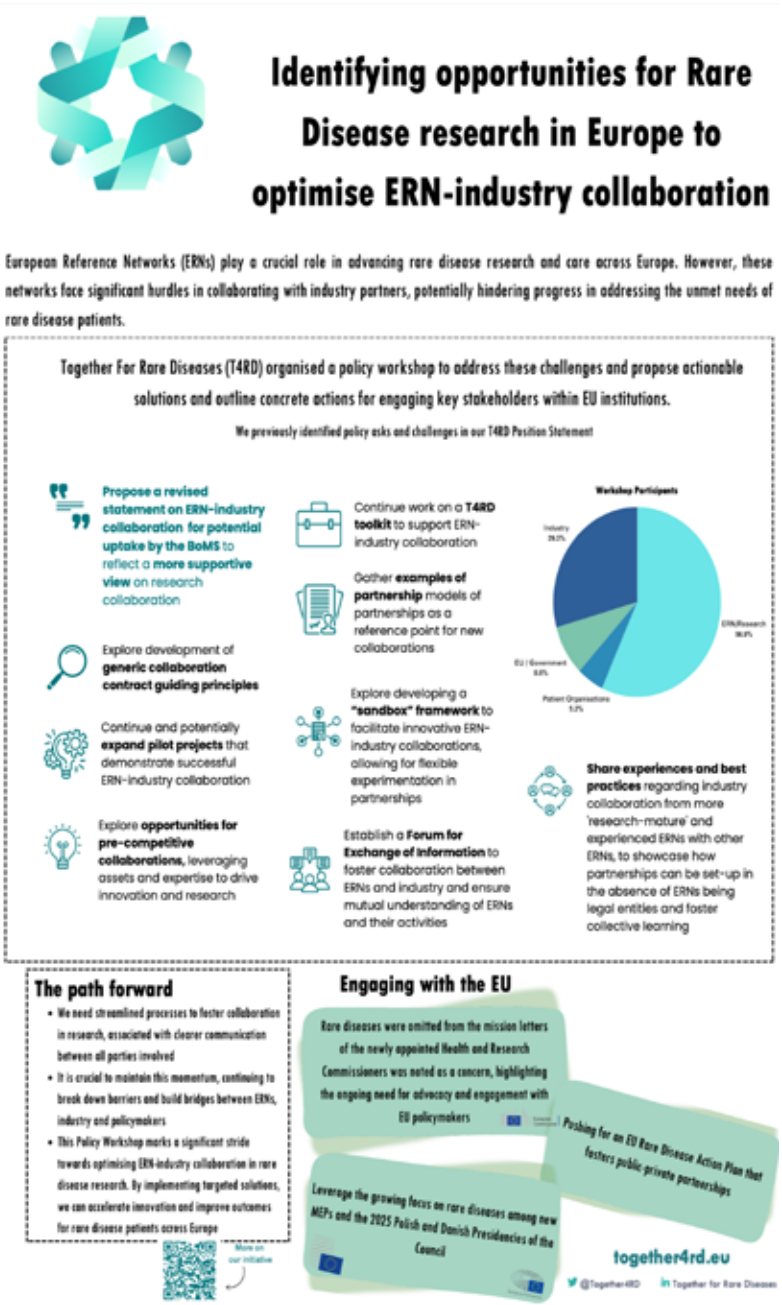
Clara Romero and **Rosalind Kenward** (Together4RD Secretariat) presented Together4RD's position paper, earlier that year published in Orphanet (see page 41), explaining the practical barriers faced by ERNs in intensifying their research efforts with industry. A third session with **Stefanie Häberle** (Project Manager, ERKNet), **Mar Mañú Pereira** (Scientific Director, EuroBloodNet), **Lu Zheng** (Vice-President, Head of Digital Health, Takeda) and **Katarzyna Mosiewicz** homed in on Together4RD's pilot projects, delivering industry and ERN perspectives on the advantages and obstacles to ERN-industry collaboration.

In the plenary our champion **MEP Stelios Kympouropoulos**, delivered a keynote speech on the role of policymakers in enabling ERNs to enhance their contributions to the rare disease ecosystem. **Anton Ussi**, **Alexis Arzimanoglou**, **Graham Slater** (Board Member, EURORDIS) and **Anne-Sophie Chalandon** (Global Rare Public Affairs – Rare Diseases Policy Head, Sanofi) followed suit, discussing how stakeholders can build impetus for political and policy support of ERN-industry collaboration.

2024: Changing lives with science in public-private partnerships: what are the success factors to scientific breakthrough?

With a panel composed of Danielle Dong (Scientific Advocacy Lead, Global Medical Affairs, Rare Diseases, Sanofi), Sheela Upadhyaya and Victoria Hedley, we explained how the initiative's pilot projects are making headwinds in rare disease research, and the scientific advancements, and what were the success factors that have been identified from these initiatives.

Danielle Dong presented data and forecasts on the tangible outcomes of PPPs, including improved patient diagnostics, novel therapeutic approaches, and enhanced understanding of rare disease mechanisms, explaining the desired outcomes of the pilot projects and value they aim to generate for research and patients. We also publicised the outcomes of a workshop held with the **ERN Board of Member States** in September 2025, highlighting the political steps that need to be taken to streamline processes, maintain political momentum and engage with the EU institutions to leverage rare diseases among MEPs, the European Commission and rotating presidencies of the Council.



2nd International Conference on Clinical Research Networks for Rare Diseases

At this conference in Heidelberg in December 2025, hosted by ERDERA, Vicki Hedley shared insights from Together4RD and the lessons learned in seeking to foster ERN and industry collaboration, for a highly specialised audience interested in progress through joint projects, data-sharing frameworks, and interoperable infrastructures.

Vicki offered several practical steps to initiate and strengthen pan-European collaboration in rare disease clinical research, relaying the successes of the Together4RD pilots to help the group understand how to move from identification and siloed excellence to pan-European and cross-sectoral collaboration and progress.

Putting ERN-industry rare disease research collaboration in practice

Three pilot projects

ERN-industry partnership on Natural history and innovative clinical trial measures in Osteogenesis Imperfecta (launched) - Sanofi and ERN-BOND

This pilot project centres on three main activities:

Firstly, value is being drawn from several sources of existing data relating to patients with the rare bone condition OI, to better elucidate the natural history and the disease burden. Genotype-phenotype correlations will be explored, as part of this drive to better understand the condition. treatment, organ ischemia and death occurs in around 90% of cases. To improve early diagnosis, partners employed an AI federated platform across key clinical centres, which will ideally be based on the hospitals own EHR systems. Whilst reducing time to diagnosis, and thus enabling treatment to begin as early as possible, the AI platform should lead directly to improved patient outcomes by alerting treating clinicians of patients at risk of relapse, who can then be monitored in appropriate ways. The initial phase of the pilot focused on scoping activities and identifying centres for the implementation phase. From the ERN side, the pilot is being delivered through an organisation known as the EuroBlooNet Association, together with the Fundació Hospital Universitari Vall D'Hebron, which is the entity in charge of the ERN's shared registry (ENROL), and also the Fondazione IRCCS Ca' Granda - Ospedale Maggiore Policlinico.

Secondly, prospectively, the project will measure the impact of disease on patient activity and quality of life using digital technologies in a real-world setting, through a combined approach of gait analysis and sensors.

Lastly, in preparation for smoother regulatory pathways for OI therapies in future, the project partners will jointly engage in early scientific dialogues with other stakeholders (such as regulators and HTA), to gain insights into approaches to foster patient access to innovative medicines.

ERN-industry partnership to unlock the potential of data in Rare Renal Diseases with harmonisation and robust interoperability model (launched) - Novo Nordisk, ERKnet and Oxal Europe

The RHINE Project aims to improve care pathways and patient outcomes in rare renal conditions, by building on existing registry infrastructure, especially the core registry of the ERK-Net ERN (named ERK-Reg). This pilot focuses in particular on an ultra-rare disease called primary hyperoxaluria (PH), and addresses a fundamental need to complement the core registry structure of the ERN with detailed data collection for specific conditions.

A 'harmonization and interoperability' model will be developed for PH, by establishing a Rare Kidney Network data registry, in collaboration with the European Hyperoxaluria Consortium (OxalEurope), to achieve seamless data

connection across ERK-Net and PH-specific registries.

Through this new data linkage approach, the project aims to understand PH diagnostic and referral pathways locally, measuring metrics like time-to-diagnosis, where PH patients are seen (by measuring the number of cases in each referring center), and the percentage of patients diagnosed before they reach end-stage renal disease (the point at which the kidneys can no longer support the body's needs). To compliment this focus on an improved data ecosystem, educational activities will be implemented at regional and local levels, to target the gaps and shortcomings identified. As of late 2024, this pilot has already generated significant added- value simply by bringing the registry owners from the ERK-REG and the OxalEurope consortia together, around the same table, having built a robust formal agreement for collaboration. The technical integration work is now underway, mapping data dictionaries to explore what each registry ecosystem currently collects.

ERN-industry partnership on improving diagnosis for rare hematologic diseases by utilising algorithms for early detection (paused)

This initiative is all about improving the diagnostic pathways for rare haematological diseases by utilizing AI algorithms for early detection. The activity is expected to focus on thrombotic thrombocytopenic purpura (TTP), a very rare and debilitating condition existing in both a congenital form and an acquired, immune-mediated form (which manifests in the 4th or 5th decades). The variable phenotype for TTP and lack of availability of the necessary diagnostic tests, leads to delayed diagnosis, which is very concerning as without a correct diagnosis and treatment, organ ischemia and death occurs in around 90% of cases.

To improve early diagnosis, the plan is to employ an AI federated platform across key clinical centres, which will ideally be based on the hospitals own EHR systems. Whilst reducing time to diagnosis, and thus enabling treatment to begin as early as possible, the AI platform should lead directly to improved patient outcomes by alerting treating clinicians of patients at risk of relapse, who can then be monitored in appropriate ways.

The initial phase of the pilot will focus on scoping activities and identifying centres for the implementation phase. From the ERN side, the pilot is being delivered through an organisation known as the EuroBlooNet

Association, together with the Fundació Hospital Universitari Vall D'Hebron, which is the entity in charge of the ERN's shared registry (ENROL), and also the Fondazione IRCCS Ca' Granda - Ospedale Maggiore Policlinico.

ERICA-EJP RD Joint Conference (November 2023)

In Amsterdam, Together4RD and explained in great length how the assets, capacities and know-how of all research stakeholders are unique and complementary and entirely compatible.

Rima Nabbout and **Mathieu Boudes** (Together4RD Secretariat) gave a refresher on Together4RD, taking audiences on a journey through the pilot projects and presented PPPs as an opportunity to tap into the enormous potential of ERNs.

A Toolkit to foster ERN-industry collaboration

In 2025, Together4RD published a comprehensive toolkit to support a broad range of collaborative activities in which ERNs and industry might partner. The Toolkit responds to a clear need: turning the promise of public-private partnerships in rare disease research into tangible, impactful action.

The toolkit is Together4RD's most comprehensive effort to **strengthen research collaboration between ERNs and industry**. ERNs, established to improve the diagnosis and care of people living with rare diseases, are recognised as key enablers of rare disease research due to their pan-European networks, data infrastructure, and deep disease-specific expertise. Yet, many of these networks operate in fields with limited prior R&D and lack experience in engaging with private sector partners.

The Toolkit is the result of 3 years of significant outreach and consultative processes with ERNs, industry, research infrastructures and patient representatives, and is intended to reflect the needs of both ERNs and of industry, having engaged key groups of stakeholders in a co-creation process. ERNs and industry may have different needs, and see value in different components of this resource, but the Toolkit provides added value for both sets of stakeholders.

Section A: Background Knowledge – ERNs, industry and the opportunity

TOOL 1: THE IMPORTANCE OF PUBLIC PRIVATE PARTNERSHIPS IN RARE DISEASES

Explains the importance of public-private partnerships or collaborations for the rare disease community, in the light of the needs of the rare disease field and the current climate around research and innovation.

TOOL 2: EXAMPLES OF INITIATIVES WHICH FOSTER PUBLIC-PRIVATE PARTNERSHIPS IN RARE DISEASES AND COMPLEMENTARY AREAS

Examples of programmes and structures which facilitate public-private partnerships in rare disease or a complimentary area.

TOOL 3: WHAT ARE ERNS?

This Tool:

- Explains the origins of ERNs
- Highlights key resources concerning the conceptualisation, set-up and operations of ERNs, including the legal documents on which they are based
- Points to useful reports and recommendations concerned with analysing the achievements and added-value of ERNs to-date, which suggest where there might be room for improvement.
- Points to key resources showcasing the achievements of the ERNs, as a whole, as well as where to learn more about the achievements of specific ERNs

TOOL 4: THE ADVANTAGES OF ERNS AS PARTNERS FOR RESEARCH

Illustrates how and why ERNs hold so much potential for research, including 2025 statistics and development connected with ERNs' research potential.

TOOL 5: NEEDS AND PRIORITIES FOR INDUSTRY – AND WHAT DOES INDUSTRY NEED IN A COLLABORATION WITH ERNS?

A summary of important considerations for stakeholders less used to working with industry, coupled with a selection of resources (webinars, reports, publications) to help convey some fundamental principles and realities for the private sector in contemplating collaborations with ERNs.

View the full Toolkit in Annex III.

*The toolkit will be hosted in the **ERDERA Innovation Management Toolbox**.*

Section B: Conceptualising and firming-up a collaborative idea of research

TOOL 6: BRIEF SUMMARIES OF THE FIRST TOGETHER4RD PILOTS

Detailed information on the public-private partnerships initiated between EuroBloodNet and Takeda, ERN-BOND and Sanofi, and ERKNet and Novo Nordisk.

TOOL 7: CASE STUDIES – EXAMPLES OF PREVIOUS OR ONGOING PUBLIC-PRIVATE COLLABORATIONS IN THE RARE DISEASE SPACE

Case studies in the rare disease arena which may also serve as food for thought for other stakeholders wishing to follow suite and engage in projects.

TOOL 8: SUMMARY OF AREAS OR ACTIVITIES FOR POTENTIAL ERN AND INDUSTRY COLLABORATION

A broad range of potential projects and activities which might be well-suited to ERN and Industry collaboration.

Section C: Practical knowledge transfer – initiating and delivering a well-developed research collaboration

TOOL 9: REPORT ON THE EXPERIENCES AND LEARNINGS FROM THE FIRST ERN-INDUSTRY PILOTS SUPPORTED BY TOGETHER4RD

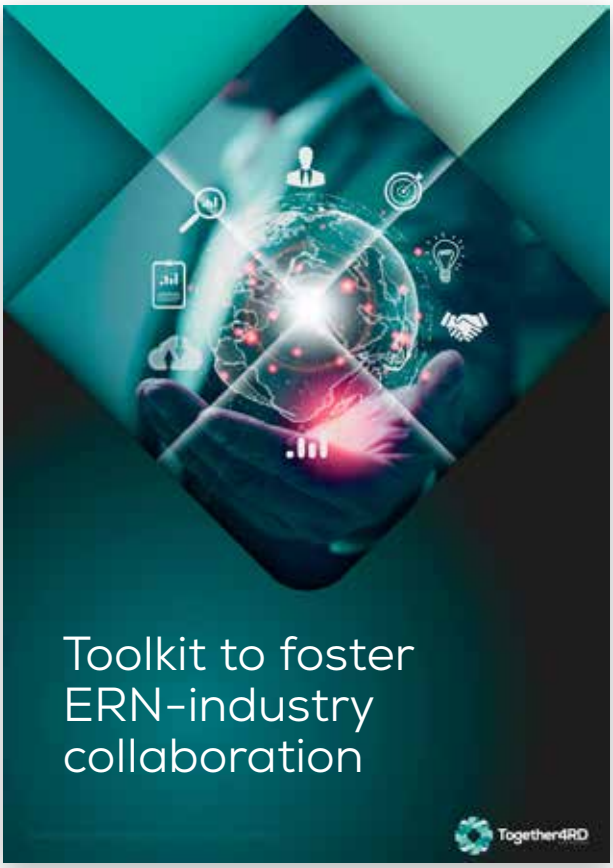
Insights from interviews with ERN and industry representatives about their experiences in launching the first ERN-industry pilot projects. These interviews were intended to better understand the respective experiences of conceptualising and initiating these pilots – from who came up with the original idea, to how the project proposals have taken shape, covering activities up to the launch phase (approximately).

TOOL 10: KEY RECOMMENDATIONS FOR BOTH ERNS AND INDUSTRY FROM THE EXPERIENCES OF THE FIRST ERN-INDUSTRY PILOTS

A list of recommendations to guide future ERN and industry projects and collaborations.

TOOL 11: QUESTIONS PEOPLE SHOULD CONSIDER WHEN APPROACHING A NEW COLLABORATION BETWEEN ERNS AND INDUSTRY

Intended as a guide, for all parties, to help stakeholders ensure they enter into co-creation and negotiations with the best chance of success. Specific and realistic expectations are important, to maximise the efficiency of those early discussions, and hopefully avoid some of the pitfalls that can occur and delay or even jeopardise a public-private collaboration.



View the full Toolkit in Annex III.

A series of workshops to inform the development of the Toolkit

A series of workshops in 2024 informed the direction and content of the Toolkit.

It was held in two instalments:

1. **Phase I:** ERN, research and academic representatives, May 2024, Bari, Italy
2. **Phase II:** Industry representatives, June 2024, online

Both workshops explored the real and perceived obstacles to furthering ERN-industry research cooperation, and what each side needed to pursue closer collaboration. At both occasions the Secretariat explained the purpose and added value of the toolkit and gathered feedback from participants about the information the Toolkit could provide which could educate all rare disease stakeholders on the precedence, possibilities and practicalities of public-private partnerships in rare diseases. Participants were asked leading questions, such as *What would have made collaboration easier?* and identified several challenges such as misalignment between parties, a lack of resources, lengthy processes and a need for greater project management.

In a second phase, held online in June 2024, Together4RD gathered industry representatives to gather their perspectives on what purpose, content and audience the toolkit could have. Industry guests were asked for their views on the major added value of the toolkit and were able to clarify what tools they felt would be helpful for them to work with ERNs, as well as what would be helpful to support ERNs in engaging with industry.

Launching the Toolkit with ERDERA

The toolkit was launched alongside ERDERA (the European Rare Diseases Research Alliance) in June 2025, followed by a social media campaign timed to coincide with the publication of the EU Life Sciences Strategy, which will be pivotal for rare disease research in the coming years.

To learn more about the toolkit, and its value to all stakeholders in European rare disease research, visit the QR code below.

> *"Forging a partnership requires ERNs and industry to appreciate each others' needs, priorities and realities."*
>
> **VICTORIA HEDLEY**
> RARE DISEASE POLICY MANAGER, NEWCASTLE UNIVERSITY

View the full Toolkit in Annex III.

*The toolkit will be hosted in the **ERDERA Innovation Management Toolbox**.*

Communications

LinkedIn by Numbers

Users and Views	**2,090** FOLLOWERS	**70,000** POST IMPRESSIONS	
Top post of 2025	**2,086** LIKES	**25** RE-POSTS	**3,341** IMPRESSIONS
Posts	**80** PER YEAR	**150–200** POSTS SINCE 2022	

Governance

Together4RD has, from start to finish, been supported by a formidable multistakeholder Steering Group, consisting of inspiring, committed and proactive members from across Europe who have dedicated their careers to improving the prospects for people living with rare diseases around the world. The initiative has been enrichened by their experience, knowledge and passion. Our thanks go to:

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- **Maciej Gajewski**, Alexion

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Annex

Annex I – Position Paper

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POSITION STATEMENT Open Access

Together4RD position statement on collaboration between European reference networks and industry

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Abstract

Notwithstanding two decades of policy and legislation in Europe, aimed to foster research and development in rare conditions, only 5–6% of rare diseases have dedicated treatments. Given with the huge number of conditions classed as rare (which is increasing all the time), this equates to major unmet need for patients (over 30 million in the EU alone). Worryingly, the pace of Research and Innovation in Europe is lagging behind other regions of the world, and a seismic shift in the way in which research is planned and delivered is required, in order to remain competitive and—most importantly—bring meaningful, disease-altering treatments to those who desperately need them. The European Reference Networks (ERNs), launched in 2017, hold major potential to alleviate many of these challenges, and more, but only if adequately supported (financially, technically, and via robust policies and infrastructure) to *realise* that potential: and even then, only if able to forge robust collaborations harnessing the expertise, resources, knowledge and data of all stakeholders involved in rare disease, including Industry. To-date, however, ERN-Industry interactions have been largely limited, for a range of reasons (concerning barriers both tangible and perceived). This Position Statement analyses these barriers, and explains how Together4RD is seeking to move the needle here, by learning from case studies, exploring frameworks for collaboration, and launching pilots to explore how best to plan and deliver multistakeholder interactions addressing real research needs.

Keywords Rare disease, European reference network, Public–private-partnership, Rare diseases, ERNs, Networking, Research

This article is part of the Topical Collection on Other.

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Part 1: The EU Context

Unmet needs of rare diseases and the status quo of European research

Rare diseases (RD) are, by definition, rare; however, there are an estimated 6–8,000 separate conditions classed as rare, based upon the definition espoused by Regulation (EC) No 141/2000, with an average of 4–5 new conditions described every week. This means that collectively, rare diseases affect a significant proportion of the population, approximately 1 in 18 people. Patients and families typically face challenges in every stage of their journey, from seeking an accurate diagnosis to finding a specialist, participating in research studies and accessing

the best available treatment and care. Beyond the clinic, rare diseases tend to impact negatively on all aspects of daily life [1]. One particularly sobering statistic illustrating the extent of these inequalities is that 95% of the conditions classed as rare have no dedicated treatment (and where treatments *do* exist, they tend to address the symptoms and have little impact on the natural history of the disease). These tend to be *very* rare conditions, affecting fewer than 1 in 100,000 people, often poorly understood; indeed, It is acknowledged that 84.5% of rare diseases have a prevalence of less than 1/100,000, yet more than 98% of people living with a rare disease have one of the 390 most common conditions (with prevalence between 1–9/100,000 and 1–5/10,000) [2]. The diseases which do have therapies tend to be clustered around one of a limited number of therapeutic areas (60% of orphan medicine products designations during the period 2010–2020 were for oncology, alimentary tract & metabolism, and musculoskeletal & nervous system disorders [3]). All of this results in significant inequalities for patients and their families, because of the rarity of the disease, whilst also posing challenges for healthcare professionals and health systems at large (which often struggle to provide expertise across the heterogeneous range of rare conditions).

The extent of these challenges have marked rare diseases out as an area of priority action at European level, for many years. Key policy documents were issued in 2008 (the Commission Communication on *Rare Diseases: Europe's challenges* [COM(2008) 679 final] [4]) and 2009 (the Council Recommendation on an action in the field of rare diseases (2009/C 151/02) [5]). These landmark policies built upon the regulatory incentives engendered by the 2000 Orphan Drug legislation (Regulation (EC) No 141/2000) to call for national action alongside key European efforts to advance diagnostics, treatment, care, research and social support for rare diseases. Much was achieved in the following decade [3, 6]; however, notwithstanding these achievements at both European and national level, the day-to-day reality for too many people living with a rare disease has sadly changed little. Major unmet needs remain, which can only be addressed through a seismic shift in the way in which research, care and social support are organised, in Europe and beyond. In recent years, much attention has been focused on where the RD field should go next—how can we stimulate new R&D for the thousands of conditions without *any* treatment options (and indeed any basic research activity), whilst also ensuring that therapies developed for conditions benefiting from a relatively strong research interest deliver meaningful and transformational change?

An important attempt was made to revitalise European rare disease policy in 2018, when the European Parliament called for a pilot Project to conduct the first Foresight Study dedicated to rare diseases. The 2-year Rare 2030 project, which eventually ran from January 2019 to Spring of 2021, was led by EURORDIS (Rare Diseases Europe). Rare 2030 aimed to stimulate the development of a new European policy framework to ensure meaningful change for the future ahead, and generated an ambitious set of recommendations [7] to guide Europe towards the future scenarios deemed most desirable. Rare Disease research, in particular, needs to operate within a supportive Research and Innovation ecosystem—it is therefore important to note that in recent years the Orphan Drug Regulation (EC 141/2000) has come under scrutiny. In 2017, a 10-year evaluation report on the EU Paediatric Regulation was published [8] which concluded that the Regulation had provided positive results overall in terms of paediatric product development, but that development for rare paediatric diseases, which is in many cases equally supported through the Orphan Regulation, often failed to materialise.

The last few years have therefore seen significant European attention placed on the challenges remaining for the approximately 30 million people living with a rare disease in Europe. The various projects and sets of recommendations launched to address the gaps and shortcomings of past activities and investments are now culminating in a renewed attempt to garner political support to actually put some of these recommendations into action.[1] This momentum around rare disease is increasingly noted not merely within Europe, but at the global level.[2]

These sorts of conclusions and policy initiatives are particularly important, given the worrying trend that R&D in Europe is increasingly lagging behind that of other parts of the world, seeing less investment and lower levels of clinical trial activity; for instance, whereas 41% of R&D investments across the board were centred on Europe in 2001, this has now dropped to 31% [9]. It is imperative that Europe regains a competitive edge, especially in terms of research and innovation for *rare* disease, given the major unmet needs. The advantages of working with the pharmaceutical industry, in particular, must be recognised by policymakers working in rare

[1] For example, the #30 million reasons campaign, led by EURORDIS, emerged out of Rare 2030 to target the French, Czech Republic and Swedish trio of EU Presidencies in an effort to place rare diseases -and specifically, the outputs of Rare 2030- firmly on the European agenda (perhaps eventually by adoption of a new Commission Communication, Council Recommendation, or an Action Plan, such as has been deployed in the cancer field).

[2] Evidenced for instance by the evolution of IRDiRC (the International Rare Disease Research Consortium), the adoption of a UN Resolution on Rare Disease in late 2021, and the WHO signing a MoU with Rare Diseases International to scope a Global Network for Rare Disease.

disease –private sector involvement generally remains a prerequisite for successful drug development in this complex field [10, 11]. The in-house knowledge that drug developers hold (particularly around clinical trial execution, regulatory pathways and data), together with their access to financial resources, may be lacking in the (often publicly funded) clinical networks focused on administering care.

Amidst this plethora of recent initiatives, reports, recommendations and policy asks relating to rare diseases, the ERNs are frequently cited as central infrastructures of unique importance: they could evolve to become the foundation of a future European health and research system for rare diseases, by maturing current collaborations into innovative partnerships, thus becoming powerful agents of the change which is so greatly needed.

ERNs and the potential they offer

The concept and origins of ERNs

ERNs are arguably the single most important innovations in health and research for rare diseases in Europe, if not globally [12]. Officially launched in 2017, ERNs were intended to connect European centres of expertise in specialised healthcare fields necessitating a concentration of expertise in order to increase knowledge and build professional capacity across the healthcare and research spheres [13]. Rare disease, though not the sole focus of ERNs, is the most natural and most significant beneficiary. The concept of an ERN was developed by a RD TaskForce Working Group, and gained traction under Article 12 of the 2011 Directive on the Application of Patients' Rights in Cross-Border Healthcare (the so-called 'Cross-Border Healthcare Directive')[14]. 24 ERNs were approved in the first call [15] representing over a decade of preparatory work [16]. These ERNs have been founded as patient-centred networks, where patient participation is fully integrated in the network governance structures and activities, as recommended by the EUCERD recommendations and Addendum of 2015 [17, 18].

At their launch, the 24 ERNs brought together over 900 specialist units in over 300 hospitals across 26 countries (25 EU MS plus Norway) whilst also integrating people living with rare or specialised conditions in a meaningful way; at present, approximately 300 patient representatives collaborate as de facto members of the ERNs. Membership of ERNs subsequently expanded, to include (as of 1st January 2022) 1450 full healthcare providers (HCPs) —which may be entire clinics or hospitals or individual specialist units or centres within a larger institution—as well as 155 so-called affiliated partners (centres which do not fulfil all horizontal and disease-specific criteria established by the European Commission and ERNs themselves, respectively, but will enable every country to access the expertise of an ERN more readily). A central pillar of the ERN concept is that collectively, across all ERNs, every rare disease would have a 'home'—in this way, ERNs would strive to go beyond the networks created by past EU funding, which were dedicated to individual diseases or small groups of diseases (e.g. E-Pilepsy, EU-CHS, EUROMAC etc. [16]) and instead sought to improve diagnostics, treatment, and care for *all* conditions under the rare disease umbrella.

For these reasons, ERNs were envisaged as powerful tools to erode inequalities for patients, firstly by ensuring an all-disease inclusive scope, leaving no one behind, but also by addressing the geographical lottery faced by so many patients. The latter goal is primarily being achieved via one of the ERNs' central missions of enabling *expertise* to travel, rather than patients, wherever possible. ERNs have dramatically altered the face of virtual, cross-border care for rare disease, developing a system for shared care, specialist advice and second opinions unrivalled in scope and ambition anywhere. The ERNs utilise a shared and bespoke Clinical Patient Management System (CPMS) [19]: to-date, over 2650 panels have been assembled to review patients referred for this kind of shared virtual care under the ERN ecosystem.

The various activities of ERNs are funded from different pots of European funding [20]. Certain Member States are now starting to provide funding for specific coordination activities.

ERNs and research

Notwithstanding the importance of these activities which one could class as primarily care-focused, a major source of the ERNs' potential stems from their mandate to also add value to *research* into rare diseases and highly specialised medicine. *Directive 2011/24/EU on patients' rights in cross-border healthcare* [14], through which ERNs were founded, stipulates this requirement, as do the legal acts on which ERNs were established: Art. 7 of the Delegated Decision (2014/287/EU) [21] states that "Among the first set of horizontal and structural criteria and conditions, those related to patients empowerment and patient-centred care; organisation, management and business continuity; research and training capacity appear to be essential in order to ensure that the objectives of the Networks are met". Annex I of the Delegated Decision further stipulates that one of the horizontal criteria (i.e. criteria which all members of any ERN should fulfil) is as follows:

> *"(5) To fulfil the requirement set out in point (iv) of Article 12(4)(a) of Directive 2011/24/EU ('make a contribution to research'), the Networks must: (a) identify and fill research gaps; (b) promote col-*

laborative research within the Network; (c) reinforce research and epidemiological surveillance, through setting up of shared registries"

It is fair to say that for most ERNs, there has been less of a focus over these first five years on 'research' per se [20]. This is not to say there has been *no* activity here: many—if not all- ERNs launched surveys internally to assess the extent of research across the broad headings with which most are concerned. This was very important, as networks did not exist at the breadth and depth of the ERN headings prior to 2017. A number of diseases already had robust research communities with well-networked expert communities (e.g. Cystic Fibrosis in the rare pulmonary field; rare anaemias and haemophilia in the haematology field, etc.); however, this was not the case for other conditions. ERNs have also engaged in advancing research via participation in a Horizon 2020 initiative called the European Joint Programme for Rare Disease Research (EJP RD), which engaged partners and linked third parties to represent all ERNs. However, the research potential of ERNs has long been appreciated.

In May of 2018, a Joint Action called RD-ACTION, the European Medicines Agency (EMA) and DG SANTE organised a workshop hosted by the EMA, which produced a report highlighting actions that would need to be taken in order for ERNs to begin to fulfil their research potential [22]. This document also elucidated how and why ERNs hold so much potential as clinical research networks and are perfectly placed to add value to rare disease research: the following summary takes this as a starting point but expands upon these areas of potential to illustrate the opportunity ERNs afford.

ERNs are permanent infrastructures

ERNs are not time-bound projects, unlike the so-called pilot networks funded during the 1st and 2nd EU Public Health Programmes (whose structures and resources risked falling into disuse once the funding period ended).

Assuming positive evaluations every 5 years, ERNs may be considered permanent structures, making them important stakeholders for partnerships in research of all kinds.

ERNs sit at the interface of the research and clinical spheres

The Legal Acts upon which ERNs are based mandate that the Networks provide added-value across both the clinical and research domains. This is essential in rare diseases, where traditionally that line between care on the one hand and research on the other has, of necessity, been somewhat blurred. All 1450 HCPs participating in ERNs as full members should possess clinical expertise in at least some of the conditions underneath the grouping of that ERN, but should also be research-active, boosting the potential for multicentre trials in Europe (and also for rapid transfer of promising preclinical research into Industry-supported trials). The proximity of research spaces and the clinic is a major strength of the ERN model, facilitating the generation and translation of knowledge and best practice.

ERNs are designed to ensure comprehensive disease (and specialised procedure) coverage

When applications for the first 24 ERNs were encouraged to establish their Networks based upon a list of suggested Thematic Grouping [23]: this was to ensure that collectively, all rare disease would have a 'home' under at least one ERN. In actuality, many ERNs followed this suggested Groupings schema very closely, and consequently the vast majority of conditions classed as rare were covered by the 24 Networks created under the first call, along with several less disease-focused ERNs more dedicated to specialised *procedures* and areas of medicine in which a concentration of expertise is also of paramount importance (e.g. ERN-TransplantChild). The fact that ERNs are founded upon this principle of inclusion of all rare diseases is a major benefit and holds real potential for research of the future. The reality, as mentioned above, is that within each ERN there is often a 'focal' disease or group of diseases which has attracted a relatively large amount of research attention (predating the ERNs' foundation), and/or is better understood and supported in terms of diagnosis and care (although many ERNs are seeking to address this, for instance by ensuring their registries collect data on all diseases covered by the Network).[3] But nonetheless, the inherently egalitarian nature of the ERN model is, in itself, a strong step in the right direct of casting much-needed light on the many thousands of so-called neglected diseases which have traditionally lacked any research interest.

Data generation/linkage and digital health opportunities

ERNs provide unprecedented opportunities to collect and share high quality, relevant, and interoperable data. People living with rare diseases have affirmed their desire for their data to be reused, to generate new knowledge and understanding, in order to help the next generation of people affected with their condition [25] —so the goal of maximising the use of precious rare disease data is widely supported. The Networks are based upon centres which have demonstrable expertise in particular areas, but the

[3] In its position paper on mature ERNs [24]. EURORDIS. Recommendations to Achieve a Mature ERN System in 2030. 2020. Page 33], EURORDIS has called for all ERNs to issue step-wise expansion roadmaps to ensure that networks move away from an initial focus on merely a subset of conditions.

Networking *tools* and platform which connect these well-established centres are being created—or at least delivered—anew. This offers exciting opportunities for the 1450 HCPs (plus 155 affiliated partners) across Europe to subscribe to best practices around creating, collecting and pooling precious rare disease data in a timely manner, to support the provision of highly specialised care and advance research. The CPMS has already resulted in more harmonised and interoperable data being collected for specialist virtual reviews. But the area of registration holds possibly even greater potential in terms of advancing research and understanding [26, 27].

DG SANTE had provided funding for all ERNs to establish new registries and/or link existing registries in their fields. Registries are essential tools for generating knowledge about rare diseases, and—depending on the data collected, and its quality—can serve multiple purposes [27, 28]. It is reassuring to see that, notwithstanding the variety in scope of the 24 ERNs, the ERICA (ERN Research Coordination and Support Action) [29] and EJP RD [30] projects have initiated cross-ERN collaboration on registries and health data management tools, processes and policies. At the same time, the European Platform on Rare Diseases Registration, initiated in 2013 by the European Commission's Joint Research Centre (JRC) in collaboration with DG SANTE is building tools to facilitate access and re-use of RD registry data, via its European Rare Disease Registry Infrastructure (ERDRI) (Fig. 1).

The creation of a European platform to increase the reuse potential of precious rare disease data is of major importance when one considers that over 800 rare disease registries exist in Europe (or are fed by European centres or actors) [32]. However, the creation of ERN registries—or platforms to link new ERN registries with historical or possibly new disease-specific registries—holds major potential for advancing knowledge and better care, but also naturally for stimulating and advancing research. Supported by projects like the EJP RD and ERICA, attempts are being made to ensure a certain level of interoperability in terms of the data collected in these new ERN registries. For instance, the Common Data Elements issued by the EU RD Platform have been turned into a richer data dictionary under the EJP RD [33]: this is just one example of efforts to make registry data FAIR (Findable, Accessible, Interoperable, and Reusable). Greater value will come with the advance of individual ERNs agreeing and standardising domain-specific datasets [34].

The summaries above are far from exhaustive, but illustrate why ERNs hold such significant potential to advance rare disease research. However, to-date, the research activity of the ERNs has been limited, for several reasons.

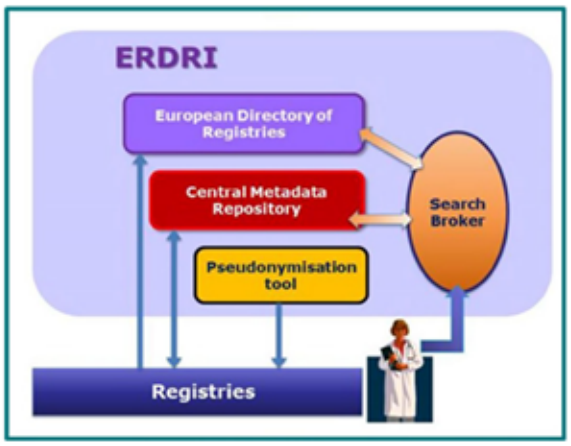

Fig. 1 Image used with permission from the Joint Research Centre [31]

Part 2: Understanding constraints on ERN Research to-date: and in particular, barriers to Industry collaboration

What factors have limited ERN-led research?

Contrasting priorities in the early years of ERNs

The relatively limited research activities of the ERNs to-date can partially be explained simply by the amount of time required to launch the networks and set up the necessary governance and operational structures, along with the apparent prioritisation (naturally enough given the fact that the ERNs were initiated under the aegis of DG SANTE, not DG RTD) of more overtly care-related activities. However, this does not mean than no ERNs have been active in the research domain. The surveying of the status quo as outlined above, the creation of intra-ERN working groups for research (plus a cross-ERN working group), engagement as key partners in the EJP RD—and more recently the ERICA project –are all important achievements.

Lack of suitable funding

One barrier often reported by the ERNs themselves is the notable lack of dedicated funding for collaborative research projects. More recently, funding for the development of the registries, the emergence of the EJP RD mobility exchange programme for ERN researchers, and the launch of ERICA (in 2019) have gone some way to address this shortfall, but there is still no specific funding scheme to foster direct clinical research activities within and across ERNs.

Some ERNs represent communities with a limited research track record

Most ERNs would agree that they have not yet scratched the surface of what might be achieved in the research space [20]. And here, the situation is actually quite dramatically different from network to network. Some ERNs have very limited research activity, which reflects the broad communities they represent (i.e. there is limited research in the Thematic Grouping with which that ERN is concerned). For these ERNs, therefore, the persistence of that traditional lack of research activity and momentum over the past 5 years is itself a barrier, as little has come along to incentivise (or indeed enable) more research in the field. Projects such as ERICA are seeking to build capacity across the board, for instance by creating a much-needed repository of PROMs (Patient-Reported Outcome Measures) relevant for rare diseases [35]. However, substantial additional resources and funding are needed to transform these less research-active ERNs into research-ready networks. At the other end of the scale though, it is acknowledged that some ERNs emerged from notably research-active communities, often bolstered by research in a handful of focal disease or disease groups if not by research across the board. Those ERNs, therefore, may report limited research activity *as an ERN* whilst acknowledging that the researchers and centres of which that Network is composed are *highly* engaged in research of all kinds.

Confusion in defining research activity 'of an ERN'

This raises another possible challenge for 'ERNs and research', namely, simply defining what constitutes ERN research. This has been a source of some confusion since the creation of the Networks: how to distinguish the achievements of a given ERN, collectively, from the day-to-day achievements of its component centres (and, at a still more granular level, of the individuals involved in that ERN)? Definitions were created in an attempt to alleviate confusion and ensure all ERNs were reporting their activity in a comparable manner [36]. It may be, therefore, that confusion over what *constitutes* research activity of an ERN has actually hampered so-called ERN research.

Barriers to ERNs and Industry Collaboration

> *"ERNs are still on a learning curve in terms of collaboration and so engagement with all stakeholders to explain the value of collaboration is important" (Franz Schaefer, Coordinator of ERK-NeT, the ERN for Rare Kidney Diseases).*

One of the most-frequently cited barriers to ERNs engaging in research is the perceived inability for the Networks to collaborate with Industry—at least when it comes to drug development. This barrier, in itself, is multifaceted. It is true that not all research requires Industry engagement: investigator-initiated research of course takes place, ranging from non-interventional studies to efforts to better understand the natural history of a disease, to trials involving the repurposing of medicines. Nonetheless, given the Herculean task of addressing the unmet needs of the rare disease community, it is very clear that fruitful collaborations between Industry and clinicians/researchers are essential. From the earliest days of the ERNs, however, tangible barriers have limited ERN-to-Industry interactions. Arguably the most significant barrier here is the reticence from the ERN Board of Member States (BoMS), which was set-up via the ERN Legal Acts to oversee the Networks.

The scope and significance of the statements from the ERN board of member states

The BoMS has issued two statements (policies, essentially) regarding permissible interactions between ERNs and companies. The 2016 Statement [37] began by acknowledging the fact that Industry plays an important role in improving knowledge of rare diseases and developing clinical tools and therapies. It approves engagement with ERNs 'where appropriate' and cites 'for example in clinical trials and research projects'. Very reasonably, it bars Industry involvement in operational and governance issues (although notably Industry is not singled out but is included here amongst a wider group of 'external stakeholders' who are debarred from such roles because there is no legal provision for this). The rest of the statement provides guidance to the Networks on 'their thinking on engagement with industry'.

An important barrier to ERNs fulfilling their research potential is the absence of robust and transparent collaborations with Industry: it is important to understand the historic reasons for this lack of interaction.

This 2016 guidance calls for policies, such as a transparency policy, and for ERN charters defining Conflict of Interest Policies. This Statement was not viewed as entirely prohibitive, in terms of ERN and Industry interactions, but rather stressed the need for careful management of any relationships. Many ERNs were unsure, however, of what –if anything—they *were* permitted to do in this space, and how. Given the fact that all ERNs were faced with tackling the same challenges, a Coordinators' Group was established soon after the launch of the Networks, and this was complemented by a number of Working Groups on specific topics. These later merged with similar groups which had developed within the BoMS of ERNs. Several Joint policies and documents have been developed through this methodology (e.g. the documents stipulating and defining core indicators for ERN monitoring). One of these Working Groups was dedicated to *Legal and Ethical Issues and relations with Stakeholders*. This body soon began work on a transparency policy and a Code of Conduct. However, the question of precisely how ERNs should handle increasing requests from companies for collaboration of various kinds remained unanswered.

On the 25th June 2019 the BoMS issued an updated Statement [38] concerning ERNs and Industry. The reason for this, it seems, was that lack of "legal provision for the collaboration between ERNs and Industry", compelled the Board to issue more detailed guidance. This new Statement arguably did little to ameliorate the uncertainty, unfortunately—and where the guidance *was* more explicit than the 2016 document, some points were questioned. With regards to Point 4, for instance, placing emphasis on ERNs seeking public funding before accepting private funding: the scarcity of public funding available for ERNs (and the transient nature of the grants available) has been a constant and significant source of frustration for many ERNs [13, 20]. The suggestion of seeking Industry funding only when more than one company was involved in an activity presented some challenges in terms of the *type* of collaboration that would fit such a set-up (and the relative scarcity of examples of such funding, beyond IMI-type grants etc.).

Point 5, however, was perhaps the most contentious (the bold emphasis is not present in the Statement itself): direct Industry funding was debarred from *"any type of activity relating to the development of diagnostic and clinical practice guidelines (CPGs) or any other clinical decision-supporting tools, development of outcome measures as well as establishing and maintaining patient registries"*. Now, avoiding Industry involvement in the creation of CPGs or similar tools is reasonable, given the potential for conflict of interest.[4] The stance on registries is interesting, however. As above, all ERNs have received grants of €200,000 over a period of 3 years, to establish a new ERN-wide registry and/or to link existing registries. This is generally considered to be an inadequate sum of money to either create a new and ambitious registry for an ERN, or to address the interoperability considerations by federating existing stand-alone disease-related registries and enabling data collected in different systems with different data dictionaries and access procedures to 'speak' to each other.

Following publication of the 2019 Statement, significant uncertainty remained as to how and where (in what activities) ERNs could collaborate with Industry. Most stakeholders (on both the ERN and Industry sides) perceive the lack of clarity on what would be permissible, and under what sort of conditions, as a major barrier to ERNs engaging in substantial research activity. This lack of clarity is accompanied by the restrictions of the BoMS Statements.

Conflict of Interest

A key challenge identified for ERN/industry collaboration relates to managing conflict of interest. This is likely at the root of some of the concerns noted to-date in the BoMS, which translated into the cautious wording noted in the two BoMS Statements. The rare disease field is, by definition, small, and it is natural for experts to be approached in their independent capacities by companies to serve on advisory groups or as consultants or similar, and be remunerated for their service. It is of course imperative that people declare their potential conflicts of interest; however, this has always been a reality in this field, and robust examples of Codes of Conduct already exist to ensure ethically responsible professional behaviour of both the experts and companies.[5] There are also established practices to avoid conflicts of interest in activities for which companies provide financial support to non-ERN networks or stakeholder associations.

Privacy and ethical concerns

Unfortunately, collaboration with the private sector is not always viewed in a positive light. If a company is

[4] That being said, the approach of the BoMS statement may be a little too black and white here: there are examples of Companies playing no role in the *development* of CPGs or Clinical Decisions Support Tools but post-publication funding their translation into different languages and/or their development into accompanying layperson summaries, support the running of workshops and masterclasses for greater implementation of the practices, etc.

[5] For example see [39].EORTC. EORTC Code of Ethical Conduct [cited 2023 22nd March 2023]. Available from: https://www.eortc.org/code-of-ethical-conduct/.

deemed to have acted unethically, particularly if perceived to be at the expense of vulnerable patients, the negative publicity can cause significant damage to the whole R&D field. Rare disease patients are of course particularly vulnerable insofar as sharing their data or participating in clinical research carries greater risks (of identification, for instance). But at the same time, rare disease patients are perhaps more likely to feel pressured into engaging in clinical research than someone with a common disease, as in the absence of a disease-modifying treatment, a trial may be a patient's only hope: thus the ethical considerations are greater [40, 41]. Patients also express concerns regarding data privacy (despite being overwhelmingly in favour of sharing their data for medical benefits). A 2019 Rare Barometer Voices survey of over 2000 respondents from 66 countries asked rare disease patients if they would feel confident with different stakeholders handling and using their health information carefully: the results for the pharmaceutical industry research were divided, with 45% in favour compared to 50% opposed and 5% unsure (compared to 89% expressing confidence in their physician handling their data) [25]. It is possible therefore that such general concerns on the part of patients have also served to keep Industry engagement with ERNs to the minimum, particularly when coupled with the other factors outlined above. These figures illustrate the need for patients to be in control of their data and consenting.

The lack of legal status for ERNs

The ERNs are virtual networks connecting hospital-based units. Each of these institutions are legal entities and the institution that is named 'Network Coordinator' is contracted directly by the EC. The Coordinating sites have individual contracts with each of their Members as part of the network governance. However, the ERNs are not legal entities per se. For some of the ERN Coordinators, and occasionally patient advocates, the absence of a legal entity has been reported as a major hindrance to ERNs performing research and collaborating with Industry. This is because a legal entity would foreseeably simplify contracting and other activities necessary for initiating research projects or delivering clinical trials. Similarly from an Industry perspective, if ERNs were legal entities, a company could contract solely with that entity, as opposed to developing agreements with potentially many separate hospitals and universities. However, it must be emphasised that other ERNs do not perceive their lack of legal status as an obstacle, as they are able to use mature policies and procedures at their individual institutions to interact with external stakeholders.

Lack of experience in the legal and bureaucratic processes involved in working with Industry

As above, ERNs are at different stages of maturity when it comes to research activity. However, even amongst those with richer, more established research communities, a lack of awareness on how to forge collaborations with Industry may be viewed as a barrier. ERN Coordinating centres are hospitals or universities (or a partnership of the two) —they are legal entities in their own right, but may be ill-suited to tackling the legal, financial and administrative aspects of formally collaborating with a private company. Such institutions are generally very risk-averse, which can hamper attempts at collaboration.

It is possible therefore to identify a range of tangible barriers to ERN-Industry collaboration. However, it becomes apparent that some of these are surrounded by a layer of confusion, and may ultimately be perceived barriers. For instance, solutions exist to manage conflicts of interest (for instance policies and templates have been used by the European Organisation for Research and Treatment of Cancer, EORTC, for many years, in the cancer community), and to address ethical and privacy concerns (robust patient participation in the governance of all relevant activities would be an excellent starting point). Other barriers mentioned here are significant at present, but can be addressed through dedicated and transparent action; for instance, both ERNs and Industry must recognise that even in the absence of the networks themselves possessing legal status, collaborative agreements can be made with key ERN HCPs. However, to utilise such routes to collaboration effectively, support and capacity-building is needed, certainly for the hospitals/units involved, to help them navigate unfamiliar processes, but also for companies engaging in such activity, to seek harmonised procedures which can be replicated in many similar settings. The content of the BoMS Statements, on the other hand, *would* benefit from revisions, to remove uncertainties and ambiguities and generally espouse a more positive and enabling vision of future ERN-Industry collaborations, avoiding clauses constituting unnecessary and impractical barriers.

Part 3: Methodology and the Added-Value of Together4RD

How Together4RD is fostering ERN-Industry collaboration

Together4RD emerged from the recognition, on many sides, that a concerted effort was necessary to strategically and concretely address the relative inertia around ERNs and Industry collaborations. It does not seek to advance ERN research per se, in all its forms, as dedicated initiatives already exist for this. Nor does the initiative seek to present itself as the sole forum in which

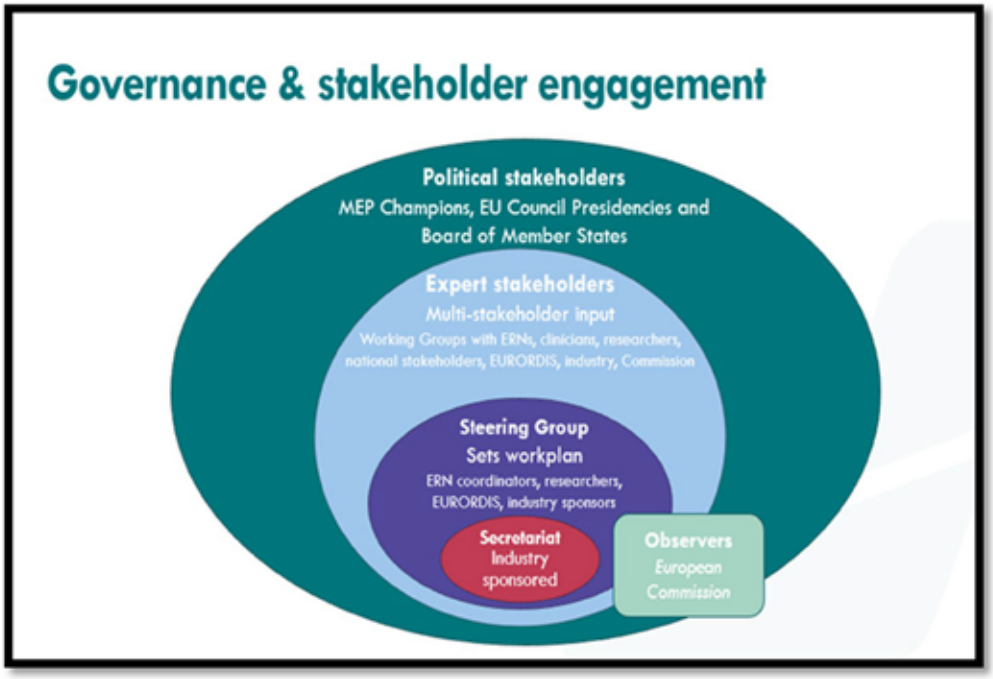

Fig. 2 The structure of Together4RD

ERNs and Industry can collaborate (Innovative Health Initiative/Innovative Medicines Initiative grants provide the option for public private partnerships, and a new Joint Action on the integration of ERNs into national health systems offers further potential here). Rather, Together4RD aims to 'move the needle' and deliver real solutions to some of the key challenges noted above, which to-date have hindered ERNs and Industry engagement and thus setback the pace of progress in rare disease research at large.

Launched in December 2021, Together4RD is led by a multi-stakeholder Steering Group, comprising Coordinators and managers from 4 ERNs, pharmaceutical industry representatives, members of the research community, and the European Organisation for Rare Diseases (EURORDIS).[6] Given its oversight role for ERNs (which includes holding the secretariat of the BoMS), DG SANTE acts as an observer. The Steering Group's role is to provide strategic input to, and oversight of, all work undertaken in Together4RD, and to promote this through their own networks. The Steering Group is supported in the day-to-day implementation of Together4RD's work by the Together4RD Secretariat (provided by FIPRA International). The Secretariat is aided financially by funding partners the European Federation of Pharmaceutical Industries and Associations (EFPIA), the European Confederation of Pharmaceutical Entrepreneurs (EUCOPE), Alexion Pharmaceuticals,[7] Novo Nordisk, Sanofi, UCB and Takeda (Fig. 2).

The core aim of Together4RD is, firstly, to uncover and expose the barriers that exist to more ERN-industry collaboration; and secondly, to offer solutions and structures to overcome those barriers, and unlock potential. Securing political buy-in has been an important pillar of this work, and the initiative currently has four MEP Champions (Frédérique Ries (Belgium, Renew Europe), Sara Cerdas (Portugal, S&D), Ondrej Knotek (Czechia, Renew Europe), and Stelios Kympouropoulos (Greece, EPP)) within the European Parliament that have helped to amplify this vision for a new landscape for rare disease innovation.

Possible frameworks to guide ERN-industry collaboration

Together4RD conducted research in 2022 into possible frameworks to structure ERN collaborations with Industry. As noted elsewhere in this Position Statement, stakeholder views differ with regards to the desirability of ERNs becoming legal entities. It may be that in future, each ERN will become a legal entity (LE) of its own,

[6] For a full list of Steering Group members, visit the Together4RD website [42].Together4RD. What is Together4RD—Steering Group [Available from: https://together4rd.eu/what-is-together4rd/steering-group/.

[7] Sponsoring company for 2021–2022.

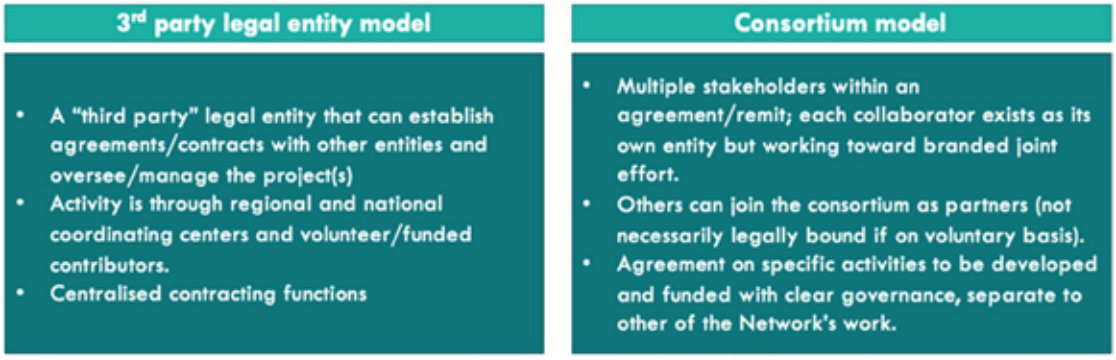

Fig. 3 A 3rd party legal entity model vs. a consortium model

although at present this is highly unlikely. Or perhaps, a neutral third party will be appointed (this could be a foundation, for instance) to oversee the contracting activities between individual ERNs or groups of ERNs, on the one hand, and single companies or groups of companies on the other. The fact is that neither solution will appear overnight, however; therefore, if pilots are to be launched sooner rather than later, it will be necessary to work within the possible frameworks available to the European rare disease community at present. The key point in both of the above is that ERNs are not legal entities, but the centres (HCP or 'affiliated' partners) of which they are composed ARE legal entities (Fig. 3).

One option would be to conduct ERN-Industry engagement via a Consortium Model. Here, a number of independent institutions collaborate based on a particular remit. An example could be the Rare Impact Phase 2 project, in which EURORDIS acted as chair and participated—supported by Dolon which acted as secretariat- alongside 17 gene and cell therapies, Fondazione Telethon, Alliance for Regenerative Medicine and EUCOPE. Individual institutions within the Consortium will be legal entities, but a legal framework is not required for them to collaborate, making this a more fluid and dynamic model. Contracts are still required if any resources are transferred between institutions. Such a model could be possible under the existing frameworks for ERNs, as an ERN HCP such as the coordinating centre or a key research centre could take charge of contracting and making agreements with a company or companies, on the one hand, and also with several or possibly even *all* of its fellow ERN HCPs/affiliated centres, through agreements. This model would of course carry financial and resource implications for the coordinating ERN, which would need to be accounted for.

An alternative would be to embrace a true Third Party Legal Entity Model. Here, one LE—outside of the ERN—would establish agreements and makes contracts with other entities and would oversee/manage the project(s). This could be a new body, in the form of a common research office, for instance inspired by the US RDCRN (Rare Diseases Clinical Research Network [43]) model or the EORTC. Whatever its form, it should be able to support all ERNs in their research activities, which hosts and provides expertise and research capacities as well as overseeing agreements and contracting and managing the financial and legal elements. Alternatively, it could be more like a foundation, serving the needs of all ERNs. A variant on this theme would be to envisage separate foundations or other forms of 3rd parties, playing such a role for each ERN individually. When considering a 3rd party Legal Entity Model, however, it is important to note that some public institutions do not allow this kind of contracting.

Perhaps this should not be viewed as an either/or situation—different sorts of framework may work better for different sorts of activities. It may be that some activities which can be envisaged between ERNs and companies would only ever require the movement of funds to a single centre within that ERN—e.g., if one ERN HCP was tasked with elaborating or expanding a platform to integrate standalone disease-specific registries, or to develop a cross-ERN platform for post-marketing surveillance; in which case, a single contract between a company or group of companies could be made with that single HCP which would deliver the work with the guidance and scientific or clinical support of the wider ERN. However, if a piece of work entailed working with multiple HCPs, each of which required specific resources, there would be two options:

1. A single HCP, which is a LE (e.g. the coordinating centre) contracts with a company/several companies, and that centre then distributes funding to other HCPs/affiliated centres, as appropriate. The onus is then on the ERN Centre to arrange for payments and

coordinate activities within the arrangement (which may or may not require an amendment to the contracts Coordinators already have with their HCP members). The bureaucracy and resource implications involved here may or may not be acceptable: such activities can be time-consuming and are not always successful. It is notable, however, that some ERNs have recently started to operate in this way, insofar as a coordinating centre provides funding from grants to individual member centres (e.g. to enter data in the new ERN-wide registry).

2. A company/companies would develop contracts with each of the multiple HCPs it wishes to work with directly, as part of an overall pilot or piece of work. Here, the onus is on the company, and on each of the individual HCPs participating to research. This model has the disadvantage of creating different contracting arrangements across multiple individual HCPs and institutions.

Learning from case studies: extrapolating lessons and good practices for ERNs and industry

From the 2016 and 2019 Statements discussed in 2.2, it appears that at least some members of the ERN BoMS harbour concerns over the prospect of collaborations between the ERNs and Industry. Although such concerns may not reflect the majority of the BoMS members, the traditional *modus operandi* of the BoMS has been to seek full consensus on the wording of key documents and policies pertaining to the ERNs. This means that the concerns of a few countries can, in theory, have a major impact on the research prospects of ERNs. This is not to suggest that public–private interactions should not be subject to the highest possible ethical and legal standards: the consequences for the whole R&D community, if there is any action that is seen to transgress or act unethically, can be severe and long lasting. What has perhaps been overlooked in past discussions concerning ERNs and Industry, is the extent to which interactions between rare disease clinicians and researchers, on the one hand, and companies on the other, take place every day—and have been taking place, in some cases, for decades, without issue, whilst providing myriad benefits all round. As noted in 2.2, in such small and specialist communities, it would be impossible for leading experts and Industry representatives *not* to be acquainted somehow.

A key milestone in the Together4RD mission to understand perceptual barriers to collaboration and identify workable solutions involved issuing a call for case studies. Examples were sought -via the Steering Group and their wider networks- of instances where Industry has collaborated with a network (largely predating ERNs or existing outside of ERNs), or other body of clinicians, to achieve a particular goal. These case studies summarised what was achieved/is being achieved in each example, what steps were taken to forge this relationship with the company/companies, the lessons learned, and the results of the collaboration. These case studies generally focus either on registries or on broader activity to support clinical research (excepting clinical trials themselves). For the full list of summaries, see Additional file 1: *'Case Study Summaries'.*

Two Working Groups were created (involving different stakeholders engaged in the consultative bodies for Together4RD, spanning patient advocates, ERN representatives, Industry, and researchers), to analyse each set of case studies via discussions with the experts involved in setting-up and maintaining them, in order to extract the most pertinent learning lessons and good practices. These Working Groups were met twice, remotely, for 1.5 h each time, and worked via Sharepoint documents.

A range of distinct *types* of collaboration emerged. Together4RD was able to distil these insights and practices into tables, one for each Working Group, to show clearly and comprehensively.

> Firstly the different sorts of collaborations possible with Industry;
>
> on the 'Registries' side, these include accessing registry data to elucidate natural history, to conduct post-marketing surveillance, to serve regulatory purposes as Real-World Evidence (RWE), and collaborating on the definition of datasets.
> In terms of broader 'Clinical Research', activities ranged from strategic fora to advance research to creating opportunities for researchers to pitch ideas to companies: and from creating or improving biobanks to diagnosing patients through electronic health records.
>
> And Secondly, to match examples of each activity to achievements of the different case studies, to show how some of these Industry collaborations have been approached to-date.

In generating these tables, and affirming the contents, the experts were encouraged to broaden their thinking from purely what has gone before, to what *ERNs*, specifically, could do in partnership with Industry. These tables are included as Additional file 2: 'Table showing a range of exemplar collaborations concerning registries, which could be envisaged between ERNs and Industry' and Additional file 3: 'Table showing a range of exemplar

collaborations concerning clinical research, which could be envisaged between ERNs and Industry'.

It is illuminating to consider how some of these case study entities have managed to deliver these kinds of activities, and to explore the kind of legal frameworks they have utilised. A long-running example of a network (founded in the pre-ERN era) which has collaborated with Industry in multiple ways is TREAT-NMD. TREAT-NMD was established back in 2007, via an FP6 grant, as a network to advance trial-readiness in all neuromuscular diseases. It has created a suite of tools and activities to achieve this goal, and in 2019 was 'spun out' of the University which coordinated it, as a legal entity. Key resources include cell and animal standard operating protocols (preclinical research); an advice service (TACT), global patient registries, ethical framework and care guidelines, and family guides, to help develop and extend translation research in the field. Many of these activities have involved Industry, and ethically-robust practices and codes have been developed to facilitate this. One key area of Industry engagement concerns patient registries. TREAT-NMD links numerous registries (and developed core and expanded datasets to standardise data in these standalone registries) to facilitate the identification of specific patient groups and boost patient recruitment. It also coordinates global patient registries for several NMDs. The inter-connected registries provide a wealth of information and can be queried by academic sites (free) or by Companies (for a fee). In the days before it became a legal entity, contracting was performed by the institution coordinating the network, namely Newcastle University in the UK. This was not always straightforward, but procedures were honed over the years to govern the collaborations with Industry, based on policies agreed by the whole consortium (composed of mainly academic institutions and patient organisations). A typical activity entailed registry data being sought by a company, for instance to assess the feasibility of conducting a clinical trial in a given neuromuscular disease. The registries associated with TREAT-NMD were largely national, standalone autonomous registries for conditions such as Duchenne Muscular Dystrophy, which had agreed to collect a common data set defined by the TREAT-NMD consortium. TREAT-NMD established an advisory board composed of the curators of these autonomous registries, called the TREAT-NMD Global Database Oversight Committee or TGDOC. A request from a company would be reviewed by this TGDOC and if favourably reviewed, the team at Newcastle University would negotiate a contract with the company. Aggregate data would be collected by the national curators of each registry, by disseminating a questionnaire via their registries (or simply providing the aggregate data themselves) —a typical query might be 'how many patients with an X deletion of Y neuromuscular disease are enrolled in your registry, between the ages of 5 and 10, and what proportion are still ambulant?'. The aggregate data from each participating registry would be compiled and returned to the company. The fee paid would sustain the posts responsible for managing these collaborations, and would also fund in-person meetings of all the national registry curators (i.e. it would be fed back into the TREAT-NMD ecosystem). In this case, the Coordinating centre of the network took care of all the bureaucracy and the financial and legal contracting. Contracts could be standardised, to make the process smoother when subsequent companies came along with similar requests. This was essentially a consortium model, therefore, and works well if the key institution taking charge of contracting within the network is well-versed in this kind of activity, and is responsible for *using* the funding to sustain the network activities (i.e. in this case, it was not necessary for the coordinating centre to distribute funds to other institutions, which would add an extra layer of complexity).

Another relevant example here is the ERK-REG case study. ERK-REG is the registry of the ERKNet ERN, for rare renal diseases. It was initiated in 2019 and acts as a single core registry for all rare renal diseases. The Registry collects data from the HCPs which are part of the ERN—this is a mix of epidemiological data concerning diagnostics, phenotypic and natural history data, and data to enable continuous monitoring of the diagnostic and therapeutic performance of HCPs (whilst also assessing guideline adherence). It can also be used for the rapid identification of patient cohorts for clinical trials. To-date, collaboration with Industry has included ERK-REG brokering contracts with sites that have patients eligible for clinical trials, and the provision of aggregate data on over 200 paediatric patients receiving a medicine off-label (which was used as supportive evidence for a Paediatric Investigation Plan). Over the first 3 years, 12,661 patients were enrolled, from 41 paediatric and 17 specialised adult units across 20 countries [44]. Here, the coordinating institution, University of Heidelberg, takes charge of the negotiating and contracting function for the ERN, and signs the contract with a particular company. Indeed, they have recently started to distribute funding from European grants to other member HCPs, to encourage data entry in the registry, and therefore the institution is becoming more adept at this kind of activity. A Data Access Committee assesses requests for access to data from Industry, or indeed any other stakeholder. They are then able to make bilateral collaboration agreements with other member HCPs, as necessary (for instance where work is required to gather or analyse data a given site has inputted to the registry platform). This

Table 1 Considerations for potential pilots

Clarity of goals and expected outcomes	Potential for scaling up to other ERNs
If there is already an established infrastructure in place	Proposal has patient group support, specifically from the patient group involved in the ERN or ERNs that would participate in the pilot
Resources available/ committed	Involvement of smaller ERNs
Single to multiple company pilot	Has potential to satisfy BoMS criteria

is essentially a consortium model, therefore. However, ERK-REG is exploring the engagement of a 3rd party legal entity, a charitable foundation, which would be able to make contracts with Industry sponsors and ERN HCPs, instead of all activity going through the University of Heidelberg.

Further analysis of the frameworks by which these kinds of case studies enable collaboration with Industry will be important, as ERNs begin to engage with companies under the aegis of Together4RD pilots. The consortium model approach, in which usually a single centre takes charge of contracting, may likely be a logical first step for many ERNs, as there Is no need to select and engage a suitable 3rd party organisation. But thinking longer term, especially where coordinating institutions -or those otherwise willing to broker collaborations involving the wider ERN—are not accustomed to such activities and lack the knowledge and/or resources to play such a role, the engagement of 3rd party models will require careful consideration (and examples such as the POC Club, and the EORTC used in the wider cancer field should be revisited).

Towards Together4RD pilots

All Together4RD activities across 2022 built towards the selection of a limited number of achievable pilots, intended to partner ERNs and companies to deliver a concrete and specific activity. The process for collecting pilot proposals involved the following steps:

- dedicated discussions exploring the types of activities which have been conducted to-date between networks (typically predating ERNs) and other groups of stakeholders, on the one hand, and Industry on the other (see above, 'Learning from Case Studies')
- extrapolating what such activities would look like under an ERN setting, specifically—what good practices could be embedded (and what resources could be leveraged, thinking of data access agreements etc.) and what would need to be avoided, to deliver the activity ethically and effectively
- Seeking input from the Together4RD Industry sponsors and from all ERNs (via communications issued by the Chair of the ERN Coordinators' Group) on potential pilots that could be implemented in 2022/23

The proposed pilots should all be able to demonstrate a basic level of feasibility and have the potential to illustrate the types of collaboration possible, as well as expose solutions that can be adopted to address the concerns raised in concerns raised in the section 'Barriers to ERNs and Industry Collaboration'—particularly in relation to conflict of interest, governance and transparency. Certain considerations were deemed especially relevant for the feasibility and added-value of potential pilots (Table 1):

A broad range of possible pilot-type activities has been elaborated by Together4RD, as per the previous section, 'Learning from Case Studies', and can be found in Additional files 2 and 3.

A range of concrete pilots will be selected, to be spotlighted through Together4RD, in order to expose different collaboration models and approaches. Lessons learnt from the pilots, such as how to manage conflicts of interest, organise governance and ensure transparency, will be extracted and disseminated broadly to ERNs, the BoMS, patients, and the broader Industry community, to present the broad rare disease field with tangible examples of how ERNs, specifically, can collaborate with Industry.

The emphasis is very much on paving the way for further ERN-Industry activity, and in this respect, it will be important to create useful tools and resources, wherever possible. As an estimated 70% of contractual data elements are similar across all activities, the Together4RD pilots will explore the possibility of creating a standardised contract template, agreed by ERNs and an Industry Association. Ideally, such a template will include standard sub clauses for contracting with individual Companies as well as other options for contracting with consortia of multiple Companies.

Pilots which are selected will need to be funded (in terms of all directly incurred costs) by the company or companies which would partner with the ERN/ERNs in question. Together4RD would continue to play a role of neutral broker, monitoring the progress of the projects from a feasibility and operational perspective, with the goal of extracting key learnings and best practices which can be shared and replicated (or indeed, approaches which prove time-consuming or unnecessarily

bureaucratic and should be avoided in future activities). However, alongside these more traditional pilots, Together4RD will work towards a pilot involving all 24 ERNs and myriad companies.

> *"It is important that pilot activities exploring ERN and Industry collaborations are able to provide added-value for ALL ERNs in some way, and do not solely focus on fields which are already reasonably mature, research-wise"*
>
> Till Voigtländer, Board of Member States of ERNs (Representative for Austria)

A pilot for all ERNs

It is acknowledged that due to the historical barriers limiting ERN and Industry discussions, Industry representatives are generally unable to participate in ERN meetings or workshops: representatives of companies occupying strategic positions, e.g. in EFPIA or EUCOPE, are involved in—and indeed help to shape the development of—projects or initiatives in the pre-competitive space, and are thus very familiar with ERNs and their potential, but there is limited engagement between individual ERNs and companies, *as* ERNs. It is also likely that many companies—especially smaller biotech companies lacking a European foothold, perhaps—are generally not aware of what ERNs actually offer nor what they have achieved and what priorities they are embracing for the coming years. This is a major gap to collaboration. It is also recognised, however, that some ERNs represent fields which are not particularly active in research generally, and thus their HCPs and individual experts perhaps do not have vast networks of professional connections and do not receive requests for collaboration. As in all ERN activities, it is critical to avoid favouring certain ERNs over others, as this would mean favouring certain diseases or disease areas over others. For these reasons, Together4RD stakeholders are interested in developing a pilot focused on a forum (or fora) or some sort, which will serve to address the gaps but in a way that will benefit all ERNs. For instance, Together4RD could envisage creating a dedicated space (i.e. beyond simply inviting Industry to a conference) for representatives of ALL ERNs and companies to come together. Perhaps a dedicated session could be included at the beginning or end of official EC Conferences. Alternatively, Together4RD could establish an ERN-Industry strategy forum, something similar perhaps to the EURORDIS RoundTable of Companies [45], in which ERN Coordinators/their research leads meet once or twice a year with Industry representatives and patient representatives to strategically discuss a subject of mutual interest, from a general (i.e. cross-disease) perspective, of interest to many or all Networks. A tier above this, Together4RD could create a new/utilise an existing forum to support more *specific* and *involved* discussions between Industry and INDIVIDUAL ERNs. This would not necessarily need to be mutually exclusive with the previous forum idea—one could envisage a shared event, which then focuses down and splinters into ERN-specific sessions, each involving representatives of the companies most interested in/active in the area with which that ERN is concerned. Alternatively, ERN-specific fora could be organised as entirely separate and distinct meetings, following the mould of the ACCELERATE initiative in the paediatric cancer field (see Additional file 1).

Part 4: Conclusions, recommendations, and policy asks

Over the course of 2022 and 2023, Together4RD has refocused attention on the lack of collaboration between ERNs and Industry (which, as explained, impacts negatively on the research potential of the Networks): assembling steering groups and multi stakeholder meetings; seeking and analysing case studies of activities to serve as precedents for ERN and Industry collaboration; initiating discussions on good practices and practical solutions to barrier, real and perceived; and most recently, initiating a call for pilots—all of this constitutes invaluable groundwork to revisit this important topic and drive the rare disease community a step closer to fulfilling a fundamental recommendation issued by the Rare 2030 Foresight Study:

> *"Clear rules are required that enable European Reference Networks to collaborate with industry across a range of pre-agreed activities, clarified and tested through pilots, using shared SOPs to accelerate research and build mutually-agreeable public private partnerships: a central business development/ tech transfer office could promote, coordinate and supervise European Reference Networks interactions and agreements with industrial partners" [7]*

Together4RD has essentially assumed some of the key functions called for in this recommendation and has joined other initiatives in working to address multiple barriers to ERN-Industry collaboration—Additional file 4: 'Overview of other initiatives complementing the work of Together4RD' summarises the most relevant of these, and Fig. 4 illustrates how these initiatives interlink with research of various types, at different stages.

As explained, particularly in section, 'Barriers to ERNs and Industry Collaboration' above, the barriers to fruitful

ERN-Industry collaboration are both numerous and multifaceted. Table 2 summarises how Together4RD is planning to address each of these barriers.

Conclusions and recommendations on moving from past case studies to ERN-industry projects

As illustrated in the methodology section 'Learning from Case Studies', and in Additional files 1–3, the core work on collecting and analysing concrete case studies to explore the strengths and challenges of past and present engagements between groups of clinicians/researchers and Industry, has garnered many conclusions: on the range of activities that could be undertaken for the benefit of people living with a rare disease, and on good practices and approaches which simplified such undertakings. Inclusion of case studies in the annexes to this publication is not to suggest that these are the only examples, nor does it mean that the design and delivery of the activity in each case is perfect or is the only way of working. Rather, they are highlighted in recognition of their demonstrable achievements in developing solutions to work successfully with Industry to achieve concrete goals—and such precedents are invaluable. Not all of these lessons can be replicated in this Position Statement, but they will be used to optimise the delivery of the Together4RD pilots, together with experiences from established consortia used to working with Industry, especially the EORTC in the cancer field and the RDCRN in the US. In this way, Together4RD will seek to match solutions with challenges.

As noted throughout this publication, there is no 'one-size-fits-all' approach when it comes to ERNs—needs and realities differ. In analysing the case studies under 3.3 and the Additional files 1–3, it should be noted that some of these resources and models come from fields which are now represented in research-mature ERNs. Where things are working, therefore, in communities like the paediatric cancer, renal, neuromuscular and others, it may be that the goal in some respects will continue to be business as usual (although the prospect of *improving* what such groups do, and doing what they do *better*, via Industry collaboration, is very appealing). In other fields, partnering ERNs and Industry will truly represent perhaps the best means of actually kick-starting research and development, and resources must be built afresh. To ensure Together4RD pilots can demonstrate tangible benefits in particular diseases whilst also serving to move the needle for ALL ERNs, the concept of a pilot dedicated to a strategic forum (or fora), as outlined in the section 'Towards Together4RD Pilots' above, will be particularly important.

Unlocking the potential of data

It is notable that in considering the most desirable sorts of pilots for ERNs and Industry, important cross-cutting points appear time and again. Many of these caveats concern *data*, the collection, management, standardisation, federation, and sharing of which—whilst always protecting privacy—is of course absolutely critical to unlocking advances in knowledge generation and research for rare diseases. For instance, it is essential that any data-related pilot leverages the advances over the past few years around making data more FAIR. Resources such as data dictionaries and data standards should be reused, wherever possible, and in developing or optimising such resources to better serve pilots, the community must ensure a global outlook (there is little advantage in developing or embracing standards to increase the interoperability of registry data in Europe if the US, for instance, is adopting contrasting and incompatible standards or other assets to optimise syntactic and semantic interoperability). This global perspective is especially important in the clinical research space, as companies tend to operate at the global level—but equally, for the most rare diseases, the critical mass required in terms of patient data can *only* come from a global collaboration.

As a major potential of ERNs lies in the fact that they are nested within leading hospitals, however, ERN-Industry projects will increasingly need to address not only the well-known issues concerning *registry* completeness, interoperability, data quality and suitability for research—increasingly regulatory—activities, but will need to truly push the boundaries of what has been doable to-date and invest in bridging the gap between health and research data. Unlocking the potential of Electronic Health Records (her) data and federating/pooling with other types of data (such as registry data, patient-reported data, clinical trial data, etc.), to support better and earlier diagnostics, elucidate natural history, monitor longitudinal outcomes, and support research and regulatory goals, will require significant resources—human, financial and technological. Even thinking purely of registry data entry, Together4RD's research has illustrated the extent of data entry challenges (although here at least, possible strategies have been identified. For instance the ERK-REG registry appears particularly successful at getting sites within the rare renal ERN to provide data on their patients,

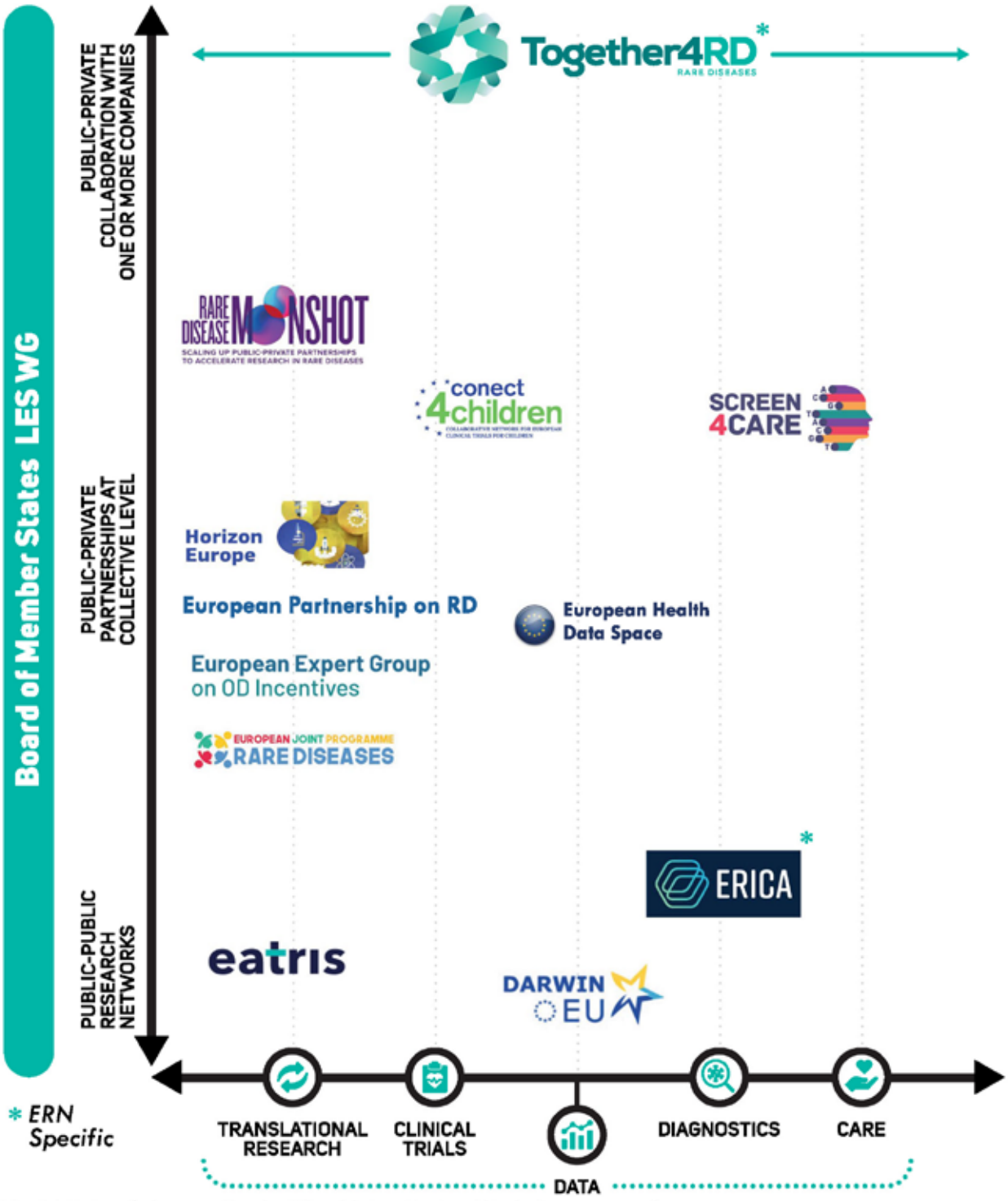

Fig. 4 Initiatives of relevance to Together4RD and their positioning within the European research ecosystem

Table 2 How Together4RD is addressing barriers to ERN-industry collaboration

Barrier to ERN-industry collaboration	Solutions in development by Together4RD (or others, as appropriate)
Concerns on the part of some members of the ERN BoMS concerning Industry and ERN interactions: stemming from a lack of awareness of the nature such collaborations can take, and of the current extent of successful collaborations outside of the ERNs	Development of rare disease case studies to illustrate a range of examples in which networks (at national and international level) engage/have engaged with Companies for particular purposes Disseminating these case studies to the BoMS, to show that win:win collaborations indeed exist
Concerns from the BoMS (and indeed from ERNs and patients themselves) over conflicts of interest	Initiating ERN-Industry engagement via Together4RD pilots, using the Code of Conflict developed by the WG on Legal and Ethical Issues, should appease concerns
Possible lack of awareness or clarity on the range of activities which could take place between ERNs and Industry	Utilising the case studies to more clearly distil the sorts of activities which could feasibly occur between ERNs (specifically, moving forwards) and Industry, to support the development of palatable pilot proposals the BoMS members would support
Concerns amongst BoMS that opening the door to ERN and Industry interactions would only benefit a few of the already more research mature ERNs	Together4RD will explore launching a multistakeholder forum to enable ERN and Industry interactions and advance strategic (and increasingly operational) collaborations across the board. Together4RD will, with the stakeholders involved, agree a preferred model for this
Administrative and bureaucratic efforts and time required to contract with Companies (exacerbated in the absence of a readily-available legal entity)	Planned development of standardised templates all ERNs could use (by making use of a designated HCP or Third Party) to contact with single Companies or multiple Companies
The fact that ERNs are not legal entities, and it appears that the European Commission is not seeking to make them so (in the near future at least)	The pilots showcased by Together4RD will demonstrate how either a consortium model or third party agreement may serve to deliver the results ERNs and Companies wish to see. It may be concluded that different Frameworks suit different sorts of activity, but either way, guidance -for now and for the future- will be proposed by Together4RD in the light of the pilot experiences
Inadequate funding for ERNs limits scope and ambition to engage in research in a meaningful way	Under the EU4Health programme, greater financial resources (provided through more amenable and appropriate and less bureaucratic grant processes) is already relieving pressure on the ERN coordination teams, which should serve to stabilise the core Network structures and services. Additional public funding is expected from the future RD Partnership and eventually from Member States to support ERN research activities and data collection. Coupled with a means of obtaining private funding for mutually-beneficial research activities, accelerated by Together4RD, and bolstered by a robust Code of Conduct issued by the Working Group on Ethics and Legal Issues, the hope is that resourcing becomes less of a barrier to ERNs fulfilling their potential
Lack of certainty on the part of ERNs of what they are able to do with Companies, and how to approach different activities	The disease-related pilots selected to be showcased by Together4RD will be closely followed and analysed, to distil good practices and lessons learned, which should serve to optimise all future interactions and should be illuminating for less-experienced Networks
ERNs and their potential are not always well understood—some companies, especially SMEs with limited European traction, are not aware of their existence or if they are, do not realise the breadth and depth of expertise ERNs offer	This Position Statement in itself should begin to raise awareness amongst the broader private sector. Foreseeably the Moonshot (and future RD Partnership, if Industry is able to eventually play a meaningful role) will also serve to boost this awareness-raising. The Together4RD pilot on a forum/fora by which ERNs and Industry can connect transparently and discuss needs and strategies with patients and other key stakeholders, should also address this challenge. And as Together4RD pilots are delivered, presumably increasingly word will spread of the ERNs in SME circles even outside of Europe
Limited basic research and Industry interest in the conditions addressed by a given ERN, which traditionally has therefore had limited research activity	Together4RD will offer benefits here firstly by simply networking the various stakeholder groups involved, and opening up the conversation. A pilot providing either a cross-ERN forum for strategic Industry discussion, or ERN-specific multistakeholder fora, will create a space for all ERNs and thus all disease domains to identify research gaps and meaningful patient-centred needs, and foreseeably make it easier to devise projects to begin to address these and build momentum for neglected conditions (which potentially could be supported through the future RD Partnership, Moonshot or other avenue)

which can then show the clinical activity and outcomes for patients in different HCPs across the ERN. To receive funding, the HCPs need to provide data. The European Society for Blood and Marrow Transplantation registry case study employs both 'carrot and stick' approaches.) But unless and until data entry and federation procedures evolve to become significantly more automated, the burden of getting data into various systems will remain a hindrance to advancing diagnostics, care and research. For these reasons, it will be essential for Together4RD pilots to synergise with efforts to implement a European Health Data Space (EHDS).

> *"ERNs are the cornerstone of clinical research on rare diseases. EURORDIS and the patient community call to establish ERN-industry collaborations under a public-private partnership framework informed by flagship pilots, to harness the research capacities of all partners, making Europe more competitive globally"*
>
> Yann le Cam, CEO of EURORDIS

Robust recommendations exist concerning strategies to making data FAIR and indeed to creating or adapting registries broadly—it is important that the first pilots between ERNs and Industry respect best practices and long-term strategic recommendations,[8] even if a 'quick win' is tempting. For instance, developing ad hoc standalone drug-registries has long been viewed as poor practice [46]. Given patient preferences to control consent over what happens to their rare disease data [25], governance issues are crucial, and data access should be maximised, to allow it to serve as many purposes as possible. It is also important to avoid setting-up entirely new registries when options exist to expand or connect existing structures: where a new registry is unavoidable, particular care should be given to interoperability with other key resources.

Therefore, in designing and delivering pilots, it will be important to agree how and where companies can best add-value to the registry landscape, and this ties in to a need for wider discussions on what different activities connected with registries should be supported by which type of stakeholder. There are a range of costs associated with building, evolving and sustaining powerful registries, from establishing the core infrastructure to providing funding for individuals based at different HCPs to actually enter data. The most appropriate roles for the European Commission, for Member State authorities, and for Industry, need to be ascertained. For instance, although some within the working groups felt that funding should be used to support the maintenance of the core registry infrastructure in future (initiated through modest EC funding), the majority seemed to feel that this should remain publicly funded. For some fields, resources are needed to federate disparate ecosystems of disease-specific registries which were often set-up in different ways (before the ERNs) and are not readily compatible, but which hold precious data which should be leveraged by the ERNs and wider community. Is this an activity Industry could support? Then at the other extreme, for some ERNs, disease-specific registries are extremely scarce, and addressing this gap would be extremely beneficial but will require funding. Many experts also see major potential in the concept of Industry collaborating with ERNs to collect data for regulatory purposes (ideally working *across* companies to co-create, develop and sustain *platforms* for newer activities such as post-marketing surveillance[9])—collaborations of this kind in the pre-competitive space would represent a real change from past investments and mechanisms will need to be developed to make such an enterprise profitable for companies whilst also serving the greater good. There is a good case for Industry support in developing more meaningful and rich modules for disease-specific data, especially where this is expected to serve a regulatory purpose. In all such discussions, it is important also to acknowledge that Industry should not be viewed merely as a source of funding—ERN and Industry pilots should embrace a broader vision of mutual added-value, beyond the purely financial.

Managing stakeholder expectations, building trust and consolidating partnerships

Another key conclusion is that meeting the goals of Together4RD will sometimes require compromise. Stakeholders need to be willing to bend from often quite rigidly-held positions and beliefs to meet in the middle in order to move things forwards. People perceive the real barriers to ERN and Industry engagement rather differently, and also sometimes have different views on what the ideal set-up of the future should be: to some, the most meaningful barrier is the fact that ERNs are not legal entities. The question of whether ERNs should or should not be legal entities is impossible to avoid in this work; however, what seems clear is that DG SANTE has no immediate plans to pursue such

[8] E.g. those espoused by the Rare 2030 Recommendations 7.Kole A, and Hedley, V,. Recommendations from the Rare 2030 Foresight Study: The future of rare diseases starts today. 2021., especially 105–6.

[9] E.g. "Post-marketing surveillance for orphan therapies should be organised at the European level, through quality-assured shared data registration platforms/disease registries" page 117 of the Rare 2030 Recommendations.

a course of action, and the field cannot wait for this possible development to commence ERN and Industry engagement. The project therefore committed to launching pilots which can be delivered using the structures and workarounds and frameworks which exist today, as outlined previously. It is necessary therefore to promote robust, real-world examples of what is possible now, without each ERN launching as a legal entity in its own right, whilst continuing to support efforts to better understand what different stakeholder groups actually wish to see (and why), in an ideal future.[10]

Another important dimension of managing often divergent expectations around how ERNs and Industry should collaborate is actually bridging the gap between Industry and the rest of the rare disease community. Often, the realities and needs of different parties are not well understood; in particular, company constraints -and indeed the constraints of drug development generally—are not always clear to those outside of Industry. There is therefore a need to communicate more transparently, on all sides. Patients' expertise in their own conditions should of course always be acknowledged and properly integrated in research design [47, 48]; to this end, patient representatives in the fields most relevant to the selected Together4RD pilots should partner in their design and delivery, wherever appropriate.

Finally, launching the first pilots between ERNs and Industry will continue to require tactful and responsible coordination and oversight—particularly, perhaps, when it comes to the more sceptical elements within the BoMS. The extent to which the BoMS has the authority to actually debar Industry and ERN activities is unclear—but even if future BoMS decisions are made via a quorum, as opposed to requiring consensus from all member nations on all words in all policies relating to ERNs, the strategy of Together4RD must be to *persuade* and assuage concerns, and to enable national decision-makers to recognise the responsibilities of individual countries to do their part to address the many unmet needs facing people with rare diseases. For these reasons, it is imperative that pilots are properly set-up and monitored by Together4RD—this does not preclude companies from setting up additional pilots with ERNs of their choosing, down the line, but it is important that these first formal engagements are held up as learning experiences, to build confidence and iron-out specific challenges that may arise in delivering the pilots. Based upon the lessons of such pilots, the expectation is that activity between ERNs and companies would continue to expand and grow in future, buoyed by agreed good practices and employing consensus safeguards to ensure mutually beneficial and ethical collaborations moving forwards.

Open and transparent engagement between ERNs and industry

There is an often-unspoken irony surrounding the status quo. Some ERNs emerged from quite research-active communities, meaning their Coordinators and constituent HCPs have an established track-record of regular interactions with Industry, assuming various forms. And despite the unease from some European countries around the notion of ERN and Industry collaborations (as exemplified in the 2016 and 2019 BoMS statements) the reality is that the individuals involved in ERNs did not cease their Industry engagement in 2017. Nor should they have done so, when to block vital research would be so injurious to the 30 million people in Europe dealing every day with the burden of rare disease. Instead, they continue their collaborations as individual experts, or as academic institutions, rather than an ERNs. The question of what constitutes Industry collaboration AS an ERN is a thorny one. The present situation is actually deleterious for the entire rare disease field, for various reasons:

- it works *against* the very spirit of open and transparent interaction sought by the companies, the ERNs and the patients and of course the BoMS itself, and actually creates more grey areas;
- it prevents Industry and ERNs from embarking on truly new activities. The sorts of collaborations summarised in part 3 have, in most cases, been happening for years—but truly *new* activities are foreseen which the ERNs are perfectly placed to usher in with Industry. Whereas it may be possible for individual ERN experts or HCPs to continue their 'business as usual' collaborations, it is likely that few would feel comfortable embarking on new and substantial projects with Industry which would very clearly be seen as activities OF the ERN, in the absence of a supportive atmosphere such as Together4RD is seeking to provide;
- it perpetuates the differences—and potentially inequalities- in experience between ERNs, as those with robust research communities continue to engage in their own capacities, if not exactly as the ERN, whilst the ERNs representing fields with limited or no research activity will surely struggle to open up opportunities and overcome the relative inertia in a climate in which Industry engagement is somehow frowned upon.

[10] It is notable that the question of whether or not ERNs should become legal entities was amongst the most polarising subjects addressed when generating the Rare 2030 recommendations concerning ERNs.

Table 3 Summarising the Together4RD Policy Asks [49]

Recommendation 1: ERN Governance	Recommendation 2: Public–Private Research Collaboration
Promote transparent governance structures and open dialogue to empower and advance ERN—industry collaboration	Create a Forum (or Fora) for public–private exchange of pre-clinical knowledge for ERNs
Recommendation 3: Independent, Well Resourced and Effective ERN Registries	Recommendation 4: EU Rare Disease Action Plan Collaboration
Ensure ERN registries are adequately financed via public funds and remain independent, whilst clarifying & optimising their potential for collaboration	Create a comprehensive European Action Plan for Rare Diseases that supports public–private partnerships

The goal of Together4RD to move the needle here is therefore particularly important. The project should elevate ERN-Industry activity from something which happens in a small number of ERNs by a roundabout route and in a piecemeal way (without being really reported or celebrated) and bring it into the light, to do things properly and more equitably.

Leveraging strategic and political opportunities

This vital foundational work should pave the way for further opportunities for ERN-Industry interaction to advance, foreseeably through the much-anticipated Moonshot and the European Rare Disease Partnership. This is the perfect moment to take these overdue steps. For one thing, the political will is there.[11] Robust recommendations exist (and will foreseeably be implemented through a post-Rare 2030 European Action Plan, a new Council Recommendation, or similar) which stipulate high-level solutions necessary to move the rare disease field forwards in leaps and bounds, as opposed to the incremental (or indeed non-existent) pace of progress seen in so many communities.

Precedents exist, such as the case studies showcased above but also crucially in the form of the US RD Clinical Research Network (RDCRN) [43], for instance, which constitutes an important model for European imitation or adaptation: the RDCRN has grown from its foundation in 2002 to now consist of 20 disease consortia collectively addressing over 190 different rare diseases and engaging ca.400 clinical sites (including around 50 international sites in approximately 20 countries). Crucially, the RDCRN has been able to leverage private funding as well as public support, and as a result has been able to conduct cutting-edge rare diseases research, including gene editing and gene therapy trials. The learnings from this may be very valuable for the European setting [11].

What could then be achieved by the ERNs—which arguably offer even greater potential[12]—if similarly unbridled in the research sphere? The European-level will to unlock the potential of precious rare disease data is greater than ever, and with momentum growing around the EHDS—with the accompanying availability of technical, legal and organisational solutions and assets- there is finally real cause to hope that ambition will translate into reality.

To leverage political support for this important work, Together4RD has issued four Recommendations, in the form of Policy Asks [49], summarised in Table 3.

This Position Statement is being launched in the period of the ERNs' first 5-year evaluation. This is a perfect moment for Europe to take stock of how far the Networks have come, and to embrace an ambitious and forward-thinking vision to guide the rare disease field in Europe and beyond to where it wants—and needs—to be. Although the barriers the Together4RD project must surmount are not insignificant, the consequences of ***not*** tackling these ingrained issues would be severe—ERNs will continue to be hampered in reaching their potential and Companies will increasingly perceive that the ERNs are not open for collaboration, with rare disease patients the ultimate casualty.

Abbreviations

BoMS	Board of Member States of ERNs
CDA	Confidential Disclosure Agreements
CoI	Conflict of Interest
CPGs	Clinical Practice Guidelines
CPMS	Clinical Patient Management System
CTSR	Care and Trial Site Registry
c4c	Conect4children
DMD	Duchenne Muscular Dystrophy
DG RTD	Directorate General Research & Innovation
DG SANTE	Directorate General Health & Food Safety
EBMT	European Society for Blood and Marrow Transplantation
EC	European Commission
ECET	European Collaboration for Epilepsy Trials
EFPIA	European Federation of Pharmaceutical Industries and Associations
EHDS	European Health Data Space
EHR	Electronic Health Record
EJP RD	European Joint Programme for Rare Disease Research
EMA	European Medicines Agency
EORTC	European Organisation for Research & Treatment of Cancer
ERDRI	European Rare Disease Registry Infrastructure

[11] See see Part 1, 'Unmet Needs of Rare Diseases and the Status Quo of European Research'

[12] See See Part 1, section entitled 'ERNs and the potential they offer' and under Part 2, 'What factors have limited ERN-led research ?'. Tumiene B, Graessner H, Mathijssen IM, Pereira AM, Schaefer F, Scarpa M, et al. European Reference Networks: challenges and opportunities. J Community Genet. 2021;12(2):217–29.

ERICA	ERN Research Coordination and Support Action
ERKNet	The European Rare Kidney Disease Reference Network
ERK-Reg	The European Rare Kidney Disease Registry
ERN(s)	European Reference Network(s)
EU	European Union
EUCOPE	European Confederation of Pharmaceutical Entrepreneurs
FAIR	Findable, Accessible, Interoperable and Reusable
HCP	HealthCare Provider
IMI2	Innovative Medicines Initiative 2
ITTC	Innovative Therapies for Children with Cancer
JRC	Joint Research Centre
LE	Legal Entity
LES WG	Working Group on Legal and Ethical Issues and relations with Stakeholders
MEP	Members of European Parliament
NH	Natural History
PCOMs	Patient-Centred Outcome Measures
PMS	Post-Marketing Surveillance
PROMs	Patient Reported Outcomes Measures
POC	Proof of Concept
RDCRN	Rare Diseases Clinical Research Network
R&D	Research and Development
RWD	Real World Data
SMA	Spinal Muscular Atrophy
TACT	TREAT-NMD Advisory Committee for Therapeutics
TGDOC	TREAT-NMD Global Database Oversight Committee
WG	Working Group
WP	Work Package

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13023-023-02853-9.

Additional file 1. 'Case Study Summaries'. (Summaries generated to support creation of this Position Statement).

Additional file 2. 'Activities suitable for ERN and Industry Collaboration (Registries)' (A table of data generated by a Together4RD Working Group to support creation of this Position Statement).

Additional file 3. 'Activities suitable for ERN and Industry Collaboration (Clinical Research)' (A table of data generated by a Together4RD Working Group to support creation of this Position Statement).

Additional file 4. 'Overview of other initiatives complementing the work of Together4RD' (Summary illustrating how the mission of Together4RD fits into a broader ecosystem of projects and initiatives working towards a more collaborative ERN-Industry ecosystem).

Acknowledgements

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VH led on the creation of all drafts of this manuscript, and oversaw the revision and finalisations process. Authors MBJ, IH, RK, RN, CR, FS, SU, and the rest of the Together4RD Steering Group (see 'Acknowledgements') made substantial contributions to the conception and design of the work. MBJ, IH, RN and FS substantially revised the document by providing substantial feedback on the first drafts. MBJ also provided verbal feedback on the integration of his comments and suggested changes to structure. RK, CR and SU provided in-depth reviews of the pre-final documents, and recommended structural changes. All authors read and approved the final manuscript.

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Availability of data and materials

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Declarations

Ethics approval and consent to participate

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Consent for publication

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Victoria Hedley and Sheela Upadhyaya are consultants for FIPRA International, which is overseeing Together4RD (see below). Victoria has received consulting fees in the past from CSL Behring. Clara Romero and Rosalind Kenward are consultants to FIPRA International, and therefore receive a fee for their work as members of the Secretariat, which is funded by the industry partners to Together4RD. Franz Schaeffer has received consulting fees from Astellas, Amgen, Alexion, Bayer, Fresenius Medical Care, GSK, Otsuka, Purespring and Roche. Rima Nabbout, Matt Bolz-Johnson and Ines Hernando report no competing interests.

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Publisher's Note

Annex II – Report: Boosting European Competitiveness through Public-Private Partnerships in Rare Disease Research: the role of European Reference Networks

Contents

Executive Summary

On the 24th of September 2025, Members of the European Parliament Stine Bosse (Renew, Denmark) and András Kulja (EPP, Hungary), Together for Rare Diseases' MEP Champions, co-hosted a high-level conference on the urgent need for EU policy to enable ERN-industry collaboration on rare disease research.

The event was organised by Together For Rare Diseases (T4RD) and joined in-person by 40 representatives from ERNs, research infrastructures, patient representatives, the European Parliament, the European Commission's DG Research and Innovation, the pharmaceutical industry and trade associations, with 89 more registered online.

The main objective was to demonstrate how public-private partnerships (PPPs) between European Reference Networks (ERNs) and industry can boost the European Union's competitiveness by accelerating rare disease research as well as identifying the barriers and needed solutions. Public-private partnerships are delivering value and should be acknowledged as essential drivers of societal progress. They have already delivered well beyond immediate market returns whilst creating long-term value for patients, healthcare systems and society as (for example) clearly demonstrated by the many Innovative Medicine/Health Initiative funded projects.[1]

> *From the first time I heard about ERNs, I knew we had a system worth investing in.*
>
> - MEP Stine Bosse

ERNs are Europe's flagship rare disease infrastructure, and operate at the heart of diagnosis, patient care, registry development and clinical trials. However, while ERNs have excelled in clinical care, education, and guideline development, their research contributions have been limited or less visible (without "ERN branding"), partly because research may not have been seen as a central part of their mission as ERNs received research funding through Horizon 2020, its successor Horizon Europe and co-funds from Member States through the European Joint Programme on Rare Diseases (EJP RD) and ERDERA. For ERNs to contribute directly to European competitiveness, they must move from being the backbone of rare disease care to becoming engines of research and innovation.

[1] https://www.ihi.europa.eu/about-ihi/impact

A change of perspective is needed to embrace public-private partnerships between ERNs and industry as flexible, well-resourced and highly productive forms of collaboration which can unlock rare disease research in Europe.

They need to be encouraged by public and private research funders. A clear signal about the expectation that some objectives are addressed by public-private consortia would be important to promote and demystify these types of collaborations. Industry are key partners for researchers, as **highlighted by ERN coordinators and industry partners in a joint T4RD and ERICA webinar** as well as by a representative of a patient organisation who shared it was easier work with industry than with ERNs.

Although several ERN-industry public-private partnerships such as Conect4Children have been highly successful, these types of collaborations are still limited by the **2019 statement by the ERN Board of Member States (BoMS)** discouraging ERN-industry data collaboration.

To fully harness the potential of PPPs, they should be allowed and promoted as effective conduits for rare disease research, notably in the ERDERA (European Rare Diseases Research Alliance) ecosystem, which already provides a coordinated EU-level framework and support for RD collaboration. Greater legal flexibility as the absence of an ERN legal entity remains an administrative hurdle, with researchers advocating for more centralised and transparent governance for ERNs.

> *Together For Rare Diseases' three ERN-industry pilot projects have demonstrated the willingness of both parties to enter partnerships to better understand rare disease burdens on quality of life, develop innovative endpoints or advance the consolidation of data registries.*
>
> *As a result, the ERN Board of Member States will look into the learnings of the pilot projects to assess the possible revision of the 2019 Statement.*
>
> **- ERN Board of Member States (BoMS)**

Europe now has a critical policy window to boost rare disease research. The Multiannual Financial Framework (MFF) for 2028-2034, unveiled by the European Commission in July 2025, **provides an opportunity to better exploit ERNs' potential by placing strategic emphasis on biotechnology**. This allows rare diseases to be woven into flagship EU funding instruments such as the proposed European Competitiveness Fund (a €409 billion initiative targeting strategic sectors including biotech) and Horizon Europe's successor programme **FP10** (with €175 billion allocated for 2028-2034). This includes ensuring that the **Life Sciences Strategy** (adopted July 2025), the forthcoming **Biotech Act**, the **European Innovation Act** (expected Q1 2026), implementation of the **EHDS** Regulation (which entered into force in March 2025), the **EU Startup** and **Scaleup**

> *An EU Action Plan on Rare Diseases would be a way of attracting investment from global pharmaceutical companies and incentivise them to develop technologies here in Europe.*
>
> - MEP András Kulja

Strategy (launched May 2025), and the **European Strategy on Research and Technology Infrastructures** (adopted September 2025) are all opportunities for unlocking rare disease research and translation. The Life Sciences Strategy is one of the main strategies under the competitiveness agenda and aims to strengthen the rare disease ecosystem by improving access to data, tools, actors and partners for collaboration. An **EU Action Plan on Rare Diseases**, strongly supported by MEPs in an April 2025 plenary debate, would ensure funding and policies are efficiently directed towards boosting rare disease innovation.

Participants called for the proposed **MFF 2028-2034 to ringfence funding for health infrastructures such as ERNs** to anchor rare diseases as a strategic, competitive investment. Suggestions for the MFF included earmarking part of the ERN core budget for clinical trial readiness and public-private partnerships, as well as establishing a network of ERN centres qualified for early human trials to accelerate patient access to advanced therapies. On the other hand, the envisaged **MFF Single Rulebook for Financial Rules,** while positive for some aspects of simplification, could impose a one-size-fits-all approach to research which will make it harder and less flexible for public-private collaborations to occur and thrive.

> *It is very hard to keep health on the top of the European agenda. As much as you need me, I need you to **speak up** and continue to talk into this obvious fact that when we work together we can do more and we can do it cheaper.*
>
> - MEP Stine Bosse

The momentum created by the European rare disease community has succeeded in placing rare diseases on the policy agenda as rarely before.

Together For Rare Diseases calls upon its MEP Champions and members to carry forward the optimism and suggestions surrounding public-private partnerships between ERNs and industry, and to disseminate them in key discussions such as the MEP Interest Group on Cancer and Rare Diseases[2] and the High-Level Meeting on European Research and Innovation for Rare Diseases.[3]

[2] https://www.europarl.europa.eu/meps/en/intergroup/details/7898/Intergroup%20on%20Cancer%20and%20Rare%20Diseases

[3] https://www.brains4brain.eu/category/meeting/

Detailed learnings

Public-Private Partnerships (PPPs) as drivers of Rare Disease innovation

PPPs must be recognised as a policy tool rather than an optional add-on. Stronger political mandates and targeted funding are essential to make PPPs routine in EU health and research policy. Clear political signals must be established in upcoming legislative packages (Life Sciences Strategy, Biotech Act and the next MFF) to earmark resources and explicitly promote PPPs as a strategic instrument for Europe's health and industrial policy.

Persistent 'perceived' obstacles remain, with the 2019 Board of Member States[4] (BoMS) statement discouraging ERN–industry data collaboration for research. There is a need for a revision to clarify conflict-of-interest rules, and build trust so that collaboration is seen as safe and legitimate.

Beyond removing barriers, stakeholders called for enablers such as robust and flexible operational frameworks, standardised contracts and data-sharing agreements, and EU-level templates that can be adapted across different disease areas to lower administrative burden and speed up project start-up.

PPPs, through the generation of real-world evidence, position ERNs as pivotal hubs for trial readiness and data-driven innovation.

> *We do not only need to remove or amend the statements that prevent us from collaboration, we also need a very clear traction from funders and decision makers saying that public-private collaboration is part of our tools to achieve objectives.*
>
> Pharmaceutical industry

> *What we are still lacking largely are PPPs that would drive therapeutics development by exploiting the unique patient and data resources available in the ERNs.*
>
> ERN coordinator

> *Agile, bespoke partnerships between ERNs and industry can move the needle in rare disease research.*
>
> Pharmaceutical industry

[4] The Board of Member States (BoMS): ERN governing board

Strengthening ERNs for research and competitiveness

ERNs' original mission was primarily clinical care, which means that research infrastructures, regulatory preparedness and systematic data integration have been limited. There is a need for **dedicated EU and national funding to build sustainable ERN research capacity**.

Participants called for a **ring-fenced share of the next Multiannual Financial Framework (MFF)** to support not only clinical-trial readiness and PPPs but also registry harmonisation, patient-reported outcomes development, early-phase trial capacity, and cross-border data platforms, so that ERNs can become true innovation accelerators.

New **governance models were explored**, including for the European Commission and member states to reconsider granting ERNs legal entity or creating shared governance/umbrella entities. These models would **simplify contracts, data use, and liability management, reduce administrative duplication across member hospitals, and create a single trusted entry point for industry and academic partners**.

Strengthening ERNs' research-capacities also requires training and resources for the academic centres teams (inc. on how to collaborate with private partners), interoperable IT systems, and incentives for hospitals to invest in research roles.

> *ERNs must not only remain the backbone of rare disease care, but also evolve to become engines of research and innovation.*
>
> MEP András Kulja

> *Creating a shared legal entity saves money and time because you harmonise and have one single entry point for the collaborations.*
>
> Researcher

> *Rare diseases are a cornerstone of the European Commission's health research, and the collaboration between ERNs and infrastructures like ERDERA and Jardin are exemplary for other health areas.*
>
> European Commission

EU policy and funding frameworks
(MFF, Life Sciences Strategy, Biotech Act)

Health must stay prominent in EU budgets, with explicit and sustained prioritisation of rare diseases. Without dedicated lines in the Multiannual Financial Framework (MFF), Europe will miss the chance to anchor rare disease research as a strategic competitiveness investment.

The competitiveness framing opens a unique opportunity to weave biotech and rare diseases into EU funding instruments such as the forthcoming European Competitiveness Fund and the next Horizon Europe work programmes. This includes ensuring that the upcoming legislative framework explicitly mention rare diseases and support translational research and advanced therapies.

These frameworks should **provide clear incentives for the co-investment from the private sector**, including risk-sharing mechanisms, tax and regulatory enablers, and predictable multi-year budgets to attract global R&D capital to Europe.

Flexibility and fitness-for-purpose are critical as concerns were raised that a proposed "single rulebook" for EU funding could unintentionally hinder diverse partnership models by imposing one-size-fits-all administrative rules. Speakers argued for **adaptable governance and regulatory sandboxes allowing different PPP formats**, lighter reporting where appropriate, and the ability to pilot innovative contracting models.

Coordination across EU directorates and member states must improve so that health, research, and industry policies reinforce each other. The group called for stronger horizontal links between DG SANTE (EU4Health) and DG RTD (Horizon) and for more structured engagement of national health ministries in EU research funding decisions.

> *What is positive about competitiveness is that it will never have been easier to talk about collaborations between industry and ERNs. There is no better time than now.*
>
> European Commission

> *Framework programmes are created based on the academic needs, not on the needs of public and private. That needs to change if we want to be competitive.*
>
> Pharmaceutical industry

> *The ERNs should no longer be denied institutional budget funding for research by the Commission, nor industry collaborations by the BoMS.*
>
> ERN coordinator

Building multi-stakeholder and political momentum to foster rare disease research in Europe

There was a call for strong(er) alignment between EU and national rare disease strategies, ensuring that European investments translate into coordinated national action plans and consistent funding across member states.

Participants highlighted the need to **integrate rare disease priorities into other EU policy areas** such as the digital health, data spaces, industrial, and education strategies so that rare diseases remain visible in broader competitiveness and innovation agendas.

Sustained communication campaigns and high-visibility events, such as regular summits and parliamentary hearings, keep **rare diseases in the public and political eye**, ensuring continued pressure on decision makers.

Stakeholders advocated for **ERN monitoring and evaluation to capture PPP outcomes**, including metrics on patient impact, research outputs, and economic returns, to demonstrate value and secure long-term political and financial support.

International collaboration beyond Europe, including transatlantic and global partnerships, such as IRDiRC[5], is vital for tackling ultra-rare conditions and for **positioning Europe as a global leader in rare disease innovation**.

> *As a parent, I want to see the EU not only talk but deliver an action plan so that families like mine know treatments will come to Europe, not leave it.*
>
> Patient organisation

> *ERNs can be the engine of change and recognising this would be a way of attracting investment from global pharmaceutical companies and incentivise them to develop technologies here in Europe.*
>
> MEP András Kulja

> *This is the moment to hard-wire rare diseases into the EU's competitiveness agenda, patients and their organisations are ready to work with MEPs and the Commission to make it happen.*
>
> Patient organisation

> **The positive aspect of this new competitiveness flag is that it has never been easier to discuss collaborations between industry and the European Reference Networks. This is an opportune moment for such partnerships.** *Biotech has been designated as a critical technology within this competitiveness framework, which represents significant progress for the rare disease ecosystem. In the current budget proposal figures provide an excellent foundation for negotiations.* **Rare diseases have frequently served as examples and catalysts for advancing other legislative initiatives.** *All the necessary instruments and tools are now available to move this agenda forward under the competitiveness framework.*
>
> European Commission

[5] https://irdirc.org/

Key actions proposed by the Together For Rare Diseases initiative

Actions	Description	Stakeholders
Revise the 2019 BoMS statement to explicitly allow and encourage ERN–industry research and data collaboration	Updating this guidance would lift a major regulatory barrier to ERN–industry collaboration. By clearly allowing data sharing and joint research, it would unlock stalled partnerships and speed up clinical innovation.	Board of Member States (BoMS), European Commission (DG SANTE)
Establish an EU Rare Disease Action Plan with measurable targets and stable funding	A formal, measurable plan at EU level would provide a long-term roadmap, attract private investment, and give Member States a shared framework to align national strategies.	European Commission (DG SANTE and DG RTD), European Parliament, Member States. And all other stakeholders to continue advocating
Ring-fence part of the next Multiannual Financial Framework (MFF) for RD research, clinical-trial readiness, and PPPs	Dedicated budget lines would secure predictable financing for cross-border clinical trials, registries, and PPPs, ensuring continuity beyond short funding cycles.	European Commission (DG BUDG and DG RTD), Council, European Parliament
Create a permanent EU-level cross-sector working group to coordinate rare disease policy and monitor implementation	This forum would keep rare disease policy high on the agenda, allow stakeholders to track progress, and foster coordinated action across Commission services, Parliament, industry, and patient organisations.	European Commission (DG SANTE, DG RTD and DG GROW), European Parliament, patient organisations
Develop and deploy a standardised EU-wide contracting and data-sharing framework for ERN-industry partnerships	A coordinated and 'centralised', EU-endorsed framework would reduce legal complexity, speed up partnership formation, and ensure compliance with privacy and data-protection standards.	European Commission (DG SANTE, DG RTD and DG CONNECT), ERN coordinators, industry associations
Support ERNs in becoming legal entities or forming shared-governance structures to streamline partnerships	Legal entity or a common governance umbrella would simplify negotiations with industry, clarify liability, and enable more agile multi-country projects.	European Commission (DG SANTE), ERN coordinators, Member States
Launch a European training and mentorship programme to build collaboration skills ("collaboration muscle") among ERN leaders, patients, and industry	Dedicated capacity-building would strengthen the "collaboration muscle," helping ERN leaders, patients, and industry partners to manage complex PPPs and to innovate jointly.	European Commission (DG RTD), ERNs, patient organisations, industry
Integrate rare disease priorities into broader EU policy areas (digital health, data spaces, industrial strategy) to ensure visibility and funding	Mainstreaming rare disease considerations into digital health, industrial strategy, and education would amplify impact and guarantee sustained visibility and funding.	European Commission (DG SANTE, DG RTD, DG CONNECT, DG GROW), Member States
Establish regular high-visibility events and communication campaigns to keep rare diseases on the EU political agenda	Ongoing public engagement would maintain political pressure, demonstrate success stories, and attract new partners and investors to the field.	All stakeholders, including the European Commission (DG SANTE, DG RTD, DG GROW), European Parliament, Member States, European Economic and Social Committee, ERNs, research infrastructures, patient organisations, industry
Include PPP outcomes in the monitoring and evaluation of ERNs	Transparent indicators on patient benefits, scientific outputs, and economic returns would provide evidence of impact, helping secure future investment and public trust.	European Commission (DG SANTE), ERNs

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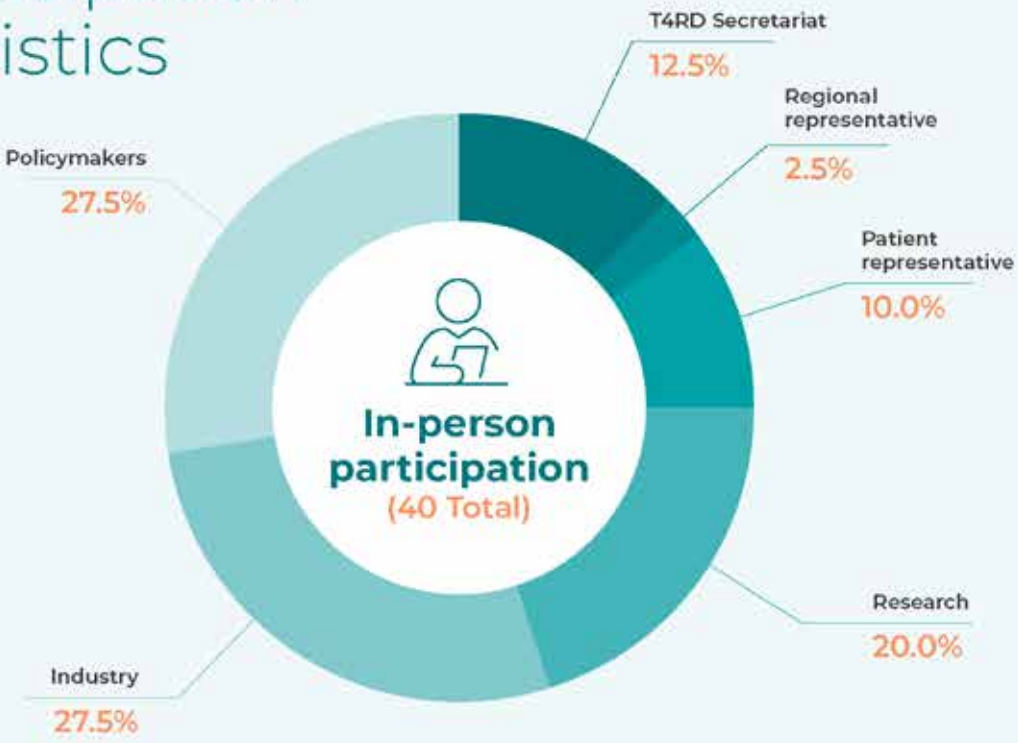


Annex III – Toolkit to foster ERN-industry collaboration

Section A: background knowledge – ERNs, industry and the opportunity

TOOL 1: THE IMPORTANCE OF PUBLIC PRIVATE PARTNERSHIPS IN RARE DISEASES

The need for a robust and supportive ecosystem for research and innovation in rare disease

The challenges posed by rare diseases to patients, families, researchers, clinicians, healthcare systems, policymakers, regulators, the private sector, and more, are well documented.

- Although individually rare, the sheer number of conditions classed as rare (often estimated as 6-8000) result in a significant population directly affected by a rare disease of one kind or another (equating to approximately 1 in 18)
- Rare diseases are typically complex, multisystemic conditions, around 75% of which are genetically inherited.
- The presentation, severity and outlook differ dramatically – some conditions do not manifest until adulthood, and patients are able to live a relatively normal life with few restrictions. Approximately half present in childhood and around a third of paediatric patients will die before their 5th birthday.
- Only 5-6% of all conditions classed as rare have any dedicated treatment, and those which do tend to be clustered around one of a limited number of therapeutic areas (60% of orphan designations during the period 2010-2020 were for oncology, alimentary tract and metabolism, and musculosketal and nervous system disorders.)[1] Furthermore, many treatments address symptoms only, and are not curative or transformative.
- There is growing evidence that rare diseases tend to impact negatively on all aspects of daily life. The 2017 pan-rare-disease survey 'juggling care and daily life', led by the RareBarometer initiative under EURORDIS, demonstrated that 7 in 10 rare disease patients or carers reduced or stopped professional activity, 8 in 10 have difficulty with daily care activities, *and* were 3 times more likely to be depressed than the general population.[2] The most recent RareBarometer survey illustrates the strong link between rare disease and disability - 8 in 10 people living with a rare disease report a disability, and the majority of these consider their disability[3] invisible, and poorly addressed.[4]
- All of these challenges result in significant inequalities for patients and their families.

The **Together4RD position statement on collaboration between European reference networks and industry (2023)** summarises[5] how Europe, in particular, has sought to address these challenges (much of the remainder of this introductory section comes from this report).

1 http://www.rd-action.eu/wp-content/uploads/2018/09/Final-Overview-Report-State-of-the-Art-2018-version.pdf 88-91
2 https://download2.eurordis.org/rbv/juggling_care_and_daily_life.infographic__final.pdf - the full report is also available
3 https://www.eurordis.org/publications/rb-dailylife-results/
4 https://www.eurordis.org/publications/rb-dailylife-results/
5 See especially part 1 – 'the EU context'

Key policy documents were issued in 2008 (the Commission Communication on *Rare Diseases: Europe's challenges* [COM(2008) 679 final][6]) and 2009 (the Council Recommendation on an action in the field of rare diseases (2009/C 151/02)[7]). These landmark policies built upon the regulatory incentives engendered by the 2000 orphan drug Regulation[8] to call for national action alongside key European efforts to advance diagnostics, treatment, care, research and social support for rare diseases. Much has been achieved in the following decade and a half, for instance

- ☑ 26 of the current EU MS have adopted a national plan or strategy for rare diseases, compared to only 4 in 2008. This does not mean all countries have kept these policies live and updated, of course, but it is an important achievement nonetheless
- ☑ 24 European Reference Networks were launched in early 2017, for rare and specialised diseases
- ☑ Transnational research initiatives dedicated at the pan-disease level (such as the successive E-Rare projects, the **European Joint Programme for Rare Disease** research (2019-2024), the ERNs' own research project **ERICA**, and most recently the European Rare Disease Research Alliance, **ERDERA**) increased the opportunities for collaboration
- ☑ Umbrella patient organisations such as EURORDIS (Rare Diseases Europe) grew to become a key stakeholder in rare disease projects, whilst also establishing, supporting and networking national alliances of rare disease patient organisations
- ☑ Orphanet (the global database for rare diseases) evolved to encompass a large suite of tools to complement its nosology and disease encyclopaedia
- ☑ Diagnostics initiatives at the pan-RD level were launched and sustained, such as **RD-Connect**, **Solve-RD**, **Screen4Care**, etc., along with the expansion of the **Undiagnosed Diseases Network** to include an International focus.
- ☑ Over 260 marketing authorisations granted for orphan products since 2000 and over 3000 with orphan designations.[9]

However, notwithstanding these achievements at both European and national level, the day-to-day reality for too many people living with a rare disease has sadly changed little. **Major unmet needs remain, which can only be addressed through a seismic shift in the way in which research, care and social support are organised, in Europe and beyond.** In recent years, much attention has been focused on where the RD field should go next – how

6 https://ec.europa.eu/health/ph_threats/non_com/docs/rare_com_en.pdf
7 https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2009:151:0007:0010:EN:PDF
8 Regulation (EC) No 141/2000
9 https://www.ema.europa.eu/en/documents/leaflet/infographic-orphan-medicines-eu_en.pdf

can we stimulate new R&D for the thousands of conditions without *any* treatment options (and indeed any fundamental research foundation), whilst also ensuring that therapies developed for conditions benefiting from a relatively strong research interest hitherto deliver meaningful and transformational change?

The Together4RD Position Statement further noted that "Rare Disease research, in particular, needs to operate within a supportive Research and Innovation ecosystem". A 'supportive' Research and Innovation ecosystem, able to tackle the needs of rare diseases, must have several components.

What should a 'supportive' ecosystem encompass?

Legislation which fosters and incentivises research

The foundation for any rich Research and Innovation ecosystem must be the existence of robust policies to incentivise R&D. Therefore, the importance of the efforts to revise the Orphan Drug Regulation (EC 141/2000) and EU Paediatric Regulation, cannot be understated. In 2017, a **10-year evaluation report** on the EU Paediatric Regulation was published. This report concluded that the Regulation had provided positive results overall in terms of paediatric product development, but that development for rare paediatric diseases, which is in many cases equally supported through the Orphan Regulation, often failed to materialise. Following this report, the European Commission announced a **joint evaluation of the Paediatric and Orphan Regulations**, which provided an assessment of the strengths and weaknesses of the two Regulations. On this groundswell of activity, a European Expert Group on Orphan Drug Incentives[10] was established and in 2021 published a comprehensive and much-needed report on 'How to address the unmet needs of rare disease patients by transforming the European OMP landscape, complete with recommendations and policy proposals.[11] A key conclusion was that to force meaningful progress in the therapeutic landscape for rare diseases requires the optimisation, application and *integration* of many elements, initiatives, and actors. The eventual changes to the EU General Pharmaceutical Legislation will be finally determined in 2025; however, the impact of proposed revisions has, over the past couple of years, dominated much of the debate around the future of rare disease research in Europe.[12]

Acknowledgement of rare disease as a priority area for research – at national, European and global level

Next, a supportive Research and Innovation ecosystem entails a broader acceptance by European bodies and national-level stakeholders that rare disease *matters*, in a world of

10 https://od-expertgroup.eu/
11 https://pmc.ncbi.nlm.nih.gov/articles/PMC8717920/
12 See for instance https://www.eucope.org/european-parliament-adopts-reports-on-the-revision-of-the-eu-general-pharmaceutical-legislation/

competing health threats and priorities and increasing financial pressures. The **Rare 2030 foresight study** issued an ambitious set of recommendations in 2021[13], intended to guide Europe towards the future scenarios deemed most favourable by its expert panel of over 250 individuals (and indeed thousands of stakeholders, globally, through Rare 2030's wider consultation sand surveys). The key message espoused across the individual chapters of recommendations is that there is an **urgent need for a new European policy framework for rare diseases**. Since the end of the Rare 2030 Foresight Study, many stakeholders, galvanised by the efforts of EURORDIS, in particular, have advocated for a renewed European commitment to rare disease, evidenced perhaps through a new Commission Communication or Council Recommendation, but most likely via an EU Action Plan.

However, as R&D for rare disease rests upon the engagement of the private sector, and companies working in rare disease tend to have a *global* outreach and footprint, **it is important to accompany any European prioritisation of rare disease research with a strong and growing global acknowledgement** of the major unmet needs facing the 300+ million people living with these conditions worldwide. Here too, there has indeed been an increase in momentum at the global level. Back in 2011 the pan-disease International Rare Disease Research Consortium (**IRDiRC**) was established, to unite researchers with research funders. The new European Rare Disease Research Alliance, ERDERA, funded through Horizon Europe, is forging closer links with IRDiRC and will more broadly pursue global collaborations in rare disease research. In the areas of healthcare, policy and general awareness-raising, important developments have been seen over the past couple of years at the global level. Rare Diseases were mentioned for the first time in a United Nations (UN) Declaration on Universal Health Coverage, in September 2019. This was followed by the adoption of a UN Resolution on Rare Disease[14] in late 2021. Recognising that rare diseases are the source of major inequalities in health and wellbeing globally, and that those dealing with these conditions face major inequities, the WHO signed a MoU with Rare Disease International (RDI) in 2021, to scope a Global Network for Rare Disease.[15] In 2025, RDI has launched a campaign for a World Health Assembly Resolution on Rare Disease.[16] All of these developments are important, to stimulate more focus on research and innovation for rare conditions across the globe, building awareness and prioritisation in regions and countries traditionally lacking rare disease policies.

The opportunity to build effective multistakeholder collaborations

It has long been recognised that addressing the many gaps and challenges in rare diseases entails a truly cross-sector and cross-disciplinary approach. Years of public and private

13 http://download2.eurordis.org/rare2030/Rare2030_recommendations.pdf
14 https://www.rarediseasesinternational.org/wp-content/uploads/2022/01/Final-UN-Text-UN-Resolution-on-Persons-Living-with-a-Rare-Disease-and-their-Families.pdf
15 https://www.rarediseasesinternational.org/collaborative-global-network/
16 https://www.rarediseasesinternational.org/wha-resolution/

are not always well-understood, which can deter people from entering into such collaborations at all, or else jeopardise initial attempts to build a co-creative project. (This is one of the gaps this Together4RD Toolkit is intended to address)

Some of these essential steps will be more challenging than others. Some require resources, others a significant mindset change. But it is important that the field focuses efforts in these directions, as the bottom line is that building more public-private collaborations IS essential, since private sector involvement generally remains a prerequisite for successful drug development in the rare disease domain.[24] There is very much a sense that the conditions without treatments, and indeed without a strong basic science footing, are the 'higher-hanging' fruit – developing therapies here will be difficult. Moving into an unstudied rare condition, which likely has a very small patient population, can means significant risks for companies – not only is there the scientific challenge of developing a products that would make a difference, but uncertainty about the regulatory processes and likelihood of a product making it to patients in jurisdictions like the EU, with all its heterogeneity around access, can be a deterrent that the traditional incentives for orphan product developers struggle to overcome. "Investing in PPPs helps organizations and stakeholders to share the risks of innovation in high unmet need areas, the cost of infrastructures, and the work required to acquire relevant scientific expertise with large datasets that translate discoveries into treatments."[25]

The expertise drug development companies can bring, around clinical trial execution, regulatory pathways, data, and much more, coupled with their access to financial resources, is a vital combination. However, the process of advertising for, selecting, and launching Together4RD pilot projects to explore how ERNs and industry can work together, have illustrated relatively entrenched perceptions and misconceptions from the non-industry research community around the needs and expectations of the private sector. Besides providing support and tools to optimise collaborations, therefore, it is important that researchers in both industry and the public sector become better acquainted with each other's realities and modus operandi. There are several useful resources to help the public sector in this respect (see Tool 5 '**Needs and Priorities for Industry – and what does Industry Need from a Collaboration with ERNs?**')

24 https://www.nejm.org/doi/full/10.1056/NEJMra1612575 and https://www.nature.com/articles/s41436-019-0616-9
25 https://ascpt.onlinelibrary.wiley.com/doi/epdf/10.1002/cpt.3428

The need for Public-Private Collaborations in Rare Disease and the barriers to their realisation

When thinking about the broader context of public-private collaborations, beyond rare disease, there are increasing challenges, not least the concerning trend of a declining pace for R&D in Europe compared with other world regions. Whereas 41% of R&D investments across the board were centred on Europe in 2001, this has now dropped to 31%.[20] The 2024 Draghi report on 'The Future of European Competitiveness' highlighted declining EU competitiveness across several key areas[21] calling for stakeholders to "boost the attractiveness of the EU for conducting clinical trials and to expedite access to markets for novel medicines." (p31). And a recent EUCOPE (EU Committee of Pharmaceutical Entrepreneurs) report[22] highlights the fact that although Europe remains popular for early-stage investment, later stage clinical investments are continuing to decline, as the EU continues to lose ground to the US and China. It is imperative that Europe regains a competitive edge, especially in terms of research and innovation for *rare* disease, given the major unmet needs. To build more, and more fruitful, public private collaborations in rare disease, requires action of several fronts.

- Leveraging developments in the wider research space, beyond rare diseases, to continue to innovate in areas such as data, AI, personalised medicine, new technologies, trial design, and mor.e
- Ensuring more, and more diverse, concrete opportunities for the public and private sector to work together, both on large-scale initiatives of the kind funded via the Innovative Medicines Initiative and supported by the Rare Disease Moonshot, for instance, but also smaller scale projects and activities within specific disease communities or spanning therapy areas (see **Tool 2**).
- The *advantages* of working with the pharmaceutical industry, in particular, must be recognised by policymakers and funders, and in some quarters, perceptions on the value of collaborating with industry need to be addressed. As noted by the Together4RD Position Statement, although there *can* be, and *have* been, examples of poor conduct, and sometimes standards fall, the messaging must become more positive, more openly supportive.[23]
- Concrete and dedicated support for those wishing to take the step of forging collaborative activities with companies. When experts or centres or networks are not used to building connections with industry, the realities of what this might entail.

20 https://www.efpia.eu/media/676753/cra-efpia-investment-location-final-report.pdf
21 https://commission.europa.eu/topics/strengthening-european-competitiveness/eu-competitiveness-looking-ahead_en#paragraph_47059
22 https://www.eucope.org/eucope-and-fti-consulting-unveil-new-report-on-life-sciences-investment-in-the-eu/
23 "This is not to suggest that public–private interactions should not be subject to the highest possible ethical and legal standards: the consequences for the whole R&D community, if there is any action that is seen to transgress or act unethically, can be severe and long lasting. What has perhaps been overlooked in past discussions concerning ERNs and Industry, is the extent to which interactions between rare disease clinicians and researchers, on the one hand, and companies on the other, take place every day—and have been taking place, in some cases, for decades, without issue, whilst providing myriad benefits all round."

research investment has achieved much, but, as the Rare2030 foresight study concluded, much remain to be done, and all stakeholders must play a part, pooling resources and skills:

"*The rare disease community aspires to a research, development and delivery ecosystem for rare disease therapies in Europe in which efforts at the local, regional, national and international levels remain concerted for success. This ecosystem must be co-designed by both public and private sectors.*"[17]

This means that any and all prospective research in rare conditions must be patient-centred, and should involve patients as early as possible, from the design of the project or activity, as partners, not merely as subjects.[18] It means that the networks and structures created to build a critical mass of experts in the clinical and research domains relevant to rare disease (most obviously the ERNs, but also considering for instance national-level networks for rare conditions, the landscape of paediatric trial hubs established by **conect4children**, and more) must be supported to perform world-leading research (which, in the case of perhaps the most important category here, the ERNs, has traditionally NOT happened as yet, for many reasons).[19] It means that funders, policymakers, regulators, HTA bodies, payers, and all the other actors necessary to:

- stimulate R&D in rare diseas.
- build new knowledge to apply in the clinical sphere.
- understand and address the social and holistic needs of people with rare disease;
- and develop new products and bring these to the people who need them.

... must collaborate in a concerted effort, spanning national boundaries, and even continental lines, to leverage advances in all areas that must be addressed if we are to leave no-one behind in rare disease and rare cancer.

A key stakeholder in this landscape is, and must remain, industry (encompassing both the pharmaceutical and devices sectors).

Again, one of the core recommendations from Rare 2030 under the chapter 'Innovative and Needs-Led Research and Development' was that "*Long-term multinational public-private research partnerships should be enhanced*": because notwithstanding the value of academic and patient-led research into rare disease, the reality is that developing new therapies to address the significant remaining unmet needs requires the commitment of the private sector.

17 http://download2.eurordis.org/rare2030/Rare2030_recommendations.pdf p.112
18 https://doi.org/10.1007/s12687-021-00524-5
19 See Part 2 of the Together4RD Position Statement https://ojrd.biomedcentral.com/articles/10.1186/s13023-023-02853-9#Sec11

TOOL 2: EXAMPLES OF INITIATIVES WHICH FOSTER PUBLIC-PRIVATE PARTNERSHIPS IN RARE DISEASES AND COMPLEMENTARY AREAS

The Innovative Medicines Initiative and Innovative Healthcare Initiative

The Innovative Medicines Initiative was set up in 2008 as a public-private partnership between the European Commission (public funding) and the European pharmaceutical industry (private funding, represented by EFPIA, the European Federation of Pharmaceutical Industries and Associations). The goal was to improve the medicines' development process and make it more efficient, and to ensure that patients will have faster access to better and safer medicines. The first phase of IMI covered the period 2008-14, before evolving into IMI2 which spanned 2014-2020. The total budget of IMI 2 was EUR 3.276 billion. Of this, EUR 1.638 billion (half the budget) was pledged from Horizon 2020, whilst EFPIA companies committed EUR 1.425 billion to the programme (up to EUR 213 million could come from other organisations that wished to contribute to IMI initiatives as Associated Partners, for specific projects).

Across IMI 1 and 2, almost 200 projects were funded, dealing with a broad range of conditions. Some of these were particularly relevant for rare diseases, including:

- ☑ conect4children (see below)
- ☑ ARDAT project (looking at Advanced Therapy Medicinal products or ATMPs, which often target rare conditions)
- ☑ Screen4Care (exploring newborn screening for rare conditions, and how to foster earlier diagnosis from health record data)
- ☑ STOPFOP, which was seeking a cure for Fibrodysplasia ossificans progressiva (FOP)
- ☑ U-PEARL, dedicated to better trial design, specifically exploring platform trials, in four focal areas, one of which was the rare condition neurofibromatosis (including types NF1, NF2 and Schwannomatosis)

At the end of 2021, the IMI became the **Innovative Health Initiative (IHI)**. This programme will last until 2027. The core principles remained the same, but the change in name reflected the recognition that different sectors need to be engaged in addressing life-sciences

challenges and that "future breakthroughs in medical science will involve cross-sectoral discoveries, such as medical device / drug combinations or diagnostics based on artificial intelligence."[1] To reflect this broader scope, the private partners now include EFPIA, COCIR, Vaccines Europe, EuropaBio, and MedTech Europe. The total budget for IHI, for the period 2021-2027 is €2.4 billion. €1.2 billion comes from Horizon Europe; €1 billion will come from the IHI industry partners; and €200 million will come from other life science industries or associations that decide to contribute to IHI as contributing partners.

IHI has already supported rare disease-related projects, specifically Realise-D and PaLaDIn, with further rare-disease-related calls expected to follow.

For general resources on IMI and IHI, see below:

- **Booklet providing an overview of the IMI**
- **Short video introducing IMI**
- **Blog on the IMI and its value**
- **IMI to IHI**
- **IMI post relating to rare disease public-private collaborations**

A deeper exploration of IMI and IHI projects fostering public-private partnerships in rare disease

conect4children (c4c)

c4c is an IMI2 project (2018-2024, with extension to 2025) establishing a European network and streamlined ecosystem for clinical trials in paediatric diseases. It involves 36 academic partners, 10 industry partners from EFPIA, and an additional 500 affiliated partners.

As so many paediatric diseases are also *rare* diseases, c4c's processes and tools to support better, more efficient and more successful clinical trials in children and young people also address broader rare disease needs. Besides developing tools to accelerate study start-up and address the pain points in initiating multinational paediatric trials, c4c included strands of work focusing on key topics such as education, training, PPIE and data standardisation. The achievements and resources of c4c, the public-private partnership, can be found on the **project website** in particular **Connect4Children Achievements**

1 https://www.ihi.europa.eu/about-ihi/imi-ihi

Useful videos : see **What is conect4children?** and **We are proud to conect4children! - The Movie**

What is conect4children?

We are proud to conect4children! - The Movie

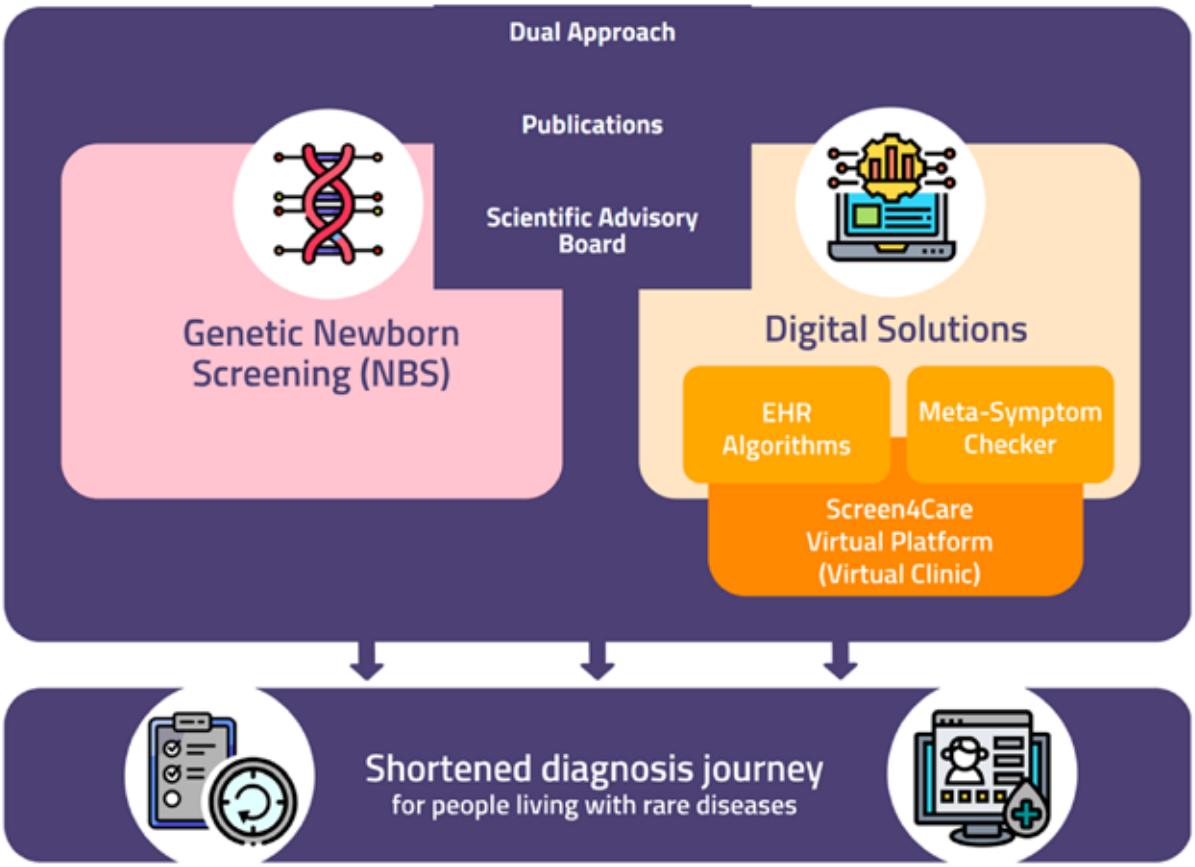
In 2023, c4c launched a dedicated legal entity, c4c-Stichting..For details of the c4c-S legal entity, see **Connect4Children** **For a 1-page overview on what the c4c-Stichting can offer to ERNs, specifically, see here**.

Screen4Care

Screen4Care is a €25 million IHI initiative which launched in late 2021. It has two broad and interconnected pillars (see the Screen4Care visual, below):

- genetic newborn screening (exploring the use of genetic testing and related advanced genomic technologies); and
- AI-based tools to bring accurate diagnoses to patients, earlier, via predictive algorithms leveraging the Screen4Care federated data machine learning environment, and algorithms embedded in Electronic Health Record (EHR) systems that will flag patients at risk for rare diseases based on the data *in* their EHR.)

It is a five year project involving 37 partners from 14 countries. For more details, see the **Screen4Care website** and publications **here** and **here**.



Screen4Care's dual approach (click to view interactive version on our website)

Realise-D

Realise-D stands for 'CompRehensive mEthodological Approach to cLinical trIalS in (ultra-) rarE Diseases'. This 5-year Realise-D public-private partnership began in January 2025, with an overall budget of €17 million. The goal is to optimise and accelerate the development of treatments for rare and ultra-rare conditions, by bringing together 40 partners representing stakeholders from many different groups (clinicians, methodologists, pharmaceutical industry researchers, representatives of patient organisations, regulatory agencies and HTA bodies) to develop cutting-edge operational and methodological tools and resources to dramatically advance treatment evaluation. The Realise-D project has a particular focus on ultra rare conditions and plans to create easy-to-use playbooks and digital tools for planning and running clinical trials.

Read more here.

PaLaDIn

This 4 year project began in 2024, with an overall budget of over €19 million. PaLaDIn is developing a state-of-the-art platform dubbed the 'Interactium' to drive innovative, real-world data collection from patients with rare diseases. The project focuses on rare

neuromuscular diseases (NMDs), specifically Duchenne Muscular Dystrophy (DMD) and facioscapulohumeral muscular dystrophy (FSHD). The Interactium is expected to be able to integrate data from diverse sources, including neuromuscular registries, patient-reported outcome/experience measures (PROMs and PREMs), as well as digital outcome measures from wearable devices, all of which will be co-created with patients. The project is coordinated by a patient organisation and the partners include experts in NMDs, patient advocacy and data science. They hope that their results will not only improve the lives of people with NMDs, but will prove useful to other rare disease communities around the world facing similar challenges.

Read more here.

The Rare Disease Moonshot

The Rare Disease Moonshot was launched in 2022, to bring together a coalition of partners able to accelerate scientific discovery and drug development in rare and paediatric diseases for which currently there is no therapeutic option. This is important, as the majority of rare conditions (approximately 95%) have no dedicated treatment, despite years of investment and research, and there has long been a question of how to shed much needed light and attention on these so-called neglected conditions (which not abandoning research in disease areas which have perhaps seen significant R&D but still lack satisfactory therapies and medicines).

The Moonshot coalition is informal, involving the CriticalPath Institute (C-Path), the European Infrastructure for Translational Medicine(EATRIS), the European Clinical Research Infrastructure Network (ECRIN), the Biobanking and Biomolecular Resources Research Infrastructure – European Research Infrastructure Consortium(BBMRI-ERIC), the European Federation of Pharmaceutical Industries and Associations (EFPIA), the European Confederation of Pharmaceutical Entrepreneurs (EUCOPE), EuropaBio, EURORDIS-Rare Diseases Europe, and the European Joint Programme for RareDiseases (EJP-RD/ERDERA).

These partners set out to both accelerate innovative research for rare conditions in Europe (for instance by developing novel trial designs, enhancing data infrastructure and trial networks, and defining specific approaches for ultra rare diseases), and ensure patients with rare and paediatric disease can *access* the latest innovations. The 'USP' of this approach is its multistakeholder ethos; in particular, the Moonshot partners extol the advantages of leveraging public-private partnerships to help pool resources and solve problems more quickly.

Key Resources from the Rare Disease Moonshot

Three key topics were selected for multistakeholder collaboration, and new sets of recommendations have been created for each. **Although not specific to ERNs, these sets of recommendations are clearly very relevant to the goal of this Toolkit, namely advancing public-private collaboration between ERNs and Industry.**

THE RARE DISEASE MOONSHOT PARTNERS IDENTIFIED THREE AREAS OF ACTION WHERE PUBLIC PRIVATE COLLABORATIONS CAN ADD MOST VALUE:

These sets of recommendations are the fruits of months of broad consultations with stakeholders including

- patient representatives
- global pharma/biotech companies
- small innovative enterprises
- academic translational research experts
- biobanking, non-profit clinical and fundamental research communities
- non-profit PPPs.

Title of the Resource	What can I find here?	Link
Rare Disease Moonshot Recommendations: How can public-private partnerships help optimise clinical trials in rare disease?	Recommendations generated by a group of experts led by C-Path and ECRIN. 33 stakeholders contributed to their development, through workshops and consultations. The recommendations address topics such as disease prevalence, patient access, data standards, and regulatory support.	Clinical trial recommendations
Rare Disease Moonshot Recommendations: How can public-private partnerships help optimise diagnostic research in rare disease?	Work began in June 2023, with a workshop that brought together 30 industry participants. The final recommendations are the results of months of teamwork between the RD Moonshot team and stakeholders including industry, the research community and patient advocacy groups. Further input came from a series of additional workshops with industry partners and discussions in the EURORDIS Round Table of Companies, which gathered more than 100 participants.	Diagnosis recommendations
Rare Disease Moonshot Recommendations: How can public-private partnerships help optimise translational research in rare disease?	Development of this resource began with a workshop in February 2023, bringing together 33 participants from a broad spectrum of sectors. The initial discussions underscored the importance of interdisciplinary approaches, research coordination, and enhancing the skills of different stakeholders. The recommendations were further elaborated and refined via additional workshops, online consultations, and direct feedback sessions, involving over 20 stakeholders.	Translational research recommendations

For more on the mission of the Rare Disease Moonshot and why public-private partnerships are so important, **see here**.

See further on this publication **here**.

Click here to access the Rare Disease Moonshot website.

The European Rare Disease Research Alliance (ERDERA)

ERDERA launched in September 2024, with an estimated budget of €380 million to support activities up to 2031. The overall goal of this large initiative is to improve the lives of people living with a rare disease in Europe and beyond. Over 170 organisations are involved, across 36 countries, giving ERDERA a global footprint to complement the European. This is a Horizon Europe Partnership, in which the EU is expected to contribute approximately €150 million, with the rest of the funding coming from EU Members States, countries associated to Horizon Europe, and in-cash and in-kind contributions **from public *and private*** partners. ERDERA is, in many ways, a successor to the EJP-RD, as it seeks to 'bring under one roof all knowledge, resources and services, boost clinical research and spur innovation' at the pan-rare-disease level. It also builds heavily on other key research initiatives like ERICA (the ERN-focused research action) and the Horizon 2020-funded diagnostics project Solve-RD.

There are many streams of interconnected activity in ERDERA, but the 3 main missions may be summarised as follows:[2]

- To bring together, in one place, a range of services, resources and cross-disciplinary expertise, in order to bring added-value to rare disease research
- To boost clinical research by ensuing every patient wishing to participate in research is somehow findable, and can be enrolled in a suitable clinical study
- To increase innovation and EU competitiveness, whilst evolving a global ecosystem for rare disease capable of linking the national, regional, European and global levels

ERDERA's activities are structured around four key pillars:

- **Funding** — including dedicated financial support for collaborative international research projects, clinical trials, and knowledge exchange and networking initiatives.
- **Clinical Research Network** — Encompassing all ERDERA's in-house research activities, this network will enhance diagnostics and clinical trial readiness
- **Support Services** — This includes a *Data Services Hub* to facilitate global data collection, integration, analysis, and sharing at a global scale; an *Expertise Services Hub* to offer guidance on specific aspects of translational and clinical research; and an *Acceleration Hub* that collaborates with industry partners to advance the most promising research projects and technologies. Additionally, ERDERA will maintain a robust *Education and Training program*.

2 Much of this summary comes from the ERDERA website

- **International Alignment** — Through existing and newly established National Mirror Groups, the partnership will ensure alignment between national and international rare disease research strategies, particularly in nations that are behind in developing and implementing national plans. ERDERA will also host the Scientific Secretariat of the **International Rare Disease Research Consortium** (IRDiRC), a unique global consortium co-established by the European Commission and US National Institutes of Health back in 2011.

The ERDERA consortium includes private sector companies, including UCB Biopharma SRL, AstraZeneca AB, and Pfizer Inc.[3] ERDERA is expected to foster public-private projects and collaborations through, for instance, the funding activities and calls, and the Acceleration Hub, in particular.

The European Joint Programme for Rare Disease Research (EJP RD)

The EJP RD launched in January 2019, involving 93 beneficiaries and 48 linked third parties, with a total budget of approximately €110 million (€55 million directly from the EC, supplemented with substantial national and in-kind contributions). The EJP RD sought to create resources, services and expertise to advance rare disease research at the cross-disease level, through workstreams centred on funding opportunities, data, training, and accelerating innovation . **The main public-private focus here came from the 'Rare Disease Research (RDR) Challenges Call'**. Industry partners were invited to identify 4 challenges to form the topics of the call, and these were validated by EJP RD Partners. A total budget of € 1.5 million was anticipated, from the European Commission, to allow 4 projects to be funded. The idea was that an independent committee would review the proposals and the industry partners who identified each challenge would then join the successful consortium of applicants, bringing in-cash and in-kind support.

The topics/challenges were as follows:

1. **Development of a non-invasive tool for measuring rare disease patient mobility in daily living** (Industry sponsor - Chiesi Farmaceutici S.p.A. (Italy), CSL Behring (Australia))
2. **Delivery system for intranasal administration of biological drugs to neonates** (Industry sponsor -Chiesi Farmaceutici S.p.A. (Italy))
3. **Characterize Rare Bone Disorders (RBD) Mobility Challenges in Real World Setting**

3 https://erdera.org/participants/

(Industry sponsor - Ipsen)

4. **Pre-clinical assay to detect instability of microsatellite repeat expansions** (Industry sponsor - LoQus23 Therapeutics)

An example of a funded project emerging from this scheme (related to the 1st challenge) is the **Digital Tools 4 Rare Disease (DT4RD) project**.

Find out more here on these challenges **here**.

IRDiRC

The International Rare Disease Research Consortium, IRDiRC, was launched in 2011, initiated by the European Commission and the NIH. It initially had two major goals: to create 200 new therapies for rare diseases and enable diagnostics for most rare disease, both by 2020. However, given the early success in meeting these goals the consortium revised its objectives in 2017. A new overarching vision was agreed, for the period 2017-2027: 'Enable all people living with a rare disease to receive an accurate diagnosis, care, and available therapy within one year of coming to medical attention'. To achieve its goals, IRDiRC has undertaken numerous dedicated actions to increase access to harmonized data and samples, enhance the molecular and clinical characterization of rare diseases, support translational, preclinical and clinical research, and streamline ethical and regulatory procedures.

IRDIRC is organised into 3 constituent committees (dedicated to funders, companies, and patient advocates respectively) and 3 scientific committees (Therapeutics, Diagnostics, and Interdisciplinary).

In terms of the opportunity for public private collaboration, companies can be members of IRDiRC, alongside public funders. Biotech, Pharma, MedTech and more can join, by investing more than 10 million USD over 5 years in rare disease research. Much of the work of IRDiRC is shaped by its three committees, which identify gaps and key issues in RD research, to be addressed via Task Forces and Working Groups who produce guidelines, recommendations & resources. These structures often involve both public and private sector experts.

Find out more **here**.

Critical Path Institute (C-Path)

Another public-private partnership of relevance to rare diseases is C-Path. This is a non-profit PPP launched in 2025 to accelerate the pace -and reduce the costs- of medical product development through creation of new data standards, measurement standards, and methods standards that support the scientific evaluation of safety & efficacy of new therapies. C-Path provides the legal, scientific, and regulatory infrastructure to generate

a unique neutral collaborative environment for stakeholders in the drug development ecosystem. The Institute fosters public-private collaboration across both rare and non-rare conditions; however, an important -and RD-specific- infrastructure under C-Path is the "**Rare Disease Cures Accelerator – Data and Analytics Platform**," where industry can share data into a centralised and standardised infrastructure to support & accelerate RD characterisation to accelerate dev. of therapies.

Read more about C-Path here.

TOOL 3: WHAT ARE ERNS?

Key Messages

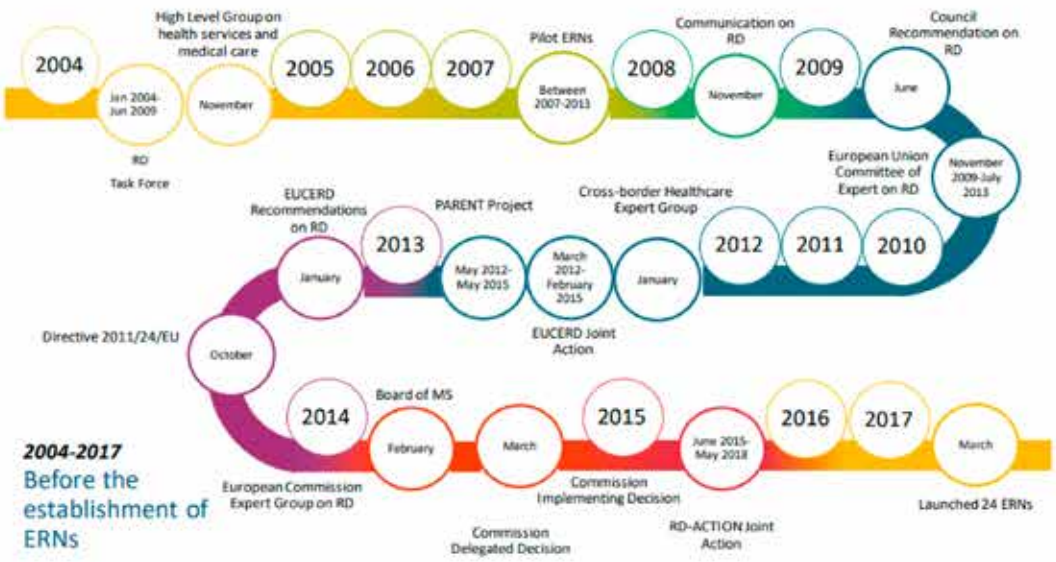
European Reference Networks (ERNs) are arguably the single most important innovations in health and research for rare diseases in Europe, if not globally.

- ☑ There are 24 ERNs, launched in 2017, established across broad rare disease groups such as rare liver diseases, rare eye disease, etc., or are dedicated to areas of highly specialised medicine such as paediatric transplantation
- ☑ ERNs are networks connecting EU/EEA centres of expertise in specialised healthcare fields necessitating a concentration of expertise
- ☑ At present, they bring together 1613 Healthcare Providers/centres/units, nested in 382 separate hospitals across all 27 EU Member States plus Norway
- ☑ The primary focus of ERNs is improving care, and the networks are officially coordinated under the European Commission Directorate General concerned with Health (DG SANTE). However, they have strong research responsibilities and priorities too, offering enormous potential
- ☑ ERNs are designed to be patient-centred, with patients embedded in the governance and in all activities – this is facilitated by the concept of ePAGs (European Patient Advocacy Groups). Today, there are over 300 ePAGs working with ERNs
- ☑ The Clinical Patient Management System (CPMS), a secure digital platform used by the ERNs, has enabled the virtual consultation of more than 4000 complex cases
- ☑ Over 95,000 patients have already been included in the dedicated new ERN registries

The Road to ERNs

The first formal call for ERNs was launched back in 2016, representing over a decade of preparatory work by so-called 'pilot' ERNs.[1] A significant amount of planning lay behind that milestone moment, driven by the European Expert Groups for Rare Disease (EUCERD and the Commission Expert Group on Rare Disease), Joint Actions (the EUCERD Joint Action and RD-ACTION, in particular) and, crucially, advocacy from patient organisations, most notably EURORDIS. A model of possible disease groupings was developed,[2] to help avoid hundreds -or even thousands - of applications seeking to set-up ERNs in individual diseases or small, clinically distinct groups of diseases. RD-ACTION worked with the European rare disease community to help ensure that each community would rally behind only one application, to avoid competing proposals and try to ensure all rare diseases could be categorised under at

1 European Commission, Consumers, Health, Agriculture and Food Executive Agency, Rare diseases 2008-2016 : EU-funded actions paving the way to the European reference networks, Publications Office, 2018, https://data.europa.eu/doi/10.2818/578367
2 https://ojrd.biomedcentral.com/articles/10.1186/s13023-016-0398-y



Source: ECA.

Fig. 1 - Successive policy developments leading to the launch of the ERNs (Image from the European Court of Auditors Report on the Implementation of Directive 2011/24/EU)

ERN BOND	Bone Diseases
ERN CRANIO	Craniofacial anomalies and ENT disorders
Endo-ERN	Endocrine Conditions
ERN EpiCARE	Rare and Complex Epilepsies
ERKNet	Kidney Diseases
ERN GENTURIS	Genetic Tumour Risk Syndromes
ERN-EYE	Eye Diseases
ERNICA	inherited and congenital anomalies
ERN-LUNG	Respiratory Diseases
ERN-RND	Neurological Diseases
ERN-Skin	Skin Disorders
ERN EURACAN	Solid Adult Cancers

ERN EuroBloodNet	Onco-Haematological Diseases
ERN EUROGEN	Urogenital Diseases
ERN EURO-NMD	Neuromuscular Diseases
ERN GUARD-HEART	Diseases of the Heart
ERN ITHACA	Congenital Malformations and Intellectual Disability
MetabERN	Hereditary metabolic diseases
ERN PaedCan	Paediatric Cancer
ERN RARE-LIVER	Hepatological Diseases
ERN ReCONNET	Connective Tissue and Musculoskeletal Diseases
ERN RITA	Immunodeficiency, Auto-Inflammatory and Auto Immune Diseases
ERN TRANSPLANT-CHILD	Transplantation in Children
VASCERN	Multisystemic Vascular Diseases

Fig. 2 – The 24 ERNs

least one of these networks.[3] The 24 Networks were officially launched in 2017.

In the end, their headings largely reflected the proposed model of disease grouping, with a few logical modifications to incorporate not only classifications of pathology but also areas of highly specialised healthcare which span across diseases. This was important, to achieve a central pillar of the ERN vision - collectively, across all ERNs, every rare disease should have a 'home'. Cross-ERNs collaborations would also facilitate the need for multidisciplinary expertise when dealing with rare or ultra rare diseases. In this way, ERNs would strive to go beyond the networks created by past EU funding, via projects, which were dedicated to individual diseases or small groups of diseases, and would instead seek to improve diagnostics, treatment, research and care for all conditions under the rare disease umbrella. A further fundamental difference here was that ERNs are not projects – subject to 5-yearly evaluations, these Networks should be considerer permanent structures, revolutionising rare disease care and research across Europe.

At their launch, the 24 ERNs brought together over 900 specialist units in over 300 hospitals across 26 countries (25 EU MS plus Norway). These figures have increased in subsequent years (see 'Getting to know the ERNs' below), to include 1613 members, in total.

ERNs, as cross-border networks, have many substantial responsibilities, spanning the care and research domains. The tables below collate a non-exhaustive set of resources which:

- ☑ further explain the origins of the ERNs
- ☑ provide analysis/recommendations for their future functioning
- ☑ and illustrate the status quo across the Networks.

Key resources outlining the scope, nature and achievements of the ERNs

Origins of the ERNs – the concept, the criteria, the Legal Acts and the background

Title	Type of Resource	Summary of what you can find	Link
EUCERD Recommendations on Rare Disease European Reference Networks	**Grey literature/ reports/ recommendations**	Foundational recommendations on what ERNs should be and should do, adopted unanimously by the EU Committee of Experts on Rare Disease (EUCERD) on 31st January 2013. Incorporated and reflected past learnings from the field and formed the basis for the legislation which followed	https://www.rd-action.eu/eucerd/EUCERD_Recommendations/ern_recos.pdf

3 https://tinyurl.com/43h3n63e

European Reference Networks for rare diseases: what is the conceptual framework?	**Peer-Reviewed Publication**	Héon-Klin, V. European Reference networks for rare diseases: what is the conceptual framework?. Orphanet J Rare Dis 12, 137 (2017). https://doi.org/10.1186/s13023-017-0676-3 Presents a comprehensive overview of the story behind ERNs	https://doi.org/10.1186/s13023-017-0676-3
Directive 2011/24/EU of the European Parliament and of the Council of 9 March 2011 on the application of patients' rights in cross-border healthcare	**EU legislation**	This is the so-called 'Cross-Border Healthcare Directive; the legislation on which the ERNs were established (Art.12)	https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32011L0024
COMMISSION DELEGATED DECISION of 10 March 2014 (2014/286/EU)	**EU legislation**	The Delegated and Implementing Acts (see below) form the key legal basis for the creation and governance of ERNs. The Delegated Decision sets out core criteria and conditions that ERNs, and healthcare providers wishing to join an ERN, must fulfil	https://eur-lex.europa.eu/eli/dec_del/2014/286/oj/eng
COMMISION IMPLEMENTING DECISION on 10th March 2014 (2014/287/EU)	**EU legislation**	Accompanying the Delegated Acts, above, this legislation set out the formal criteria for establishing and evaluating ERNs and their Members, and for facilitating the exchange of information and expertise on establishing and evaluating the Networks	https://eur-lex.europa.eu/eli/dec_impl/2014/287/oj/eng
EC Consumers Health Agriculture and Food Executive Agency. Rare diseases 2008-2016: EU-funded actions paving the way to the European reference networks	**Grey literature/ reports/ recommendations**	Grey literature/ reports/ recommendations	European Commission: Consumers, Health, Agriculture and Food Executive Agency, Rare diseases 2008-2016 – EU-funded actions paving the way to the European reference networks, Publications Office, 2018, https://data.europa.eu/doi/10.2818/578367
Rare Disease European Reference Networks: Addendum to EUCERD Recommendations of January 2013	**Grey literature/ reports/ recommendations**	Addendum issued by the Commission Expert group on Rare Disease (successor to the EUCERD) to supplement the original 2013 Recommendations. Provides further detail on 1) meaningful patient involvement and patient-centredness in ERNs; and 2) a proposed disease-grouping model to ensure comprehensive coverage of ERNs	https://health.ec.europa.eu/publications/rare-disease-european-reference-networks-addendum-eucerd-recommendations-january-2013_en

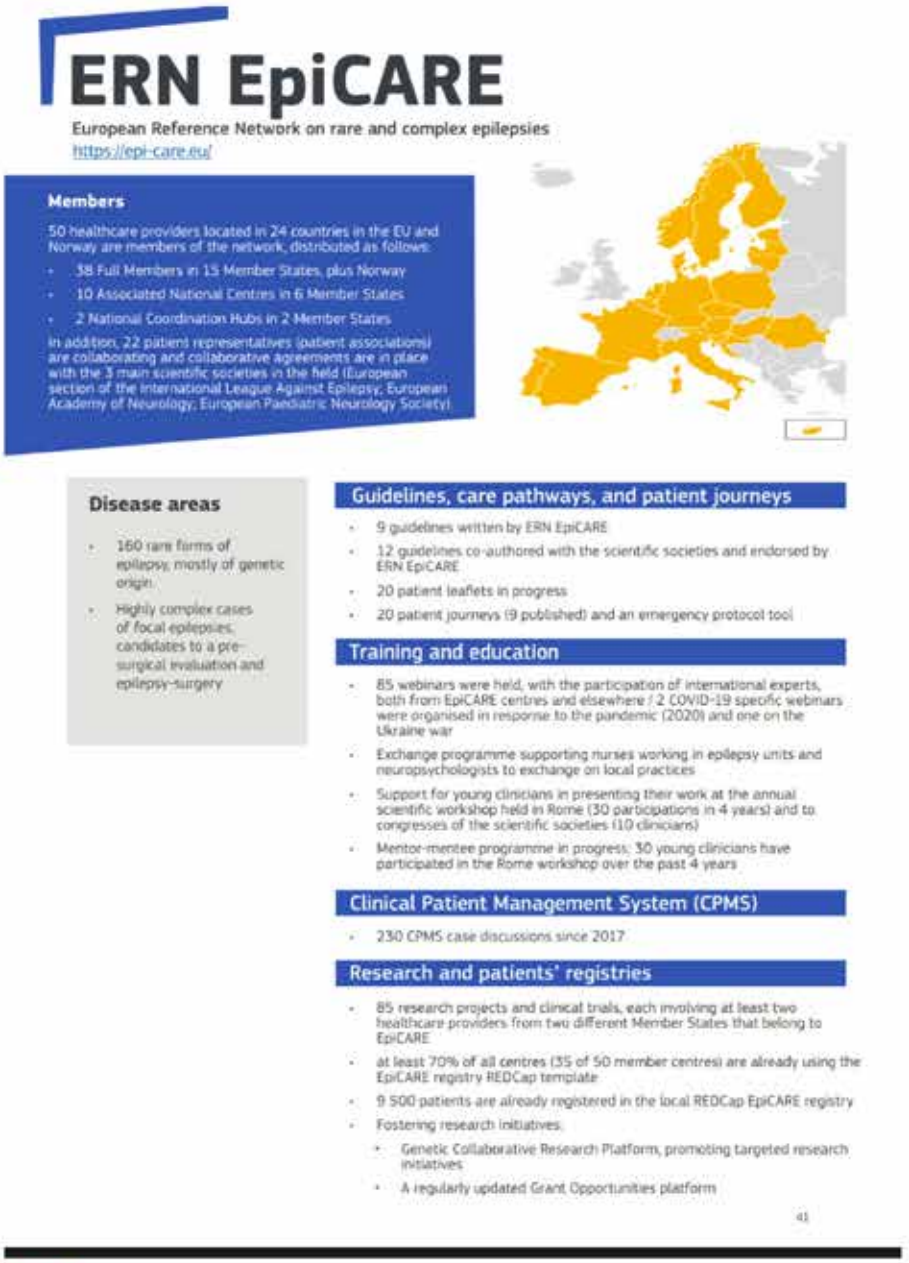
Rare 2030 Knowledge Base Summary on 'Access to Healthcare'	**Grey literature/ reports/ recommendations**	This was the eighth in a series of 'knowledge base summaries', essentially status-quo documents, published by the first foresight study for rare disease, Rare2030, in 2019. Section 3 summarises the background to ERNs, and lists some early achievements. It also includes a focus on the related concept of centres of expertise (section 2)	https://www.rare2030.eu/knowledgebase/
Overview Report on the State of the Art of Rare Disease Activities in Europe, 2018 Version	**Grey literature/ reports/ recommendations**	This large report summarises the status quo of a broad range of key topics related to rare disease, based on data and research collected in 2018. Section 5 is dedicated to the rise and early activities of ERNs and provides good background to the early years.	https://www.rd-action.eu/wp-content/upl

Analysis of the ERNs To-Date – Evaluations, Recommendations, Statements

Title	Summary of what you can find	Link
Tumiene, Birute et al. "European Reference Networks: challenges and opportunities." Journal of community genetics vol. 12,2 (2021): 217-229. doi:10.1007/s12687-021-00521-8	Journal article by many key people closely involved in ERNs. Analyses the ERN progress and vision comprehensively, and identifies challenges to the Networks fulfilling their potential	https://pubmed.ncbi.nlm.nih.gov/33733400/
Kole A, and Hedley, V,. Recommendations from the Rare 2030 Foresight Study: The future of rare diseases starts today (2021)	Full Recommendations published in 2021, emerging from the first foresight study for rare disease. Created through the input of over 250 experts from all stakeholder groups, these Recommendations cover a very broad range of topics, and include a section dedicated mainly to recommendations concerning ERNs (section 3 p.49 onwards). Useful for understanding how and where the RD community sees a need for ERN evolution and support	https://download2.eurordis.org/rare2030/Rare2030_recommendations.pdf

ERNs evaluation results report - Independent Evaluations of European Reference Networks and of Healthcare Providers	Official report published in 2024 and commissioned by the European Commission, to fulfil the legal requirement for ERNs and their member HCPs, to be evaluated every 5 years. The report presents a mix of self-evaluations, document reviews, ERN interviews, on-site HCP audits and stakeholder interviews. The results showed a high level of commitment of ERNs to their objectives, with a significant proportion (100% of ERNs and 89.7% of their members) achieving satisfactory results in the evaluation. The report shows areas of strength, as well as areas where improvements were recommended.	https://health.ec.europa.eu/latest-updates/erns-evaluation-results-report-independent-evaluations-european-reference-networks-and-healthcare-2024-11-29_en
Recommendations to Achieve a Mature ERN System in 2030	Recommendations generated by EURORDIS, reflecting the perspectives of their member patient groups and individual ePAGs, on the vision for a mature ERN system - reflects what patients feel is needed for these Networks to fulfil their potential	https://download2.eurordis.org/documents/pdf/Our_vision_on_mature_ERNs.pdf
Hedley, V., Bolz-Johnson, M., Hernando, I. et al. Together4RD position statement on collaboration between European reference networks and industry. Orphanet J Rare Dis 18, 272 (2023). https://doi.org/10.1186/s13023-023-02853-9	Peer-reviewed Position Statement addressing many key issues: outlining the historical reasons for limited ERN and Industry collaboration; explaining the work of Together4RD to improve the status quo; presenting case studies, precedents and ways of working between public and private sectors; and presenting recommendations to advance collaborations. This Statement includes many publications relevant for specific topics such as virtual care practices in ERNs, examples of ERN approaches to establishing new registries, etc.	https://doi.org/10.1186/s13023-023-02853-9
Statement of the ERN Board of Member States on Integration of the European Reference Networks to the healthcare systems of Member States.	Board of Member States Statement from 2019, proposing 5 ways in which ERNs need to be better integrated to national health systems	https://health.ec.europa.eu/system/files/2019-07/integration_healthcaresystems_en_0.pdf
Statement of the ERN Board of Member States on European Reference Networks and Industry.	The first Statement on this topic, issued in 2016.	https://health.ec.europa.eu/document/download/1ea98fa6-10be-4a84-bb79-ba7678efc8bf_en?filename=2016_statement_industry_conflictofinterest_en.pdf
Updated Statement of the ERN Board of Member States on ERNs and Industry.	This is an updated Statement from the Board of Member States, issued in June 2019	https://health.ec.europa.eu/system/files/2020-03/statement_industry_conflictofinterest_en_0.pdf

- reactiveness under the Covid-19 pandemic.



ERN EpiCARE

European Reference Network on rare and complex epilepsies

https://epi-care.eu/

Members

50 healthcare providers located in 24 countries in the EU and Norway are members of the network, distributed as follows:

- 38 Full Members in 15 Member States, plus Norway
- 10 Associated National Centres in 6 Member States
- 2 National Coordination Hubs in 2 Member States

In addition, 22 patient representatives (patient associations) are collaborating and collaborative agreements are in place with the 3 main scientific societies in the field (European section of the International League Against Epilepsy; European Academy of Neurology; European Paediatric Neurology Society)

Disease areas

- 160 rare forms of epilepsy, mostly of genetic origin
- Highly complex cases of focal epilepsies, candidates to a pre-surgical evaluation and epilepsy-surgery

Guidelines, care pathways, and patient journeys

- 9 guidelines written by ERN EpiCARE
- 12 guidelines co-authored with the scientific societies and endorsed by ERN EpiCARE
- 20 patient leaflets in progress
- 20 patient journeys (9 published) and an emergency protocol tool

Training and education

- 85 webinars were held, with the participation of international experts, both from EpiCARE centres and elsewhere / 2 COVID-19 specific webinars were organised in response to the pandemic (2020) and one on the Ukraine war
- Exchange programme supporting nurses working in epilepsy units and neuropsychologists to exchange on local practices
- Support for young clinicians in presenting their work at the annual scientific workshop held in Rome (30 participations in 4 years) and to congresses of the scientific societies (10 clinicians)
- Mentor-mentee programme in progress: 30 young clinicians have participated in the Rome workshop over the past 4 years

Clinical Patient Management System (CPMS)

- 230 CPMS case discussions since 2017

Research and patients' registries

- 85 research projects and clinical trials, each involving at least two healthcare providers from two different Member States that belong to EpiCARE
- at least 70% of all centres (35 of 50 member centres) are already using the EpiCARE registry REDCap template
- 9 500 patients are already registered in the local REDCap EpiCARE registry
- Fostering research initiatives:
  - Genetic Collaborative Research Platform, promoting targeted research initiatives
  - A regularly updated Grant Opportunities platform

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Fig. 5 - Example of an ERN summary in the 2025 report 'ERNs: A success story for patients living with a rare disease'

TOOL 4: THE ADVANTAGES OF ERNS AS PARTNERS FOR RESEARCH

Introduction

European Reference Networks (ERNs) are often viewed as structures dedicated first and foremost to care – and indeed, they *do* have significant duties under the heading of 'advancing care' (e.g. supporting virtual case review, generating guidelines, supporting training activities). However, ERNs also have a formal mandate to contribute to research into rare diseases and highly specialised medicine. Although these research goals have perhaps been somewhat overshadowed to-date, this research mandate is clearly there, in the legislative acts on which ERNs are based: Annex I of the Delegated Decision (2014/287/EU)[1] stipulates that one of the horizontal criteria (i.e. criteria which all members of any ERN should fulfil) is as follows:

"(5) To fulfil the requirement set out in point (iv) of Article 12(4)(a) of Directive 2011/24/EU ('make a contribution to research'), the Networks must: (a) identify and fill research gaps; (b) promote collaborative research within the Network; (c) reinforce research and epidemiological surveillance, through setting up of shared registries"

Although some ERNs have embraced research goals from their launch, in one way or another -particularly those which emerged from communities which were already quite research-focused - it is probably fair to say that for most Networks, research *per se* has been less of a priority to-date.[2] The Together4RD Position Statement explains in more details some of the reasons for this.[3]

An important step in enabling ERNs to reach their research potential, particularly when it comes to fostering collaborations with industry, is ensuring that the advantages and potential of ERNs as partners for research are understood and appreciated.

1 https://health.ec.europa.eu/rare-diseases-and-european-reference-networks/european-reference-networks/establishing-ern_en

2 https://pubmed.ncbi.nlm.nih.gov/33733400/

3 https://ojrd.biomedcentral.com/articles/10.1186/s13023-023-02853-9 see part 2

ERNs in Numbers

ERNs are arguably the single most important innovations in health and research for rare diseases in Europe, if not globally.

- ☑ There are 24 ERNs, launched in 2017, established across broad rare disease groups such as rare liver diseases, rare eye disease, etc., or are dedicated to areas of highly specialised medicine such as paediatric transplantation
- ☑ ERNs are networks connecting EU/EEA centres of expertise in specialised healthcare fields necessitating a concentration of expertise
- ☑ At present, they bring together 1613 Healthcare Providers/centres/units, nested in 382 separate hospitals across all 27 EU Member States plus Norway
- ☑ The primary focus of ERNs is improving care, and the networks are officially coordinated under the European Commission Directorate General concerned with Health (DG SANTE). However, they have strong research responsibilities and priorities too, offering enormous potential
- ☑ ERNs are designed to be patient-centred, with patients embedded in the governance and in all activities – this is facilitated by the concept of ePAGs (European Patient Advocacy Groups). Today, there are over 300 ePAGs working with ERNs
- ☑ The Clinical Patient Management System (CPMS), a secure digital platform used by the ERNs, has enabled the virtual consultation of more than 4000 complex cases
- ☑ Over 95,000 patients have already been included in the dedicated ERN registries

How are ERNs Well-Placed to Add Value to Rare Disease Research?

A number of fundamental advantages of ERNs for research are highlighted below (NB: these are based upon Part 2 of the aforementioned **Position Statement** from Together4RD, which itself incorporated and expanded upon conclusions from the first EMA and RD-ACTION workshop dedicated to ERN research.[4] These earlier ideas have been supplemented here with additional and updated content.

4 https://endo-ern.eu/wp-content/uploads/2018/12/Conclusions-and-Next-Steps-from-the-workshop-%E2%80%98How-ERNs-can-provide-added-value-in-the-area-of-clinical-research%E2%80%99-1.pdf

ERNs are permanent infrastructures

For many years, EU projects dedicated to rare disease - funded both through the Framework Programmes and the 1st and 2nd Public Health Programmes, in particular - often made good progress in establishing networks:[5] these were dedicated to a diverse range of rare conditions, sometimes quite specific diseases (such as McArdle Disease; Duchenne Muscular Dystrophy; Wolfram, Alstrom and Bardet-Biedl Syndromes; etc.) and other times focused on broader clusters such as intoxication-type metabolic diseases, rare anaemias, and paediatric cancers. These projects were often called 'pilot networks', once the concept of ERNs was born in the lead-up to the publication of the Cross-Border HealthCare Directive. They built consortia linking expert centres across Europe, and undertook crucial activities like establishing registries, developing guidelines, creating patient support materials, setting-up biobanks, developing educational resources, and much more. A major challenge, however, was finding routes to sustain these networked communities and, in particular, sustain their newly-created infrastructure and tools, after the funding period ended. This was not conducive to such communities developing into research-active networks or communities with which industry might partner. **ERNs, therefore, have a major advantage here, in the sense that they are NOT projects, and are not temporary**. DG SANTE committed to formally evaluating the ERNs and their constituent HealthCare Providers, or HCPs, every 5 years. The process and results of the first evaluation, initiated in late 2022 and concluded in 2023, can be viewed here[6] – in a nutshell though, the first evaluation concluded that "the ERN ecosystem is functioning well, meaning they are delivering on highly specialist work for rare disease patients such as consultations for diagnosis and therapies, the production of clinical guidelines and specialised trainings". All 24 ERNs obtained satisfactory results, meaning none were targeted to be disbanded (88% of their member HCPs also obtained satisfactory results[7]). Presuming the ERNs continue to be evaluated positively in future, they may be viewed as **permanent** structures, making them important stakeholders for partnerships in research of all kinds. These are not groups of experts united by individual projects, whose structures and resources are likely to fall into disuse once the funding period ends.

ERNs sit at the interface of the Research and Clinical Spheres

The Legal Acts upon which ERNs are based mandate that the Networks provide added-value across both the clinical and research domains. This is essential in rare diseases,

5 See **Rare diseases 2008-2016- EU-funded actions paving the way to the European reference networks** (https://op.europa.eu/en/publication-detail/-/publication/fd1f05fc-6def-11e8-9483-01aa75ed71a1)

6 https://health.ec.europa.eu/rare-diseases-and-european-reference-networks/european-reference-networks/erns-evaluation_en

7 *Ibid.*

scope of the 24 ERNs, there have been robust attempts to ensure a baseline compatibility and interoperability via a concerted European approach. The best example of the latter is the European Platform on Rare Diseases Registration, initiated in 2013 by the European Commission's Joint Research Centre in collaboration with DG SANTE. An important component of this platform is the ERDRI or European Rare Disease Registry Infrastructure.[12] ERDRI seeks to make data held in rare disease registries searchable and findable. It does this via a suite of tools: the European Directory of Registries (ERDRI.dor); a Central Metadata Repository (ERDRI.mdr); a Pseudonymisation Tool (ERDRI.spider); and a Search broker (ERDRI.sebro).

The creation of a European platform to increase the reuse potential of precious rare disease data was an important step, given the variety of registries which exist (845 globally, according to Orphanet) but also the fact that only 1000 of the known rare conditions are included in at least one of those 845.[13] Into this complicated ecosystem, **the creation of ERN registries -or platforms to link new ERN registries with historical or possibly new disease-specific registries- holds major potential for advancing knowledge and better care, but also naturally for stimulating and advancing research**. Supported by projects like the EJP RD[14], ERICA[15], and now ERDERA[16], attempts are being made to ensure a certain level of interoperability in terms of the data collected in these new ERN registries. For instance, the Common Data Elements issued by the ERDRI were turned into a richer data dictionary under the EJP RD: this is just one example of efforts to make registry data FAIR (Findable, Accessible, Interoperable, and Reusable). Greater value will come with the advance of individual ERNs agreeing and standardising domain-specific datasets.[17] 5 of the ERNs received EC funding to develop their registries early on in the ERN story with the remaining 19 receiving their funds via the 2019 work programme of DG SANTE. Although still relatively young registries, the number of patients enrolled is increasing (and now exceeds over 95000). Different ERNs are approaching their registry set-up/linkage in different ways and increasingly, tools are being created to optimise their potential (see below).

Beyond the registry space, the fact that ERNs connect so many of the leading centres of expertise for rare disease across Europe also offers huge potential to increase the standardisation and reuse potential of electronic health data – rare diseases are a natural beneficiary of the anticipated EU Health Data Space.

12 https://eu-rd-platform.jrc.ec.europa.eu/erdri-description_en
13 https://www.orpha.net/pdfs/orphacom/cahiers/docs/GB/Rare_Disease_Registries.pdf
14 https://www.ejprarediseases.org/
15 https://erica-rd.eu/
16 https://erdera.org/
17 https://pubmed.ncbi.nlm.nih.gov/35594066/

ERNs are networks centred on patients

Patients sit at the heart of the ERN concept (and indeed, the concept emerged largely from the patient community in Europe). The Addendum to the EUCERD Recommendations stipulated that patients should have a meaningful role in all levels of ERN activity, governance included. To facilitate this, EURORDIS created the concept of an ePAG – a European Patient Advocacy Group[18]- to work with each ERN. Over 300 ePAG advocates have been approved and are working closely with the Network most connected to their particular condition. ERNs have conducted surveys on people living with rare conditions under their Thematic Grouping which is helping to understand patients' needs and realities better than ever before. Just as clinician networks are growing under ERNs, so patient communities across Europe are coalescing around the ERNs, making it easier to engage patients and develop patient partnerships in research and care (though challenges persist).[19] The ePAG advocates address cross-cutting issues together, across ERN boundaries, and their existence constitutes an excellent opportunity for external stakeholders to work with networks that are genuinely patient-centric.

ERNs offer Independent Expertise

Another advantage of the ERNs, for industry, is the fact that these networks -which as above, should be considered permanent, for all intents and purposes- are established independently of any industry influence. Companies often remark that the existence of structures and networks like this, assembled by the communities themselves, can be helpful in avoiding any accusations of bias.

18 https://www.eurordis.org/our-priorities/european-reference-networks/epag/

19 https://www.oaepublish.com/articles/rdodj.2021.001

Important Resources to Showcase the Power of ERNs for Research

Together4RD Webinar

One important resource, to showcase the value and advantages of ERNs as partners for research, is the **webinar** organised jointly by Together4RD and the **European Rare Disease Research Coordination and Support Action consortium (ERICA)** in late 2024

Resources Created by/With the dedicated ERN Research Action, ERICA

The ERICA website is actually an important gateway to ERN resources, especially pertaining to research. This 4-year project was specifically designed to advance ERN research, and has developed resources to improve various aspects of rare disease research (e.g. developing more effective data collection strategies, optimising patient involvement etc.). A few key resources generated by ERICA are linked below.

Title/Summary of ERICA Resource	Link
In terms of understanding the development choices, progress, and potential of the ERN registries, the 1st Monitoring Report on ERN Registry Data Collection (updated in 2024) is a useful resource	https://erica-rd.eu/wp-content/uploads/2024/11/ERICA_D2.5_02_24_NEW.pdf
Informed Consent Form templates were created via the European Joint Programme for RD, EJP-RD, specifically for ERN registries. The templates can be adapted at ERN, national and site level, and include versions for patients and for parents/legally-designated representatives. They have been translated into 26 languages.	https://erica-rd.eu/work-packages/data-collection-integration-and-sharing/generated-documents/
Data Sharing Agreements. In a centralised registry, where all the data collected by a ERN centre is transferred to a centralised server, a Data Sharing Agreement should be signed between the registry and every HCP contributing data. A customisable Data Sharing Agreement template was developed for the ERNs, for this purpose.	https://erica-rd.eu/work-packages/data-collection-integration-and-sharing/generated-documents/

The ERN registries have established Data Access Committees. If such a Committee agrees to grant access to the registry data to an external stakeholder, a data transfer agreement should be signed between the registry and the data requestor. A customisable Data Transfer Agreement template for the ERNs has been developed in the framework of ERICA, for this purpose.	https://erica-rd.eu/work-packages/data-collection-integration-and-sharing/generated-documents/
Patient Reported Outcome Measures are very important in rare diseases. ERICA has developed a PROMs Repository - as the first attempt to identify and centralize Clinical Assessment Outcomes questionnaires of relevance for rare diseases. This Resource has been created through the joint collaboration between Orphanet, Mapi Research Trust/ICON and ERN EuroBloodNet (VHIR, APHP), with the active contribution of ERNs more widely, and ePAGs. The repository should be regarded as 'a centralized and standardized access gate to more in depth information contained in PROQOLID™.'	https://erica-rd.eu/work-packages/patient-centred-research/proms-repository/
ERICA delivered a series of webinars of relevance to clinical trials in rare diseases. Some were developed within ERICA itself, whilst others showcase partnerships with other initiatives such as c4c. Some of these webinars should help external stakeholders to become more familiar with the ERNs.	https://erica-rd.eu/events/webinars/

The status quo of ERN registries

The registries established by the ERNs are perhaps particularly attractive resources for stakeholders who might be considering partnering with the ERNs for a range of research-related activities. The ERICA project generated a report, updated in late 2024, which summarised the status quo of these registries, in terms of the different approaches ERNs have taken to creating these infrastructures, the number of patients registered to-date, the size of their respective data dictionaries, and more. This report is linked in the ERICA resources table above, but is highlighted **here** too.

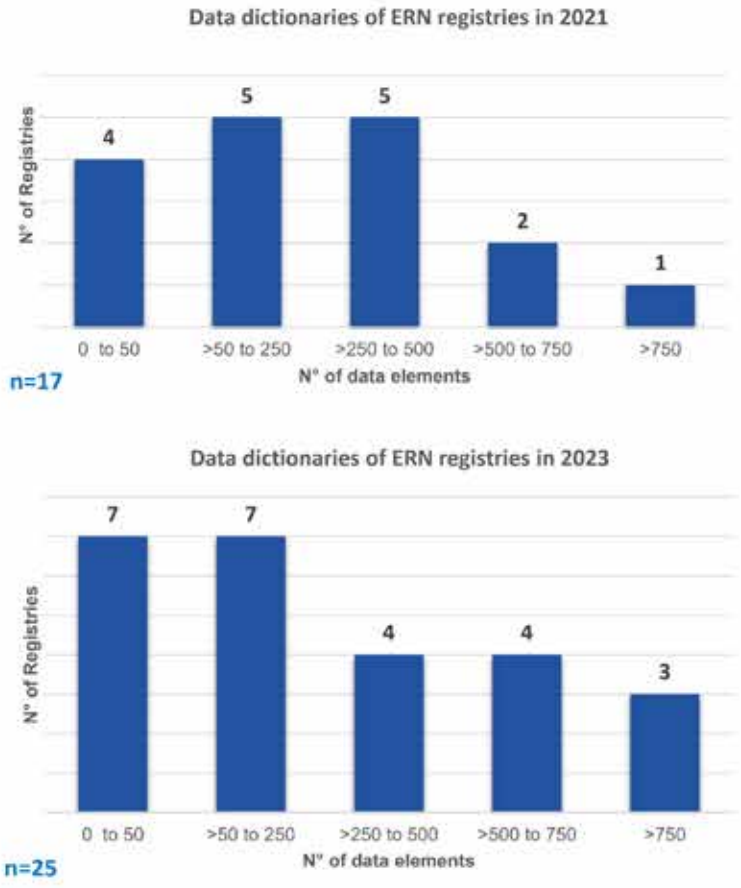
Amongst the highlights of this important report are the following:

- Most ERNs have opted to establish a core patient registry, using a centralised system (20 registries).
- Others have established/integrated multiple registries, or are in the process of doing

so. Therefore, the number of ERN registries (29) actually exceeds the number of networks (24).

- These multiple registries are sometimes embedded within the same infrastructure of the core registry (e.g. as is the case of the subregistries in ERKNet, the ERN for rare renal conditions), or else have been implemented separately, often following different design principles (i.e., centralised vs. federated in VASCERN, the ERN for rare vascular diseases).

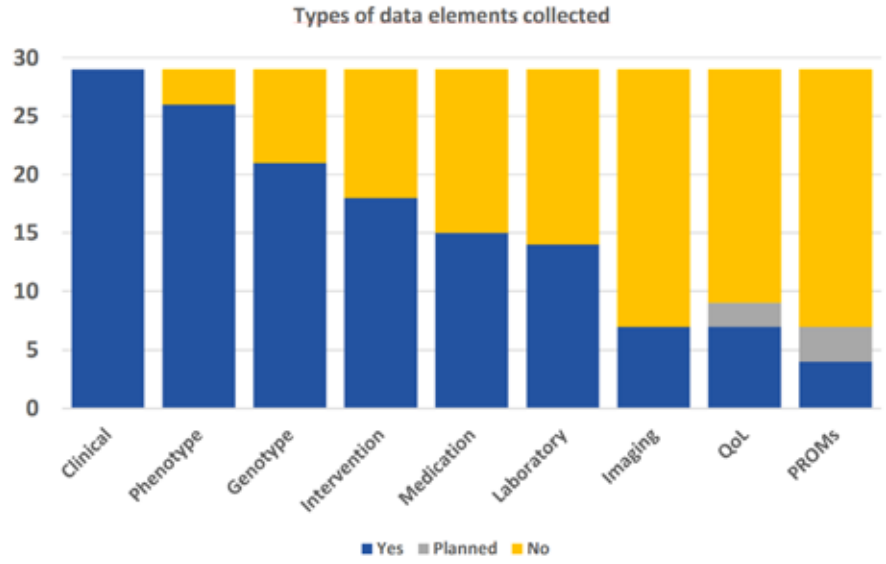
- Occasionally, multisystemic diseases are 'shared' under the scope of 2 or more ERNs; therefore, some ERNs have chosen to collaborate in shared patient registry projects. For example, the Core Registry, originally established as part of the European Registries for Rare Endocrine and Conditions (EuRRECa) project, now supports the activities of both EndoERN and ERN BOND. In these cases, collection of shared data elements is supplemented with the inclusion of more specific condition-dependent modules.



[Figure 3] Progression of finalised ERN registries data dictionaries and their sizes, from 2021 (above) to 2023

Figure directly from ERICA Deliverable D2.5

- Most ERN registries use external software solutions, including Molgenis (3), Castor (7), and RedCap (4), as well as other providers (10). Only a minority of ERNs have decided to develop their registries in-house (5).
- ERN registries have been steadily increasing their data dictionaries. Whereas in 2021, 8 registries had data dictionaries with over 250 data elements, in 2023 that figure was 11 (see figure on previous page).
- The type of data items collected by ERN registries is quite broad – whereas all collect clinical data, and almost all collect phenotypic and genotypic data this figure, few collect imaging, QoL or PROMS data at present.



[Figure 4] Data element categories present in ERN patient registries

Figure directly from ERICA Deliverable D2.5

TOOL 5: NEEDS AND PRIORITIES FOR INDUSTRY – AND WHAT DOES INDUSTRY NEED IN A COLLABORATION WITH ERNS? NEEDS AND PRIORITIES FOR INDUSTRY – AND WHAT DOES INDUSTRY NEED IN A COLLABORATION WITH ERNS?

Forging a successful collaboration entails all parties understanding and appreciating each other's needs, priorities and realities. The needs and priorities of ERNs, on the one hand, and Industry, on the other, are quite different, in many respects.

It is important for ERNs to understand the motivations, requirements and priorities for private sector organisations, especially perhaps for stakeholders (whether researchers, clinicians, patients, or otherwise) from disease communities which have not worked extensively with Industry to-date, and for whom, therefore, public-private collaborations are very new.

Several helpful resources exist to build awareness of the needs and priorities of private sector organisations in the context of public private partnerships or collaborations; and although not always specific to ERNs, the messages therein are useful for ERN stakeholders.

One essential message to convey is that Industry brings more to a partnership or collaboration than simply financial resources. **A dedicated webinar hosted by Together4RD and ERICA** (the European Rare Disease Research Coordination and Support Action) in early 2025 highlighted what industry can bring to partnerships and projects beyond funding, and provided attendees with concrete examples of how industry has brought value to research projects conducted with ERNs in recent years:

A useful resource for understanding some of the needs and realities of the private sector, specific to working in rare diseases (if not specific to working ERNs), is a 2021 report prepared for EFPIA (the European Federation of Pharmaceutical Industry Association). This report, entitled ***'Addressing unmet needs in extremely rare and paediatric-onset diseases: how the biopharmaceutical innovation model can help identify current issues and find potential solutions'*** focuses on medicines' development, but is helpful in conveying the complexity and risk for companies working in this area.

- For instance, it explains how Industry is central to medicines' development, and

illustrates the high costs of drug development, the timescales involved, and the high failure rates – all of which made developing medicines a very risky enterprise, from an investment point of view, not least in areas such a rare disease which carry particular challenges of their own. "When making investment decisions, companies first consider the scientific opportunity, then examine commercial viability within the policy environment". Key aspects of the decision-making process are explained.

- The report summarises some of the additional challenges of seeking to develop medicines in extremely rare diseases, knowing that 80% of all rare disease patients are affected by one of the approximately 150 diseases with the highest prevalence, but that 84.5% of the conditions classed as rare have a prevalence of lower than 1 in a million and affect only 0.33-0.55% of all people living with a rare disease. It explains why, as a rule of thumb, the rarer the disease, the more significant the scientific and commercial challenges inherent to rare disease therapeutic development.

The report is available here.

The International Rare Disease Research Consortium, IRDiRC, has recently released a **report** which is extremely valuable in helping to convey the benefits which Industry can bring to a collaboration (and, in connection with this, illustrating the needs and priorities of the private sector).

This report 'The different contributions of the industry in Public-Private Partnerships in Rare Diseases Research continuum' stems from a collaboration between EFPIA, the Rare Disease Moonshot, and the IRDiRC Companies Constituent Committee. It highlights "the unique value pharmaceutical and biotech companies bring to Public-Private Partnerships", providing four key takeaway messages:

- **Scientific & Regulatory Expertise**
  Companies provide cutting-edge infrastructure, data, technical know-how, and a deep understanding of regulatory pathways.
- **Operational Capacity**
  With a global footprint and strong project management skills, industry partners help scale innovations, manage risks, and drive efficient implementation.
- **Collaborative Leadership & Patient-Centric Approach**
  Industry actors know how to meaningfully engage patient organizations early in the

R&D process, supporting co-creation of impactful solutions.

- **A Strategic Role in Rare Diseases**

  In a fragmented and resource-scarce field, industry involvement helps connect the dots, enrich efforts with real-world data, and accelerate impact.

*Fig 1 – Graphic to accompany '**The different contributions of the industry in Public-Private Partnerships in Rare Diseases Research continuum**' report, taken from the launch page for this report.*

Last but not least, **other tools within this Together4RD Toolkit serve to illustrate the needs and priorities of the private sector**, when considering or embarking on public private collaborations or partnerships with ERNs; in particular, Tool 9 '**Report on the Experiences and Learnings from the first ERN-Industry pilots supported by Together4RD**' and Tool 10 '**Key recommendations for both ERNs and Industry from the experiences of the first ERN-Industry pilots**'. The latter includes recommendations to support an effective partnership, and there are several layers to this; however, some of the points in this document relate specifically to the need for non-Industry partners to understand certain parameters and realities for private sector partners, such as the following:

- Understand that public and private actors tend to place value on different sorts of outputs.
- Consider how research can result in wider impact, beyond publications, in terms of changing patient pathways and diagnostics practice, and outcomes beyond publications.
- Acknowledge that companies in the rare disease space may have goals and vision to improve the wider rare disease ecosystem, beyond simply developing and selling a product.
- Accept that industry partner(s) will wish to have input to the scientific development of a project plan and should be viewed as an equal partner. Indeed, this should be welcomed, as it will bring significant advantages to the research, as it will bring access to the vast in-house scientific expertise but also expertise in medicines development, HTA, data science, and much more.
- Have realistic expectations of both the level of resources industry can contribute to projects, and the way in which it does this. Avoid thinking of companies as purely funders of research. Companies are generally unable to dedicate large sums of money, for the subsequent definition of a detailed project plan – in fact it is the reverse: funding can only be found, internally, based on the contents of a proposed plan. Companies do not award funds as unrestricted grants, without any direct involvement.

Section B: conceptualising and firming-up a collaborative idea of research

TOOL 6: BRIEF SUMMARIES OF THE FIRST TOGETHER4RD PILOTS

Osteogenesis Imperfecta, natural history and innovative clinical trial measures

This pilot project centres of three main activities:

Firstly, value will be drawn from several sources of existing data relating to patients with the rare bone condition OI, to better elucidate the natural history and the disease burden. Genotype-phenotype correlations will be explored, as part of this drive to better understand the condition.

Secondly, prospectively, the project will measure the impact of disease on patient activity and quality of life using digital technologies in a real-world setting, through a combined approach of gait analysis and sensors.

Lastly, in preparation for smoother regulatory pathways for OI therapies in future, the project partners will jointly engage in early scientific dialogues with other stakeholders (such as regulators and HTA), to gain insights into approaches to foster patient access to innovative medicines.

Improving time to diagnosis for unmet patient needs in rare hematologic diseases

Who is involved? EuroBloodNet, Innova, ENROL and Takeda in partnership

This initiative is all about improving the diagnostic pathways for rare haematological diseases by utilizing AI algorithms for early detection. The activity is expected to focus on thrombotic thrombocytopenic purpura (TTP), a very rare and debilitating condition existing in both a congenital form and an acquired, immune-mediated form (which manifests in the 4th or 5th decades). The variable phenotype for TTP and lack of availability of the necessary diagnostic tests, leads to delayed diagnosis, which is very concerning as without a correct diagnosis and

treatment, organ ischemia and death occurs in around 90% of cases.

To improve early diagnosis, the plan is to employ an AI federated platform across key clinical centres, which will ideally be based on the hospitals own EHR systems. Whilst reducing time to diagnosis, and thus enabling treatment to begin as early as possible, the AI platform should lead directly to improved patient outcomes by alerting treating clinicians of patients at risk of relapse, who can then be monitored in appropriate ways.

The initial phase of the pilot will focus on scoping activities and identifying centres for the implementation phase. From the ERN side, the pilot is being delivered through an organisation known as the EuroBlooNet Association, together with the Fundació Hospital Universitari Vall D'Hebron, which is the entity in charge of the ERN's shared registry (ENROL), and also the Fondazione IRCCS Ca' Granda - Ospedale Maggiore Policlinico.

RHINE Project: Rare Renal and PH International Network

Who is involved? Novo Nordisk, ERKnet and OxalEurope

The RHINE Project aims to improve care pathways and patient outcomes in rare renal conditions, by building on existing registry infrastructure, especially the core registry of the ERK-Net ERN (named **ERK-Reg**). This pilot focuses in particular on an ultra-rare disease called primary hyperoxaluria (PH), and addresses a fundamental need to complement the core registry structure of the ERN with detailed data collection for specific conditions.

A 'harmonization and interoperability' model will be developed for PH, by establishing a Rare Kidney Network data registry, in collaboration with the European Hyperoxaluria Consortium (OxalEurope), to achieve seamless data connection across ERK-Net and PH-specific registries.

Through this new data linkage approach, the project aims to understand PH diagnostic and referral pathways locally, measuring metrics like time-to-diagnosis, where PH patients are seen (by measuring the number of cases in each referring center), and the percentage of patients diagnosed before they reach end-stage renal disease (the point at which the kidneys can no longer support the body's needs). To compliment this focus on an improved data ecosystem, educational activities will be implemented at regional and local levels, to target the gaps and shortcomings identified. As of late 2024, this pilot has already generated significant added- value simply by bringing the registry owners from the ERK-REG and the OxalEurope consortia together, around the same table, having built a robust formal agreement for collaboration. The technical integration work is now underway, mapping data dictionaries to explore what each registry ecosystem currently collects.

TOOL 7: CASE STUDIES – EXAMPLES OF PREVIOUS OR ONGOING PUBLIC-PRIVATE COLLABORATIONS IN THE RARE DISEASE SPACE

Introduction

As part of the significant preparatory work leading up to the submission for publication of the Together4RD Position Statement, Together4RD sought examples of ongoing or past public private partnerships in the rare and highly specialised healthcare field. The reason for this information gathering was three-fold:

- ☑ To ameliorate any concerns within the ERN Board of Member States (BoMS) about public private partnerships in this field
- ☑ To collect learnings on the set-up and delivery of the activities involved.
- ☑ To inspire ERNs and Industry (especially in less research-mature fields) as to the kind of activity ERNs might enter into with Companies

These case studies tended to fall into two categories – registry-connected, or else concerned with advancing clinical research broadly, outside of clinical trials specifically. They were presented in brief as part of the supplementary material for the **Together For Rare Diseases Position Statement**.

TREAT-NMD

This case study highlights the achievements of a specific community, namely the neuromuscular field, in establishing both registry-related and broader clinical research activities involving partnerships with Industry.

TREAT-NMD was established back in 2007 as a European 'Network of Excellence', via an FP6 grant, in order to advance trial-readiness in all neuromuscular diseases. **It has played a key role in bringing together the right experts - patients, advocacy organisations, healthcare professionals, researchers, AND pharmaceutical organisations – to drive progress**. It has created a suite of tools and activities to achieve its goals, and in 2019 was 'spun out' of Newcastle University (the original grant holder and thus Network coordinator), as its own legal entity. Many key resources were established under that initial grant, to help extend translational research, these include:

- cell and animal standard operating protocols (for preclinical research);
- a unique advice service, TACT (**the TREAT-NMD Advisory Committee for Therapeutics**)
- global patient registries
- care guidelines, and family guides
- and more

From the early stages of TREAT-NMD, **Industry has always been acknowledged as a key stakeholder and driver of treatment development.** In the original project phase, companies were included as members of the consortium, to ensure the tools developed during the grant funded period actually met the needs of industry. Consequently, many of the activities and outputs listed above involved close public-private collaboration, and ethically-robust practices and codes have been developed to facilitate this.

One key area of TREAT-NMD Industry engagement concerns patient registries, to improve understanding of disease, help build trial-ready patient cohorts, and boost patient recruitment. TREAT- NMD created tools and approaches to connect numerous autonomous registries for the more common neuromuscular diseases (NMDs) NMDs like DMD and SMA. To create greater interoperability and increase the power of standalone registries for these conditions, TREAT-NMD developed both core and expanded datasets to standardise data. At the same time, TREAT-NMD coordinated the creation of global patient registries for rarer NMDs, for which one single registry worldwide makes better sense. The result of all this work

is a network of inter-connected registries able to provide a wealth of information, which can be queried by academic sites (for free) or by Companies (for a fee). Industry have purchased anonymised data of this sort for many years, which supports feasibility studies or enables patient recruitment in clinical trials. The model established back in the days when TREAT-NMD was coordinated by Newcastle University saw those funds from Companies invested back into the core staff involved in running the network, and/or to support networking of the registries themselves. Now that neuromuscular therapies are approved, TREAT-NMD Services Ltd (a dedicated legal entity which spun out of Newcastle University in 2019) is expanding the registries to be able to carry out Post Marketing Surveillance on a global scale.

These days, there are 65 registries collaborating with TREAT-NMD as the 'TREAT-NMD Global Registry Network (either for NMD generally or for a specific condition) and they together collect data on approximately 88,800 people living with an NMD. Many of the processes initially established under the days of the TREAT-NMD network remain in place, to support Industry interactions. **One major form of interaction with Industry concerns access to registry data**. When a Company wishes to purchase data from the global registries, for instance to perform a feasibility assessment, the requests are considered by a committee set-up very early on in the TREAT-NMD lifetime – the is the TGDOC or TREAT-NMD Global Registries and Data Oversight Committee. It has been very important to TREAT-NMD, both as an initial Network of Excellence funded by the EU, and now as a ltd company, as well as its 'in-between' stages, to ensure Industry interaction around accessing registry data is appropriate and handled robustly, recognising the key importance of this stakeholder group but also acknowledging the need for the highest ethical approaches. Tools have been developed to support this, and build transparency, such as the **TGDOC Charter**. **However, the engagement has been far more substantial than individual Companies simply purchasing data (whether as a one-off or on a longitudinal basis). Crucially, TREAT-NMD has always partnered, and continues to partner, with Industry on all activities**, as appropriate, to ensure the end products and outputs will be useful to Industry – and this is very much the case with the registry-related activity. For instance, Industry experts are always consulted when core and expanded datasets are being developed or updated for the individual conditions, to ensure the needs of Companies are reflected in the type of data being collected, and that the way in which the data is being collected is standardised and appropriate.

Beyond the registry-related activities, TREAT-NMD engaged with Industry to advance clinical research via other means. One important tool developed by the initial Network of Excellence is the CTSR (care and trial site registry), which was designed to provide information on personnel facilities, patient populations, and prior experience with conducting clinical trials. Sponsors can use the resource to help select experienced trial sites, and provided input to its original creation.

Another key resource -which is perhaps more in the category of 'Industry as a customer' rather than a co-creator- is the TREAT-NMD Advisory Committee for Therapeutics (TACT), which allows a better prioritisation of compounds to be taken from preclinical studies into clinical trials. TACT was established in 2009 to de-risk trials and ensure compounds moving into clinical trials have the best possible chance of making it to patients. Anyone can apply for a TACT review, and the goal is to help the applicant – commercial or otherwise- to position a candidate therapy along a realistic and well-informed pathway to clinical trial and eventual registration, by identifying potential pitfalls in the translational process and by providing transparent advice. Each application is given a bespoke international expert panel made up of preclinical, clinical, regulatory, patients and industry experts. Where the application is a Company, there is a fee for this advice and the report which follows an in-depth real-time review meeting. The way the model was set-up under the TREAT-NMD network saw all funds raised in this way being used to support the core running of TACT. Naturally, a high level of confidentiality is maintained.

Other TREAT-NMD interactions have included Industry funding training events, summer-schools and educational webinars (without playing a direct role in setting agendas).

In terms of the mechanisms of governance for Industry interactions – in the original grant, everything was covered by confidentiality agreements within the project consortium. Outside of this, and in the years since that grant came to a close, bespoke contracts and agreements have been set in place, such as the TGDOC Charter to govern the registry enquiries, as above, CDAs (Confidential Disclosure Agreements) and other contracts. The way in which contracting has worked has changed over the years. These days, TREAT-NMD is a not-for-profit organisation and its own legal entity, and so can undertake contracting directly with any given Company. For many years, however, when the TREAT- NMD Network was NOT a legal entity, contracting was performed by and centred around Newcastle University, as the representative of all the other entities involved in the network. This was not ideal, in some ways, as it meant the University legal department had to be brought on board and learn how to do this kind of work, which is not always obvious (especially in risk-averse organisations). Some of the processes involved in contracting and handling funding, for instance, were more bureaucratic than the experts involved would have liked. This was one of the reasons, in the end, that TREAT-NMD became a spin-out. However, the key point is that a great deal of collaboration *was* possible through this model of a non-legal-entity network, with one party (which *was* a legal entity) acting on behalf of the rest.

In summary, TREAT-NMD has been very influential in advancing clinical research in the NMD field. Considering the activities and collaborations with Industry summarised above, an important ingredient for success was building a truly multistakeholder network and community from the start, which entailed recognising the value of Industry as a stakeholder,

even in the early days. The approach was very much to develop any and all tools which would have a relevance to Industry, WITH Industry, and also ensuring an international and global approach.

The Sanofi Genzyme French Pompe Registry

This is an example of a national registry for a particular condition, established by Industry as part of a multistakeholder collaboration.

The main treatment for Pompe Disease is enzyme replacement therapy (ERT), and Sanofi provides two ERT products – Myozyme, approved almost 20 years ago, and Nexviazyme. This national registry was first qualified by the French National Committee for Rare Diseases Registries (CNR-MR) supported by INSERM and institut national de veille sanitaire (InVS), in 2008, to collect prospective clinical, functional and biological data on all French patients with a Pompe disease diagnosis (whether treated or not). The different stakeholders first discussed need and goals for the registry, and, after agreeing a plan, Sanofi established contracts with a group of French hospitals (individual contracts with each), to obtain consent from patients and provide the data. These contracts are updated on a one-to-one basis, as needed. Funding is provided by Sanofi to the research teams of the hospital, to support the data entry, but is also supplemented with funding from the French Association against Myopathy (AFM), French Glycogenosis Association (AFG), INSERM, and InVS. The registry serves multiple purposes:

- Elucidates the natural history of Pompe disease
- Enables the medical community to develop patient monitoring recommendations
- Optimises patient care
- Enables an assessment of the long-term effectiveness of the ERT

The results of the Registry data collection are published annually. Details of the registry dataset and patients enrolled are **available here**.

Key to success here was the fact that both main parties (the hospitals and Sanofi Genzyme) were 'on the same page' and saw value in the proposal. In terms of challenges, the need to contract with each hospital can be time-consuming. Furthermore, when regulators request data from the Company, regarding the ERT, it is the individual clinicians who are actually having to provide the data – in other words, the data access process could be improved.

ERK-REG

This case study is an example of how one of the registries created by the ERNs, for rare renal conditions, has interacted with Industry in its early years.

ERK-REG is the registry of the ERKNet ERN, for rare renal diseases. It was initiated in 2019 and acts as a single core registry for all rare renal diseases. The Registry collects data from the HCPs which are part of the ERN and is able to serve multiple purposes:

- Epidemiology of rare kidney diseases Information on level of diagnostic ascertainment (inc. access to genetic testing)
- Phenotype and natural history information
- Continuous monitoring of diagnostic and therapeutic performance and guideline adherence for optimized patient outcomes
- Rapid identification of patient cohorts for clinical trials

Early collaborations with Industry (i.e. prior to the Together4RD pilots) included ERK-REG brokering contracts between an Industry sponsor and sites that have patients eligible for clinical trials. Another example involved contracting with large pharma to provide aggregate data on over 200 paediatric patients receiving a medicine off-label (which was used as supportive evidence for a Paediatric Investigation Plan). There is an aspiration to use fully anonymized patient-level registry data to create external control arms for clinical trial, in future.

By 31st December 2023 a total of 22,687 patient records had been included in the ERK-REG (8928 by adult units (39,4 %), 13,758 by pediatric units (60,6 %), across 53 ERKNet Member centres, 5 Affiliated Partner centres, and 42 other external centres - **see here**.

European Society for Bone and Marrow Transplantation Registry (EBMT)

This case study involves Industry accessing a key registry established by a non-profit society, and using that data for a range of regulatory purposes.

The EBMT (European Society for Bone and Marrow Transplantation) is a non-profit Society founded in 1974. Originally, the scope was purely clinical bone marrow transplantation, but more recently, cellular therapies have also been included. It is a collaborative network for professionals working in centres and individuals in field of HSCT, gene and cell therapy – it has over 5000 members in over 70 countries, including over 600 transplant centres (covering >90% of all transplant centres in Europe).

The three pillars of the EBMT are research, education, and patient care. The EBMT Registry is the backbone of EBMT's research and educational activities. It contains patient clinical data, including aspects of the diagnosis and disease, first-line treatments, haematopoietic stem cell transplant (HSCT) or cell-therapy-associated procedures, transplant type, donor type, stem cell source, complications, and outcomes.

EBMT provides data to its members (ranging from individual physicians and nurses to Centres) and is able to perform studies and assess epidemiological trends. Industry are long-time collaborators in the EMBT broadly. Companies can become partners of excellence, without voting rights. If they wish to participate in one of the EBMT scientific studies, using the Registry, they negotiate payment. Of particular note is the success in gaining EMA qualification (specifically of the cell therapy module): to- date, EBMT has made various agreements with Companies on a one-to-one basis to support their Post Authorisation Safety Studies, based on secondary use of the Registry data. At present, no direct access is provided to the Registry data - rather, Companies approved as partners of excellence can access data collected in reports. In addition, Companies can contract for individual research projects, such as feasibility reports, surveys, conducting retrospective or prospective studies, etc. Where possible, only anonymous data is shared (although pseudonymised data can be shared with explicit patient consent). The Registry facilitates over 100 publications per year.

https://www.ebmt.org/ebmt-patient-registry

French Proof of Concept Club (POC Club)

This is an example of a national (French) initiative to promote more rare disease research collaborations between the public and private fields

The POC Club is a national (French) resource to promote innovative research and develop new treatments for rare diseases by offering coaching and guidance for researchers and clinicians and, crucially, connecting them with suitable Industry partners. Established in 2017, it is recognised in the 3 rd French National Plan for Rare Disease. POC is essentially an effective business model, based on a research valorisation tool & implemented through a group of industry partners. The initiator for the idea was the Foundation Maladies Rares, and the goal was to bridge the gap between academia and industry in rare disease. POC Club is financed through company partners and wider fundraising. Webinars allow academics to present 10 minute 'elevator-pitches' for projects they wish to conduct, and the Industry feasibility of the research proposals is assessed. They run two sessions per year – over the first 5 years, 85 projects have been presented to Industry through the POC Club, with 70 connections made, and an 80% interest rate from the Industry participants. If a project is taken forward by a Company, partnership agreements can be signed between the key actors and a tech transfer office.

The first success of the POC was the creation of a **partnership** (signed in April 2018) between industry, an academic researcher, and a Tech-Transfer Office, to develop a gene therapy for Fragile X Syndrome.

This partnership led to an Exclusive Worldwide License Agreement in 2021. Factors for success in this arrangement included:

- The stakeholders coming together at an early stage in the research
- Each partner contributing with their unique experience and capabilities, and valuing what the other could bring
- An understanding of the expectations and constraints of the other partner
- A neutral and trusted third party to initiate and facilitate the partnership

The POC Club has encountered several challenges in attempting to establish collaborative projects between academic researchers and Industry. For instance, there are different expectations from Industry depending on the size of the company – large pharma companies have different needs, perspectives and expectations to small biotech companies. The gap between academia and industry is very much real, and has to be addressed. In particular, academic researchers are not aware of the expectations and constraints Industry

has to deal with. It has proven very important, therefore, to coach researchers and clinicians to better understand the key milestones of drug development. POC Club plays an important role by acting as a third party to facilitate the discussions and help move things forward (**especially when addressing IP matters**).

Innovative Therapies for Children with Cancer (ITTC) Consortium

This is a well-established case study from the paediatric cancer community, dating back over 20 years, in which Industry is a long-term collaborator in efforts to improve the whole lifecycle of product development in paediatric oncology.

The Consortium involves 63 Paediatric Oncology Departments in 18 European countries with expertise in conducting early phase trials in children and adolescents, together with 25 European research laboratories. **ITTC** launched in 2003, long before the Paediatric Cancer ERN (ERN PaedCan). ITTC is a non-profit organisation established under French Law. The goal is to accelerate the introduction of new, effective, and safe therapies for the treatment of children and adolescents with cancer. The ITTC offers a wide range of collaborations with Industry, across the whole lifecycle of product development, from early portfolio evaluation to advice on generating phase 1 data, through to support with paediatric trial design and finally implementation. In this way, ITTC increases the likelihood of the most effective therapies entering development, optimising the chances of these medicines eventually becoming available to patients.

European Collaboration for Epilepsy Trials (ECET)

This case study concerns a relatively new collaboration across Europe, to improve clinical trials in epilepsies, with strong ERN engagement and leadership

ECET was launched in 2021 by the regional Executive Committee of the International League Against Epilepsy (ILAE-Europe), and was endorsed by the **ERN EpiCARE**, the European Consortium for Epilepsy Trials. The goal is to provide advice and expertise to optimise the design and implementation of clinical trials in epilepsies across Europe, for both adults and children. Despite the approval of numerous antiseizure medications, many individuals with epilepsy syndromes continue to experience seizures, suffer from comorbidities, or experience adverse events. Well-designed trials are essential to provide the necessary

evidence for rational treatment choices in rare epilepsies, but historically, antiseizure treatment trials have been poorly designed. There remains a critical need for well-powered and representative clinical trials to develop novel treatments that can enhance quality of life, reduce seizure burden, minimize adverse effects, lower healthcare costs, reduce the risk of sudden unexpected death, and ultimately, modify the natural evolution of the underlying aetiologies.

ECET is a collaborative group of European investigators with shared interests and a good track record in designing and performing epilepsy trials. These experts have links to over 80 centres across 35 European countries. The priorities include innovative trial design and outcome measures; genetics and targeted therapies; epileptogenesis and disease modification; epilepsy surgery outcomes and follow- up; and more.

ECET offers a range of expert services to both academia and Industry, including the following:

- Leading and supporting natural history studies
- Promoting precision medicine
- Advice on clinical drug development
- Advice on trial design
- Selection of trial sites in Europe
- Centralised/standardised adjudication processes to reduce variability in multicentre trials
- Organising educational activities to enhance the skills of researchers and healthcare professionals.

The ECET is still in its early days, but structures are being develop to contract with pharma companies and CROs. Importantly, the ECET is now an established legal entity.

ACCELERATE

Another long-established case study from the paediatric cancer community, which centres on multistakeholder meetings

The ACCELERATE Consortium was initiated in 2012, in the paediatric cancer field. The goal is to accelerate the process of developing and evaluating innovative therapies for children and young people with cancer. Pharma companies participate in the activities, which are essentially multistakeholder fora in which the group analyses the state quo of research and development and identifies activities necessary to drive forwards the pace of progress. Industry representatives are part of the Steering Committee, as equal partners, and Industry is part of projects designed to push the field forward (which include education and working groups on clinical research topics, but not specific trials).

TOOL 8: SUMMARY OF AREAS OR ACTIVITIES FOR POTENTIAL ERN AND INDUSTRY COLLABORATION

One barrier to ERN-Industry collaboration, especially for research communities which have not traditionally seen significant R&D effort, and for Companies which are not very familiar with ERNs and what they have to offer, is a difficulty in envisaging tangible collaborative activities. The following tables of activities were originally created following lengthy Together4RD consultations with dedicated working groups, around existing public-private collaborative projects or activities in the rare disease space. The experts in these working groups were encouraged to identify and then analyse a range of such activities and brainstorm on their suitability for possible ERN and Industry collaboration.

Where relevant, examples of case studies advancing each activity, were included. For further details of these case studies, see Tool 7 '**Case Studies - example of previous or ongoing public-private collaborations in the rare disease space**'. These tables were originally included as supporting material for the **2023 Together4RD Position Statement**, **and have been further adapted in 2024-5 for this Toolkit**. The contents are intended to be illustrative, though not exhaustive. Activities are divided into two broad tables – one relating to registries, which are key resources for the ERNs: the other is concerned with activities to support clinical research and knowledge-generation more broadly.

NB: Concerning clinical trials, please see the note below the tables. Together4RD has not prioritised a goal of fostering ERN-Industry collaboration in clinical trials, specifically. The Steering Group recommended a focus on less traditional activities one could envisage between Industry and ERNs, which could reasonably be expected to conclude within a year or two of initiation, in order to yield some early lessons to support more -and more effective- collaborations in future. Furthermore, there was a hope that targeting activities more in the realm of building resources in a given group of diseases, or addressing barriers to R&D, might hold a greater potential for multicompany engagement and could generate added-value downstream for specific companies whilst also serving an important goal of enriching the wider rare disease research ecosystem. For instance, projects concerned with linking previously distinct data sources -e.g. by building interoperable registry platforms- could foster new research and drive new knowledge for the same or broader disease communities going forwards, whilst also answering the research question at hand. This kind of approach, in which stakeholders increasingly collaborate to put in place tools and advance knowledge able to drive progress and advancements across the wider rare disease research arena, is part of the 'paradigm shift' called for in the Rare2030 recommendations, and is very much in-line with more recent calls to embrace innovation in European therapy development.

Types of collaboration involving Registries that should/ could be pursued	Points to consider/ best practices	**Case Studies** - examples of industry and non-industry partnerships or projects exploring this kind of collaborative activity (for more on specific case studies, see Tool 7)
Using registry data to understand the natural history of a disease or identify unmet medical need	"Longitudinal data collection can help to elucidate the natural history (NH) of a condition. Not enough is known about the NH of many rare diseases, which lack adequate registries to collect data (and often, for the rarest conditions, such registries need to operate at the global level). As registries are all about structured data, careful thought must be given to the initial data dictionary (including any associated mandatory or recommended datasets), as it needs to be sufficiently broad to detect unknown effects as well as monitoring known symptoms (i.e. without a robust starting knowledge of the NH, especially of complex multisystem conditions, it may be that a meaningful data item which should be monitored will not be recorded). Patient engagement in establishing registries to collect NH is therefore especially meaningful. Related to this, registries hold the potential to illuminate unmet medical need; for instance, a registry dedicated to a rare lung or rare liver disease may capture other presentations or comorbidities that have not emerged in clinical trials, and which -in addition to elucidating natural history- therefore highlight unforeseen medical needs. It is important for companies to know the full clinical picture. However, it is also worth considering whether registries are the most appropriate sources of such knowledge - electronic health records (EHRs) possibly hold more potential here, or will, in future. The potential for ERN registries (as in, the new structures created by European Commission grants over the past 4-7 years) to elucidate NH will be variable, as many have opted not to collect large numbers of data items in the first instance, but are instead collecting data of relevance to all conditions under the scope of that given ERN. Having said this, the data dictionaries of ERN registries are growing (as of late 2024, all but 6 ERN registries included over 50 items in their data dictionaries, with 7 including over 500 items). Plus, in addition to ERN registries, several manage disease-specific registries."	An example of a public-private collaboration here is the Sanofi French Pompe registry, which has been prospectively gathering clinical, functional and biological data of all French patients with a diagnosis of Pompe disease confirmed by enzymatic and/or molecular analysis, whether treated or not - untreated patients can help to reveal NH of the diseases. **https://together4rd.eu/tool-7-case-studies-for-public-private-collaborations-in-the-rare-disease-space/**
Using registry data as real-world data to serve regulatory purposes	"This is an often-cited goal for rare disease registries, but examples are quite challenging to find. One goal would be reducing the use of placebos in future trials by using registry data as a control arm. Such an activity is arguably more feasible and effective when data in	ERK-Reg is a rare example of an ERN registry which has already begun to explore how its data could support regulatory activities. It has been able

	registries is more standardised (and it is probably necessary to think less about ontologies, as has been the case with rare disease diagnostic platforms and project traditionally, and think increasingly of standards for data structure, such as OMOP Common Data Model, and perhaps standards specifically relevant for clinical trial data, especially CDISC). There is a real need for regulatory buy-in for these sorts of uses, and there is still perhaps quite a poor understanding of what sort of data is acceptable to the regulatory bodies for particular types of activity. **(The EMA has issued some guidance here)**. A recent workshop organised in Feb 2025 by the ERICA and conect4children initiatives explored the aspirations of ERN registries around supporting a range of regulatory purposes. There is a high level of interest in this kind of functionality, although almost all view this as being a future activity, something they envisage embarking on in 5 years' time. A key point here is, to serve this kind of ambitious use, registries need to be collecting the right sort of data - data which will be of use to Sponsors and Regulators. Some more specific forms of registry data serving as Real World Evidence are highlighted below.[11]	to provide aggregate data on over 200 paediatric patients receiving a medicine on an off-label basis, to be used as supportive evidence for a Paediatric Investigation Plan. This data broadens the evidence base especially for safety, but also the efficacy of the drug, to inform the regulatory process. The EBMT registry has received a positive EMA qualification opinion, making its cellular therapy module a suitable data source for regulatory purposes. Both therefore offer insights to this kind of activity.
Using registry data to conduct post-marketing surveillance (see also a related activity below)	This is another type of activity which tends to be viewed as highly desirable, but apparently happens little in practice at present. A key consideration here is that patient-level data would be required for this. It has long been a goal of registries to replace the need for Industry to create drug-specific registries, but Companies frequently reply that existing registries are not capable of meeting strict regulatory criteria. Therefore, a real partnership between the registry creators/managers, Companies, and the EMA, would be required. In particular, tools would be required to ensure the quality of data in registries. The EMBT registry case study should be illuminating here.	EBMT has entered into various agreements with industry partners to support their EMA-mandated Post Authorisation Safety Studies (though even here, the studies are based on secondary use of EBMT registry data). The EBMT registry does include data quality checks that should promote consistency at the point of data entry, but there is no onsite Source Data Verification (SDV) or comprehensive remote SDV in terms of the entire registry as a whole; however, within the context of individual studies, additional quality checks can be performed (remote and/or onsite). The experiences of the few rare disease registries (EBMT and Cystic Fibrosis) which have received EMA

		qualification should be leveraged here, along with any guidance from the EMA Registry Taskforce. The TREAT-NMD Registries Platform is also an interesting example, as here, the goal is to enable multiple companies to fund a common platform for PMS.
Collaborating on defining data sets or data dictionaries	It is important to consider the purpose of a registry – what must it be able to do? The data one needs to collect for a simple epidemiological study will be less than (and different to) data required for Post-Marketing-Surveillance. Several projects are looking strategically and technically at how to increase the interoperability and FAIRness of registries (along with other sources of rare disease patient data), to try to allow data to speak with other data from other relevant registries, to serve particular goals. These activities (e.g. the work on making the ERN registries more FAIR under the EJP RD, continuing under ERDERA; the data tasks of conect4children which have explored how registry data could support better clinical trials or function as RWE in the paediatric space; and disease-specific projects like Duchenne Data Project in the Netherlands) present a number of important best practices. However, there has been less emphasis to-date on co-developing key resources like data dictionaries with Companies (partially because the ERNs have not felt able to do this to-date). Such activity, in the future, should include defining and implementing Patient Centred Outcome Measures within registries (aligning with work on PCOMs and PROMs under ERICA and the ERDERA, for instance)	The TREAT-NMD registry work is one example of where companies have been involved in developing disease-relevant datasets and dictionaries for the global registries.
Use of registries to improve care	It is very much in the interests of companies to see the standard of care raised, which can happen when clinicians, researchers and patients use registry data to identify good practices and enshrine 'what works' into clinical practice guidelines or similar. Implementation of such guidance can create a more harmonised clinical ecosystem, which presumably then means a more equal baseline for patients with the same disease in different countries.	A good example here comes from the DMD field: registry data enabled a good understanding of NH but also showed what worked, in terms of interventions – researchers could see that in countries where steroids were used, boys were ambulant for longer than in countries where they weren't provided routinely, and night-time ventilation improved health and wellbeing significantly, etc. Those observations then made their way into

		international diagnosis and management guidelines, which are an important tool for standardising the level of care.
Use of registries to identify the best clinically-performing sites	Companies value knowledge about HCP/site expertise and outcomes. By benchmarking centres, companies can gain information of respective HCP outcomes, life expectancy etc. Registries can thus yield valuable information on regional and national performance and assist with decisions on which sites to contract with for clinical trials, as well as potentially supporting decisions on where to concentrate ATMPs provision. When it comes to identifying key sites for paediatric clinical trials, the mapping and resources created by the conect4children IMI2 initiative, which has now spun-out into a legal entity, the c4c Stichting, are also very important.	The ERK-REG registry provides the ability to benchmark in this way, and other ERN registries are working towards this goal.
Using registry data to do feasibility assessments and trial planning	This is linked to the previous activity, but goes a step further.	A good practice noted in the ERK-REG case study is the brokering of Sponsor contacts with sites that have patients eligible for particular clinical trials: the registry allows Companies to assess the feasibility of their studies. Another good example comes from the TREAT-NMD registries, which use a global network of autonomous registries (most using core and extended datasets to promote more harmonised and interoperable data). A system of checks and balances is in place to ensure companies can make a request to an oversight committee made up of curators of national registries for conditions like SMA and DMD. If this TGDOC, as it is called, approves the request, the data is collected from the registries (in aggregate form) and Companies can see how many patients they would likely be able to recruit in particular countries, how many

		patients meet particular inclusion criteria etc. This is very valuable in terms of letting Industry plan whether a trial is feasible or not and gives insight on how to structure it. The Companies pay for this aggregate data and the funds go back into the TREAT-NMD system, supporting the curators of the registries to meet and network, for instance. The EBMT also provides data for Companies, based on individual requests. Such research projects include (feasibility) reports, surveys, support for statistical analyses, performing retrospective or prospective studies (depending on the informed consent – specific projects sometimes require new informed consent forms, different to that requested when originally inputting data.) It is interesting to consider how registries might complement other approaches to identifying sites for clinical trials, such as the structures created for the paediatric community via conect4children **http://dx.doi.org/10.1016/B978-0-323-88459-4.00019-5**
Industry funding registries or registry platforms	This activity may involve some or all of the activities specified above, but goes a step beyond, in one key way - here, Industry contributes resources to the setting-up, maintenance or expansion of a registry/registry platform. There are multiple benefits here, including the ability to avoid the creation of drug-specific registries. It would probably be necessary to think of a collaborative funding approach here, with modules for specific conditions. As yet, no examples were forthcoming from the Together4RD stakeholders, across the consultative activities, so this would very much be an aspirational future goal for the ERN ecosystem to explore.	

Types of collaboration involving 'clinical research' which should/could be pursued	Points to consider/ best practices (where specific case studies are mentioned, see further Tool 7)
Enabling broad (all-ERN) multistakeholder forums to build mutual awareness of achievements and open a dialogue	Given the lack of opportunities to-date for ERNs and Companies to enter into dialogue openly, it might make sense to create a dedicated once-a-year event for ERNs and Industry, for the latter to learn more about what ERNs are really doing and see where their strengths lie. This would be a relatively simple but important 'catch-all' activity, to help shape more specific collaborations. This is based somewhat on the idea of the Accelerate example, and also on the EURORDIS RoundTable of Companies, but in this option would be envisaged as a single forum for all Networks and all interested Companies to attend. It may be that such a meeting could be part of the EC-organised ERN conference (assuming these recommence, post-covid), or else could be envisaged as a standalone event. Perhaps individual ERN meetings with Industry could branch-off after the plenary.
Establishing disease-specific (or area specific) multistakeholder forums to advance trial-readiness and prioritise collaborative activities	This is a similar activity to the previous, but here fora would be ERN-specific. Multistakeholder groups/fora, organised at more disease-area-specific levels, could be very beneficial to accelerate the pace of trial-readiness and maturation: a good example here is the Accelerate initiative, where all stakeholder, including Industry, gather to discuss the state of the art and identify strategic needs and gaps in their disease area/intervention. Accelerate organise such events for paediatric cancers, but specific fora could be established under the aegis of ERNs, perhaps funded by companies, with the programme created by academics and patients. Forums like these could address some of priorities this WG identified, in terms of ERN: Industry interactions, such as what patient-centred trials in that area look like, agreeing relevant endpoints for studies in X and Y diseases, etc.
Establishing a 'match-making' forum for researchers to pitch their ideas to companies and bid for funding support	The case study of the French POC (Proof of Concept) is a good model for this sort of activity. There are certain requirements, if the POC would be replicated in other countries, or indeed established as a vast all-ERN opportunity. This would differ from the activities above, as here, specific research proposals from academics would be presented and assessed. If expanded to the ERNs, it is difficult to see how this would work on a national level; in France, the presence of French Tech Transfer Offices has been crucial. Perhaps a pan-European entity such as EATRIS or other similar body could play such a role, if POC events were organised along ERN lines. The role of the Foundation Maladies Rare here has been critical in the French POC example, as a 'Neutral and trusted third party' to initiate and facilitate the partnerships (over the first 5 years, 85 projects have been presented to Industry through the POC Club, with 70 connections made, and an 80% interest rate from the Industry participants)
Enabling assessments of clinical trial feasibility and/or finding patients for clinical trials	A number of activities can be identified which collectively help to de-risk clinical research in rare diseases for Industry. Registries can play a key role in this as (anonymised, aggregate) data can be provided to Companies to help them assess the feasibility of a study in a given condition, with particular inclusion criteria, in particular countries or regions. e.g. the TREAT-NMD case study shows us how registries have been used to inform Companies about the number of patients in particular countries or regions with a particular type of Duchenne Muscular Dystrophy, for instance, within a certain age range, who meet particular inclusion

	criteria (e.g. are still ambulant, have not taken steroids etc). The aggregate data provided by the national registries associated to TREAT-NMD can then be used to help that Company plan its trials effectively. See further the 'Registries' sub-group table. Another useful asset here is TREAT-NMD's CTSR (Care and Trial Site Registry), which is a registry not of patients but of sites, providing information on those sites, the cohorts they can provide, etc. Some ERNs have developed (and others may be developing) registries able to support with finding patients for trials - indeed, the ERK-Reg case study can perform such a role. Naturally, any activity aimed at indicating to Companies how many patients they might be able to recruit for research and where they are based needs to be kept separate from actual recruitment efforts (but again, the case studies gathered by Together4RD ensure this a matter of good practice)
Providing expert, tailored and confidential advice to companies for optimised therapy development	Several case studies demonstrate the importance of this function, which, when provided within disease-specific fora, seems to have a major added-value beyond the sorts of early advice offered via Regulatory bodies alone, for instance. For instance, ITTC (Innovative Therapies for Children with Cancer) assesses the relevance of mechanisms of action for experimental paediatric oncology medicines and – if there is potential in the therapy – provides advice to a company on a 1-2-1 basis, ranging from early portfolio evaluation (preclinical) through to support for trial implementation. Having ITTC established as a non-profit legal entity (under French law) has facilitated this service. The ACT (Advisory Committee for Therapeutics) model, which originated from the TREAT-NMD case study, was also presented as a good (and very replicable) model here. Work is ongoing under the EJP RD to try to take this model, used for over a decade in the neuromuscular field and apply it (with any necessary adaptations) to other RD areas, strategically overseen by ERNs wherever possible. Several fields have expressed interest. However, some form of seed funding is really required to do this well, until the model is established and becomes self-sustaining. Companies could foreseeably look at precompetitive funding of some kind (or if they know they will wish to use the services of an ACT in a given area in the near future, they might consider funding the initial costs.) For many years, the Neuromuscular ACT was run from a single University, which oversaw the contracting etc and used fees from Companies (on a sliding scale, depending on size of the Company) to pay for costs of the panel review meetings. In the absence of a new legal entity, this model could be replicated in ERNs by channelling contracting through a single HCP playing a leading role in the ACT for that ERN. In recent years, largely though the EJP-RD, the ACT model has been expanded to other disease areas, including rare ataxias and the brain tumour community. The ECET (European Collaboration for Epilepsy Trials) is also starting to provide a trial advisory service in the epilepsy field. It is of course essential that such expert advice services maintain confidentiality for the Companies seeking them – the resources names above have developed templates and CDAs (indeed full toolkits, in some cases) which could be used here.
Creating/Improving biobanks	Some communities have their own disease-related biobanks. Other samples are part of very large biobanks and networks of biobanks e.g. EuroBioBank. Projects like RD-Connect embraced the EuroBioBank network and created a biobank and registry finder. BBMRI also maintains a biobank catalogue. It may be, however, that many fields are not using biobanks effectively and would benefit from support to do so.

Diagnosing patients for clinical research through EHRs from ERN centres (HCPs and 'affiliated' centres)	Together4RD has not yet received case studies of this happening; indeed, it is likely that this falls into the category of 'new activity which would be possible between ERNs, specifically, and Industry'. The fact that each ERN connects HCPs across the EU and EEA countries should, in theory, make it more feasible for electronic health record (EHRs) to be federated somehow, to enable the diagnosis of patients not currently diagnosed and enrolled in registries etc. There would be potential for AI approaches to be incorporated here. However, the scope of such activity would require careful consideration: if patients are coming to the attention of ERN HCPs, is it likely that they will remain undiagnosed (and if they are, would AI algorithms be able to solve these cases, or would referral to Solve RD or similar not be more promising?). To really optimise a diagnostic yield of previously undiagnosed patients, perhaps one would need to access EHRs in more general hospitals, rather than specialist clinics, or even in primary care settings. (NB: the Screen4Care IMI 2 project is exploring routes to early diagnosis of people with a RD, through Newborn Screening but also other routes – their work should be illuminating here, perhaps). Therefore, perhaps the added-value here would be less about diagnosing patients who do not have a diagnosis and rather finding patients with particular phenotypes, e.g. stratifying cohorts.
Supporting educational events, to impact the sharing of good practices in diagnosis, treatment, care or research	There is a major need for better educational resources and training in the rare disease field. Some activities in the 'educational domain could be particularly suitable for ERNs and industry to collaborate on. Examples of educational activities in rare conditions, which receive industry support whilst avoiding conflict of interest, are the masterclasses initiated by TREAT-NMD whilst still coordinated by Newcastle University and now handled by the legal entity which spun out, TREAT-NMD Services Ltd. In 2018 a TREAT-NMD Education Committee was established, comprising both academic and patient experts affiliated with TREAT-NMD who share an interest in supporting educational events for the neuromuscular community. This Committee ensures the independence and appropriateness of all activities endorsed by or delivered by TREAT-NMD, as well as the quality. Companies are able to financially support masterclasses in conditions including Duchenne Muscular Dystrophy, Spinal Muscular Atrophy and Limb-Girdle Muscular Dystrophy. These could be dedicated to professionals in particular countries or regions, to help build capacity around how best to diagnose patients and manage their care. Or they may involve experts from many countries and focus on particular elements of high-quality care provision, such as physiotherapy practices and how to measure and monitor outcomes. Companies value the ability to spread good practices and build professional capacity in conditions they are interested in, and they also benefit indirectly in the sense that such activities will raise -and help to equalise- the standard of care across countries and regions, which is advantageous when it comes to delivering multinational clinical trials and benchmarking. The ERNs are very much committed to advancing training and education, in various ways. All networks deliver webinars on particular conditions or topics relevant to their ERN domain, which support the sharing of best practices. In addition, ERNs participate in training exchanges, in which staff from some HCPs are funded to visit more experienced centres within the Network, to deepen their knowledge and learn new skills. This exchange programme has been operated by DG SANTE to-date.

	Together4RD is not aware of Industry engagement in any of these ERN-led activities to-date, but there may be potential here for unbiased and independent agenda-setting, supported under the right conditions by a company/companies. Another category of education and knowledge generation, more specifically, concerns the creation of clinical practice guidelines.
Generating clinical practice guidelines or clinical decision support tools	An important duty of all ERNs is to generate, update or endorse clinical practice guidelines (CPGs) or clinical decision support tools. A dedicated Tender from DG SANTE supported the creation of many new sets of CPGs, whilst also facilitating the review and possible updating of existing resources. Whilst it would not be appropriate for a company to directly fund a guideline which would recommend use of its own therapy, there could be a role to support this kind of activity less directly, which would be of interest to companies wishing to both improve the level of care patients receive, and 'level' the standard of care across countries (both of which can be very important for multinational clinical trials which could otherwise involve patients with very different phenotypes at baseline, purely based on varying approaches to diagnosis, treatment and care from one country to the next.) This might take the form of funding key meetings, e.g. in-person consensus-building meetings to agree on the content of the eventual guidance, or of supporting translations of guidance, once finalised, in different language. Another beneficial activity could be for companies to fund the generation of a lay-person version of the finalised and published scientific guidance (thus removing any suggestions of commercial influence on the contents and recommendations relating to specific medicines). The Together4RD consultation process identified limited examples of such activities but it may be something for ERNs to discuss – perhaps this kind of activity would be especially appropriate for ERNs and Learned/Professional societies to work on together.

A note about clinical trials

One obvious activity in which the two parties may engage are clinical trials, especially as there is a particular need to stimulate more clinical trials in Europe. The Draghi report on 'The Future of European Competitiveness' highlighted declining EU competitiveness across several key areas[1] calling for stakeholders to "boost the attractiveness of the EU for conducting clinical trials and to expedite access to markets for novel medicines." (p.31). And a recent EUCOPE (EU Committee of Pharmaceutical Entrepreneurs) **report** highlights the fact that although Europe remains popular for early-stage investment, later stage clinical investments are continuing to decline, as the EU continues to lose ground to the US and China. It is therefore essential that clinical trials continue to take place in Europe, especially in rare conditions where the unmet needs are so significant (and increasingly, it seems that the traditional, RCT model of clinical trials, will need to be supplemented or substituted for more innovative and adaptive designs and a broader concept of 'evidence' (whilst retaining the necessary safety and quality standards for bringing a therapy to market)).

1 https://commission.europa.eu/topics/strengthening-european-competitiveness/eu-competitiveness-looking-ahead_en#paragraph_47059

The role of ERNs, specifically, in partnering with Industry for better and more numerous clinical trials in rare disease and highly specialised healthcare, has yet to be fully determined; one reason being, the HCPs which are directly part of a given ERN, either as full members or as 'affiliated' partners of various formal categories, will always, of necessity, be limited. The vision of ERNs -at least for the larger countries- was not to directly engage every centre or unit with expertise in rare disease across the EU, but rather to engage key players who could then engage other expert units or centres within their country – a so-called 'hub and spoke' model. Clinical research focusing on rare conditions typically needs to recruit as many patients as possible, to reach viable numbers for whatever type of trial is intended: and this will surely include reaching out to centres 'outside' of an ERN, rather than solely targeting patients visiting the centres which are directly part of a given Network. Therefore, it may not always be possible or even desirable to envisage clinical trials being delivered solely across ERN HCP sites.

Section C: practical knowledge transfer – initiating and delivering a well-developed research collaboration

TOOL 9: REPORT ON THE EXPERIENCES AND LEARNINGS FROM THE FIRST ERN-INDUSTRY PILOTS SUPPORTED BY TOGETHER4RD

Introduction

The principal goal of Together4RD is to stimulate scientific collaborations between European Reference Networks (ERNs) and Industry. Achieving this goal entails overcoming a variety of historical barriers hampering interaction in this space, by adopting a multi-pronged approach which includes practical support for collaborations, as well as policy and advocacy. A key pillar of the activities in Together4RD centres on launching pilots. In 2024, the Together4RD Secretariat interviewed key individuals from both Industry and ERNs, about their experiences in launching the first 3 ERN-Industry pilot projects. These interviews were intended to better understand the respective experiences of conceptualising and initiating these pilots – from who came up with the original idea, to how the project proposals have taken shape, covering activities up to the launch phase (approximately). The main insights are summarized below, and key lessons have been distilled from each pilot, covering positives and areas of innovation for these pilots, whilst also highlighting ways in which these kinds of collaborations might be improved in future ERN-Industry activities.

NB: it is important to remember that these are true pilots, in every sense: this is really the first time ERNs have openly collaborated with Industry, in transparent public collaborations. In multiple respects, these pilots represent very new ways of working, for both Companies and the non-Industry partners; therefore alongside the plaudits that should undoubtably come from actually having managed to *launch* three tangible projects, there is - as anticipated- a plethora of valuable lessons, which should be shared widely (as many of these not only elucidate some of the challenges in attempting to form public-private collaborations, broadly , but also introduce issues specific to ERNs).

A set of more concise recommendations, distilled from these extensive learnings, are included in this Toolkit as Tool 10 '**Key Recommendations for both ERNs and Industry from the experiences of the first ERN-Industry pilots**'

For a summary of what each pilot is addressing, see here.

Generating an idea – how did these three collaborations begin?

A call was launched by Together4RD in mid 2022, explicitly seeking pilot research project ideas on which at least one ERN and one company could collaborate. These proposals could be submitted, in the first instance, by either ERNs or the companies sponsoring the Together4RD secretariat. Several proposals were received, and after discussions to assess their feasibility by the T4RD Steering Group and facilitated by the secretariat, and to shape ideas into clearer proposals, three pilots were selected for deployment. As it turned out, the initial applications for each of these eventual pilots were in fact submitted by Industry partners. Before drilling down to what worked well in the project initiation phase, for each of these pilots, and where there is room for improvement, it is helpful to explore the different routes each of the pilots have taken, towards their respective launch.

TTP Pilot: Takeda & ERN EuroBloodNet

Takeda submitted a short proposal outline to the Together4RD secretariat, which then formally connected them with ERN EuroBloodNet, the ERN in which expertise in the condition Takeda were interested in here -TTP (Thrombotic Thrombocytopenic Purpura) - would most naturally suit Takeda had performed such a mapping exercise to better understand the patient journey and elicit where the gaps are for patients in the healthcare ecosystem back in 2022 and drafted several possible projects to address the unmet needs identified, which they brought to a hackathon of external stakeholders. This all proved a useful background for approaching Together4RD and the EuroBloodNet team.

From the ERN, the key actors in the pilot are experts in the University of Milan, and the EuroBloodNet research coordination team. They had forged strong connections with the coordination team of the ERN, particularly around a shared interest in using AI to improve diagnosis, and had had some interaction with Takeda in previous years (although not the individuals they ended up working with). Therefore, when the Takeda team submitted the initial proposal to the Together4RD secretariat, the latter was able to facilitate interactions with the ERN.

RHINE Pilot – Novo Nordisk, ERK-Net and Oxal Europe

Similarly, in the case of the **RHINE** pilot, in rare renal disease, the initial impetus came from Novo Nordisk, who submitted a proposal on Primary Hyperoxaluria (PH). They saw great value and potential in the ERKNet registry, known as ERK-REG, despite it being relatively new (for instance, they were aware that there had already been publications from the registry, and it had been widely presented, which assured them of the research potential). Although an older registry also collected data on PH patients, run by Oxal Europe, there was no real collaboration between those resources, preventing the field from consolidating precious data. Novo Nordisk was initially interested in understanding the barriers to diagnosis for the PH patients, and how this can happen earlier, and then explore what 'best care' looks like for people after they receive that diagnosis. A collaborative project with the ERN and the pre-existing registry thus seemed a good opportunity to understand clinical care pathways and the patient journey in rare renal disease but also to harmonise registry efforts for an ultra-rare disease. The Novo Nordisk proposal came about through discussions across the public affairs and medical affairs teams, and once Together4RD brought in the ERN coordination team, that proposal was further co-created with ERKNet and Oxal-Europe to forge a concrete, innovative and mutually beneficial project.

Rare Bone Pilot – Sanofi and ERN-BOND

Here again, the initial proposal came from the industry partner, in this case Sanofi. Sanofi has extensive experience in building registries and in this proposal, they were interested to explore the extent to which the registry held by ERN-BOND contained adequate and appropriate data to enable a better understanding of the rare bone disease landscape. A particular goal was to better understand the natural history and burden of Osteogenesis Imperfecta (OI). The opportunity of a pilot project was identified by the public affairs and research advocacy teams and brought to the medical affairs team (which explores the wider ecosystem within rare disease, and identifies opportunities to collaborate, whether with patient advocacy groups or academic groups). The coordinator for ERN-BOND was a key opinion leader in the OI field, and had been involved in running registries for many years. The Together4RD secretariat helped to make contact with the coordination team, and a number of discussions exposed the opportunities to utilise the registry that would benefit of both ERN-BOND and Sanofi.

Co-creating a mutually beneficial research project plan

In the **RHINE pilot project**, the actors were efficient in isolating a precise research question

centred on PH. The initial proposal by Novo Nordisk did not contain too much detail but entailed bridging previously distinct registries (the ERK-Reg plus the long-standing registry run by Oxal-Europe). The RHINE consortium did consider a different primary research question to the one it ended up with, which was more concerned with what delays the diagnosis in another disease might cause. This was something Novo Nordisk was keen to explore; however, neither of the registries could really elucidate that, with the data they currently had. Therefore, the partners decided to elucidate the patient pathway and the time from someone being registered as a person with a rare renal disease, to the point when they are diagnosed with a specific subtype, and what specialists they would then consult.

A turning point in agreeing a central research question to shape the RHINE project was that the parties all agreed that as this was essentially a proof-of-concept project, the plan had to be achievable within approximatively a year, and thus they should aim for concrete, deployable and meaningful project objectives without being overly ambitious. The consortium decided not to merge the existing registries, but to combine datasets, through a retrospective data approach. This simplified some of the next steps, such as establishing a governance board involving the 3 organisations involved, and facilitated contracting discussions.

The ERK-NET coordination team brought the proposals to the scientific committee and the registry board, to ensure buy-in of the wider ERN.

Nevertheless, the process of finalizing the proposal still required patience all round:

> "*The final project scope reflects a middle ground after numerous revisions*".

In the **TTP pilot**, some of those involved in the pilot initiation felt that although all parties were agreed that there was scope to collaborate around TTP, drilling-down to a primary research question and project plan was challenging, partially because those involved could identify so many challenges to address.

For the rare bone pilot, Sanofi came with several research questions they wished to work on with the ERN, supported by insights from medical colleagues. However, their representatives were very aware that those questions needed to align with what the ERN partners were interested in exploring:

> "*If our questions were not aligned... or if we were not willing to change them or work together, then I think it would have been a less successful agreement on those research questions and the scoping.*"

What are the key strengths and major added value of these pilot projects?

The very fact that three pilots successfully launched, after years of **very notable and much-bemoaned inactivity between ERNs and Industry**, is itself a major positive. However, all three pilots highlighted more specific ways in which these pilots have broken new ground and offer major added value.

Several industry representatives emphasised that the call for proposals came at a perfect time for them, offering fresh opportunities "to build a brand-new collaboration" in fields and areas which perhaps were 'less-well-trodden'.

All three companies were keen to emphasise that they viewed these pilot projects as the start of, hopefully, long and fruitful collaborations with the ERNs concerned:

"[We will] start in a humble way, but with a great ambition"

For instance, some industry experts noted that **entering into more co-creative partnerships like this in the future is very much the way forward**, and offers advantages over the traditional one-directional (and purely transactional) approach. Those interviewed noted the enormous potential to understand each other's strengths and find common interests, and enrich research. The overwhelming learnings from one pilot project initiation have been that this is all about breaking new ground and trying new approaches to get ERNs and industry working together. And naturally, this has meant that some things have not gone to plan – or rather, some steps of the project initiation process could have been conducted more efficiently. But this can be viewed alongside positives; for instance, most of the parties interviewed responded that a **good level of trust had been built-up** over the proposal preparation process.

Other company representatives were also keen to emphasise that "there was no cookbook here". Ways of working together had to be figured out, step-by-step. Nonetheless, they highlighted, as major positives in the experience, the excellent relationship established, citing **transparency and the absence of any hidden agendas**. Where there were uncertainties, these were mutual, so that helped to cement a real partnership.

The academic experts these projects seemed to appreciate the fact that the companies could, and should, **have a say scientifically, on the course of project proposal**. In some cases, especially, they really highlighted the scientific *advantages* to working with industry. For one thing, there is a recognition that companies like this can bring greater impact to academic research, and faster. Scientific research is obviously important, and is traditionally the 'bread and butter' of researchers: but industry have experience of putting in place

methods, strategies, and tools, globally, and managing discussions with regulators and HTA bodies to help ensure the impact of the scientific research the ERN experts wish to do. And all of this was -at least by the time of these interviews, when all parties had been working together for some time- understood and appreciated. **This was very important, as for partnerships to be fruitful and trust to be built, all actors need to appreciate the broad expertise and experience each other can bring**: in the case of public-private interactions, it is especially important that the industry partner is not viewed merely as a 'bankroller' for the research, who should not have a say on the scientific direction, as explained further below.

For their part, even before this Together4RD-initiated opportunity, Novo Nordisk colleagues familiar with ERNs saw great value and potential in the ERK-NET registry, in particular, even though it is still relatively new. Takeda highlighted significant advantages in working with EuroBloodNet, as an existing ready-made network, is highly beneficial, as it offers the possibility to more easily pool enough data to train an algorithm for AI.

There was a sense across all pilots that collaborating with ERNs should bring major efficiencies for companies working in highly specialised fields:

> *"If we want to do things around diagnostics or education, any existing network is really important for us. [Rare disease areas] may be better taken care of by an existing network collaborating with pharma rather than pharma kind of building from scratch every time".*

Besides the convenience of having a read-made network, several participants highlighted other important advantages of working with an established community like an ERN. This is a departure from the norm, in some ways, as here, Industry isn't assembling its own bespoke group of experts; instead, the experts are already there and are being proposed, in a sense, to the Company. This is obviously desirable, as the expert base is much more likely to be unbiased. The openness of this approach, therefore, is very beneficial, although, because it is a new sort of approach, it is not without its challenges (as below).

As another added value, several industry respondents mentioned that engaging in these pilots has raised awareness about ERNs internally. The companies involved in these pilots are large, with a global footprint, and although those engaging directly in Together4RD, as sponsors of the initiative, were of course familiar with the networks, they appreciated the fact that many of their colleagues were not at all aware of ERNs, what they have achieved, and what their potential is.

The interviews with pilot participants also highlighted the fact that different actors within the same ERN also value the collaboration structures these pilots have set in place. One

expert reported that it was very positive that the coordination team of the ERN was engaged, as they felt able to focus on the scientific components of the project planning, and not worry about legal and bureaucratic issues that wouldn't sit within their usual area of expertise. It is worth pointing out that, for all ERNs, researchers in the many HCPs which make up each ERN are still very much getting to know one another professionally, and these kinds of activities really help to iron out the *way* in which ERNs can operate to support this sort of work. For example, it need not be the case that the scientific expertise in the particular project being proposed actually sits in the coordination team of the ERN – they might have expertise in different conditions under that ERN's broad heading, and thus it is necessary to bring in experts from other ERN centres, to make the consortium robust.

Lessons we can take-away

There have been many positive lessons learned in the conceptualisation and initiation processes of all three pilots; however, those involved in these pioneering efforts also highlighted where there might be room for improvement. In seeking to share some of these learnings, it is important to emphasize that these issues are often not black and white, stemming from the actions -or lack thereof- of one 'side' or the other. Indeed, interestingly, sometimes both the academic/clinical experts and the Industry experts identified the same issues as 'needing improvement' but saw room for improvement in addressing these challenges, from *both* sides.

These pilots – and ERN-Industry activities, generally – represent a departure from the norm

Generally speaking, companies are figuring out how to work with 'the ERN' as opposed to with a single academic centre, seeking to clarify where the difference lies (especially as each ERN is not a legal entity). Although the industry colleagues more used to working at EU level, with understanding of the rare disease research ecosystem, were keen to collaborate with the ERNs, some admitted that they needed to advocate internally to convince some of their colleagues of the added-value here, educating them on the status quo of the networks, and what the vision for their company could be. In the case of the non-industry parties, they are either learning how to work with industry for the first time, or else are ascertaining how to work with a company *as* an ERN, above and beyond any experiences they may have had in an individual PI or university hospital capacity.

When facing new ways of working all round, it is not surprising that new uncertainties and barriers to efficiency are encountered. Representatives from the industry partners explain that companies have processes in place to seek out and strengthen collaborations (or 'partnerships', as one respondent prefers to call them). As explained by the interviewees,

companies typically award a grant to an expert centre/PI, approaching them with a set of research questions for them to address and publish on. Another classic form of public-private engagement centres around clinical trials. But many of those interviewed, from both industry and academic institutions, emphasised that these are all situations where a company is seeking specific expertise from outside their company. Occasionally this drive comes from the other direction, i.e. someone proposes to the company to run a research project that might actively benefit that company. But either way, traditionally, interactions have tended to be a transactional one-way-street, and to have relatively specific goals.

In these pilot projects, however, although the initial proposals came from the Industry partners, the project plan had to be developed and agreed in a co-creation process -which was sometimes lengthy – involving all parties, which was consequently often marked by a key question: 'who is really leading and pushing things forward?' Industry was a *partner* at the table, rather than a lead – intentionally so, to make each pilot genuinely collaborative.

A robust co-creation process is essential

As above, the pilots all demonstrated that a robust co-creation process is crucial to build a concrete project plan and agree a mutually beneficial research question. Those involved in the pilots wanted a co-creation process in which all parties contribute to the development of ideas, to turn initial proposals into feasible and meaningful projects aligned on the strategy, the expectations and capabilities of all parties involved.

> *"Although we may have ended up with slightly 'safer' research questions than we might usually have gone for, it was essential for all parties involved to feel comfortable with these, and therefore it was a good compromise."*

The most effective approach, from the feedback received, was to genuinely shape the documents and plans together with an iterative co-creation process. The industry parties involved in the pilots welcomed ERN experts providing input during the co-creation process; indeed, in some cases, more vocal input would have been welcomed, e.g. to hear the academics more explicitly stating their ideas, their needs, what they would like to do.

Finding common ground can be challenging. One key insight from the interviews was to focus research questions on unmet needs that go beyond specific therapies—prioritising a deeper understanding of the disease itself to drive progress. However, public and private partners, while working toward the same goal, may have different priorities for these projects. It's essential to recognise these differences early on and either accept them or find a way to ensure all parties achieve their desired outcomes.

Avoiding assumptions around public-private collaborations

There are many misconceptions, and unrealistic expectations surround public-private collaborations and interactions. These are not all specific to ERN-industry interactions, but all three pilots shed light on the importance of understanding the perspectives and needs and realities of other stakeholders within a multistakeholder interaction, to make collaborations more fruitful and try to minimise misunderstandings and frustrations. From the interviews, it was clear that the parties involved in the pilots did not feel they were all '*speaking the same language*'. Overall, the pilot initiation process had some major positives, especially in building trust between industry and non-industry stakeholders. However, it took time for everyone to fully understand each other's priorities and needs.

Early on, there was sometimes a tendency to oversimplify the other side's motivations. Some of these issues stem from differences in the way in which companies, hospitals and universities are established, and what fundamentally drives them. For the academics involved in these kinds of pilots, there should be a recognition that companies naturally want to diagnose as many patients as possible to maximise the market for their product. However, an industry representative reported feeling that the ERN collaborators initially perceived that company to be driven solely by a desire to sell a product and failed to recognise that some companies "*[genuinely prioritize] working in a different way and... really want to address health care ecosystem gaps*".

The takeaway message is not as simple as 'ERNs need to understand what drives industry' – although this is absolutely a need, the truth is that different companies may have different priorities, and will value different sorts of outcomes. Naturally, all need to make sure their products have the best chance of making a return on investment. However, in the rare disease space, companies genuinely pride themselves on working towards the greater good, on addressing unmet needs, and they naturally want their would-be collaborators to understand their ethos and trust their goals.

From the industry perspective, there is sometimes a sense that academics can be a little too focused on the scientific outcomes, especially around publications, and do not always see the wider route to impact for the knowledge and tools generated. One industry representative reported that the non-industry parties in their pilot were, to the company's way of thinking, a little too wedded to academic outputs like scientific publications, whereas they initially envisaged as objective to better understand the patient journey, with the ultimate objective of improving it. The reality is that, for those in academia, scientific publications so often remain the foremost mark of achievement and distinction.

A common frustration—seen beyond ERNs as well—is the belief that ERN researchers primarily wish to collaborate with Industry just to secure funding. This perception can hinder

the development of strong, transparent, and trust-based relationships.

> *"I have things in mind [from a scientific perspective] but can't do that without that money".*

This is not necessarily a problem, nor is it surprising, given that companies have more financial resources than ERN institutions. Perhaps it is fair to say that issues arise when researchers see industry purely as a funding source. There is a common misconception that companies are both willing and able to simply hand over significant budget to academics to conduct research independently, without collaboration. This misconception is unfortunate, as it creates false impressions of the way in which companies can actually expend funds, but -more importantly, perhaps- can serve to work against the collaborative spirit needed in the rare and highly specialised domain, when seeking to promote more -and more effective- public-private collaboration. Industry has a huge amount of expertise and experience to offer in the design and delivery of projects such as these, and the win:win scenario is one in which public actors seek to leverage that expertise, and recognise the added value of working with a company/companies, beyond the (understandable) desire to plug a financial gap, of sorts. It is important to emphasise that the future success of ERN and Industry interactions will absolutely depend upon this message being disseminated and understood, because the reality, unfortunately, is that ERNs are under resourced to do the myriad of things they are expected to do. Funding for registries, in particular, has been far below what is really needed, to make these resources as powerful as they can be. It is therefore natural that the private sector can easily be viewed as a source of redress for these monetary shortcomings; however, Together4RD wishes to emphasize, and promote, and awareness of the wider value industry can bring to a collaboration.

As mentioned above, a real positive for these pilots *is* the recognition of the diverse expertise housed by the three Companies involved here – they complement funds with an ability, for instance, to connect the academic partners with their own in-house data scientists and real-world evidence experts. Although ERN registries are a wonderful tool, and their respective communities may have rich experience pre-dating the newer ERN infrastructures, some of the companies in these pilots also have experience in building registries, with many lessons they can share.

But in some cases, it took some time for these kinds of messages to really take hold. For instance, the RHINE project found it was important to have Novo Nordisk included as an equal partner on a steering committee, so that their expertise could really contribute to the development of the project.

The importance of keeping on track and ensuring continued progress

One major area where all parties tended to desire improvement concerned the timelines for the initial scoping, proposal discussion, and project initiation phases. Although it is possible to view the lengthy deliberations as positive in some ways, e.g. enabling time for the proposal to improve and become more meaningful (as one respondent explained), the sentiment all round is that this process took longer than necessary. Helpfully, some ways to improve, in future, were identified, but it is important to explore the varying perspectives as to why things took longer than expected, in other to learn from these experiences.

In all pilots, there was a sense that all participants felt that the timelines for moving from the initial project discussion, to agreeing a revised project and research question, to then generating a more detailed project plan, were longer than would be desirable. Industry parties and academics alike reported that industry tended to push the ERN partners forwards. The RHINE ERN partners reported that Novo Nordisk encouraged them 'with just the right amount of urgency' and pushing. However: "*the expectations around timelines were not the same*".

The industry participants generally seemed to assign these delays to the significant workloads of the academic partners. Some emphasized that delays are not unexpected when working with academics, and the timelines here were not really very different to those found outside of an ERN; however, there was a general consensus that things should move faster in future.

It *may* be the case that the conditions in which the Companies proposed these pilots originally were not necessarily amongst the top research priorities of the respective ERNs. Although ERNs were established at a high level, to collectively include all rare diseases, this does not automatically translate to all conditions under those broad headings having the same levels of expertise and prioritization amongst the individual experts of the ERN. It may be that the 'readiness' for public-private collaborations, or indeed any research project, is not as high for some conditions as for others. The lack of availability of researchers, to engage with the discussions and project planning, meant that one proposed arm for a pilot, around education, was dropped as it was proving too challenging to secure the necessary time commitments. Again, this illustrates the need to be aware that initial research questions and project parameters may change, from first contact to firming up a project plan.

The ERN/academic experts interviewed about the pilots also acknowledged that the timelines from first contact to really agreeing the project focus and then developing a more detailed project plan, have been too lengthy. Some fully appreciate that this was partially due to their own challenges in prioritising the pilot initiation. However, interestingly, some respondents felt that this is more complex simply than 'industry pushing for a quick

agreement and the non-industry parties hold things up' – and that some delays have resulted from the nature of the processes within companies, and the perception that the discussions can be sometimes repetitive at the expense of action and decision-making. More than one reported a sense that despite the proposals being submitted by the companies, there was some hesitancy to fully commit to developing a plan – several recall sensing 'a lot of internal deliberation' from their respective companies. Another cited the fact that, although the ERN researchers could quite readily be identified, early-on in the process, industry contacts tend to be quite changeable. Colleagues one begins discussions with, at the start of a process like this, may not be the same people one is dealing with further down the line, as there is a high staff turnaround in industry. This can make it challenging to build relationships and keep momentum going, as different people need to pick up the discussions second-hand – this is obviously more of a risk, the longer the process takes.

One consequence of protracted project planning and initiation, which future collaborations might wish to bear in mind, is that as one industry expert pointed out, a company's priorities can sometimes change over time, and individuals working in these companies have very little power over such things:

> *"Something that may be a priority today, and could be signed off in a timely way, may not still be a priority five years later"*

One challenging component of the pilot initiation phase identified by multiple pilot participants, is budget discussions. Some of the ERN partners reported that they were expecting to be told, quite early on, what the company would be willing and able to contribute financially, to support the work, in order to define what they could include in the scientific proposal. They found it unusual that the companies asked them to define the budget, in the first instance, because again, people were used to being told such things for more traditional types of engagement e.g. in a clinical trial, the company contract with the hospital and they already have the protocol and are explicit about what budget is available. Companies cannot dedicate a set amount of funding (in the way a Horizon Europe grant stipulates a maximum budget, for instance), for a scientific proposal to then explain how it will *use* that budget ceiling. Rather, the detailed proposal should dictate how much funding a Company is *able* to dedicate, and hence delays in receiving a specific scientific proposal meant budget envelopes could not easily be agreed. However, with the parties sometimes feeling that they did not know what level of budget was actually available (the ERN parties) or what budget would be requested for a revised scope of work (on the company side), it is easy for a 'chicken and egg' situation to develop. Therefore, the earlier in the proposal that budgets can be negotiated, the better. But again, there is a lesson here in understanding and appreciating each other's modus operandi, and it was suggested that budget envelopes

should never be the starting point for project discussions, as it is then easy for the project to come across as having a traditional 'Industry as hands-off funder' nature.

> *"It is important to discuss expectations around resource - because expertise, time, people, understanding and budget are all wrapped into the resources, we're all committing to this".*

Deep-seated issues such as academic workloads, the need for clarity and agreement around budgets, and the relatively high turnaround of staff in the private sector will not be easily changed; however, the impact of some of the challenges behind the lengthy process of agreeing a robust research question and generating a specific project plan may be ameliorated, somewhat, through greater clarity on who is -and who should- be driving these collaborations forwards.

Who takes the lead? The importance of champions or project managers – people to move forwards

Although it is worth emphasizing again that the nature of the call for these pilot proposals could itself be responsible for some of the issues around delays, as explained above, the fact that these kinds of interactions are new for ERNs and industry makes it especially important to consider who is going to drive the process forward and how. In those earlier, traditional and more one-directional interactions typically seen in previous examples of public-private collaboration, the questions of who does what, by what deadline, for what amount of money, were more straightforward. There was a feeling, from both sides, that academic experts and KOLs are more used to working with pharma "when pharma is running the project":

> *"When we do a clinical trial, we have timelines and we are kind of pushing, pushing, pushing because, you know, we're investing 100 million and it's important it happens on time. And the problem here I think could be that we're not certain who is really the driver here. And that's a challenge."*

Several respondents reported a lack of clarity, on both sides around who was really supposed to be driving some of this work, and, consequently, who was responsible for pushing each stage and seeking consensus and action. It is a new experience for some of these non-industry experts to be asked to do the feasibility work, and the calculations. But because these pilots are viewed as a partnership, there is not that strong sense of 'ownership' one way or another. This means that it needs to be handled carefully and early, and these discussions aired, ideally through a third party, to make sure that the process is not stalling simply because of uncertainty either around who is supposed to be doing what, or because one partner does not actually have the knowledge, the experience nor the capacity to

perform certain activities they have never done before.

All pilots, one way or another, stressed the value of dedicated project management here. In the PH pilot, this was provided by the ERN Coordination Office and was deemed extremely valuable at enabling good progress at a reasonable pace. But all highlighted how important this is, to have someone either within the consortium or within the Together4RD secretariat -which was identified as a major support - or even completely outside. Some of the industry partners felt it would not be wise for the key project management role to sit within the company itself, as it might change the dynamic. Having a dedicated person—such as a champion or project manager—along with a project tracker was seen as essential for future collaborations. This helps all parties identify delays, understand what the consortium is waiting for, and who is responsible, so support can be provided to keep things on track. Without clarity on the cause of a delay—whether it be workload, waiting for input, or uncertainty about a task—it is difficult for others to step in and help.

One learning lesson that is unique to this new situation of ERNs and Industry seeking to work together, as opposed to any and all public-private projects, is that ERNs may need to consider who should be the driver within the ERN: what should that internal ERN process look like? Ideally, in future, it would be good to see multiple centres *within* a single ERN collaborating on a project with one company, or even multiple companies. Here, 'the ERN' part of the partnership will involve multiple experts, playing different roles, in different institutions. This exposes a major change in public-private collaborations involving networks (as opposed to a unilateral discussion Industry might have with a single Principal Investigator in a single University or Hospital). To make this activity an ERN activity, multiple actors need to be involved, and the ERN itself needs to provide support and endorsement; however, the decision-making processes, and modus operandi for this, is not really clear yet, in most -or even all- ERNs. It will be important for consortia to agree, in future, if decisions always need to come from – or be endorsed by- the ERN coordination team, as this could potentially slow things down and make processes less efficient. Perhaps coordination teams should defer some decision-making to other scientific experts involved in the pilot (who very likely may not sit in the coordinating structure). This is arguably an issue all ERNs are grappling with, for many activities i.e. how to avoid all activities needing sign-off and active participation from the coordinator/coordination team, whilst still maintaining something as an 'ERN activity' in spirit. In public-private collaborations, as in all ERN activities, it will be essential to get this balance right, and for coordinators to feel increasingly able to delegate key decisions to other members of their Networks, avoiding the whole process of project planning grinding to a halt until they are able to rededicate some time and attention amongst their overwhelming number of commitments.

The value of face-to-face discussions

All parties agreed the benefits of an in-person meeting (1.5 or 2 days) where everyone gathers around the same table and thrashes out what the project should look like. Such meetings were cited as key tools to speed up progress, allow all parties to air their views, understand the views and needs of others, and generally build partnerships as well as more concrete proposals. All seemed to agree that short virtual meetings, every 6 weeks or so, were not sufficient to drive forwards the discussions and really agree a firm research question. In some cases, a face-to-face meeting (or meetings) with all stakeholders complimented separate discussions with specific stakeholders, to build trust and address concerns on a one-to-one basis when necessary (another valuable lesson is the importance of taking the time and effort to build trust with parties who have not worked together previously).

Some chose to begin their F2F meetings by "*sharing concerns, ambitions and limitations*" and enabling participants to address some of the common misconceptions and prejudices, on all sides, highlighted above:

> *"Deep diving... only happened when we spent six hours together or eight hours together. It's very challenging to be able to accomplish that with one hour Zooms with where you really don't know each other"*

Navigating legal issues

As most of the pilots had not yet concluded the contracting phase at the time of the interviews, the learnings here are somewhat limited. The RHINE project was in the midst of this process, however, having advanced relatively easily to contracting due to streamlining the proposal. Data transfer agreements are relatively straightforward here, as only the two academic partners access the data directly. Again, having a dedicated project manager, and being based in an institution which has undertaken contracting with the private sector in the past, has made the process straightforward. The ERN coordination team did mention that it is proving a little more challenging to include their Industry partner in a trilateral contract, which commits all three legal entities involved in RHINE around one study plan (with milestones and budget plan). But they note that this is understandable and not unusual with these sorts of discussions.

Another piece of advice from a different pilot was to avoid allowing legal contacts in the different institutions to discuss these kinds of projects without the key leads being present. The ERN and Industry experts know what they need, and what they'd like to contract, but leaving this to the legal people can bring about a 'total misunderstanding' of what is intended, which overcomplicates the whole process and sets everything back.

TOOL 10: KEY RECOMMENDATIONS FOR BOTH ERNS AND INDUSTRY FROM THE EXPERIENCES OF THE FIRST ERN-INDUSTRY PILOTS

Key recommendations for both ERNs and Industry from the experiences of the first ERN-Industry pilots

The recommendations below stem from the lessons learned in the process of initiating the first three Together4RD pilot projects (for the full report, see Tool 9 '**Experiences and Learnings from the first ERN-Industry pilots supported by Together4RD**'. They essentially function as an executive summary of that detailed report.

Initiating a collaboration

Approach prospective partners as soon as possible – especially if the project is in response to a call or specific opportunity. This will allow input from all future partners in that very early project idea.

Embrace a co-creative process from the start, when it comes to reviewing and refining proposals and agreeing a research question. If possible, introduce a face-to-face meeting very early in the process, in which all are encouraged to review all the options on the table, in terms of how to orientate an activity, and share their perspectives, needs, and concerns.

Take time to do your research and understand as much as possible about your prospective collaborators:

- for industry parties, if you do not have deep knowledge of the ERN most connected to the condition(s) you are interested in, consider reviewing Tool 3, **What are ERNs?**.
- For ERNs, take a look at Tool 5: '**What does Industry need in a collaboration with ERNs?**'.

For Industry - consider how best to pitch an ERN-focused project with colleagues internally (who may not have a strong understanding or awareness of ERNs) and ensure a smooth and early transition from policy to medical departments.

ERNs – be realistic and honest from the beginning in terms of how high a priority a particular condition is for your network. Ideally, share and publicise your research priorities as widely as possible. Be open to research out of the usual 'comfort zone', to address unmet needs in the field, but try to balance this with your realistic capacity and levels of internal ERN interest and expertise.

Developing a robust and specific project plan

Be clear with a shared vision and mission statement at the start to align partners.

Be prepared to compromise and 'meet in the middle' when agreeing a concrete research question and firming-up a project plan.

Opening discussion around outcomes and impact early on should help to build transparent working relationships based on trust.

Understand that public and private actors tend to place value on different sorts of outputs.

- Industry - be prepared that ERN parties will likely place significant emphasis on generating peer-reviewed publications. ERN experts, often anchored in academic institutions as well as hospitals, have professional requirements to publish their work, This is an important marker of esteem, and thus publications will likely be a key output for any project.
- ERNs – consider how research can result in wider impact in terms of changing patient pathways and diagnostics practice, and outcomes beyond publications.
- ERNs – it is useful to accept that companies in the rare disease space tend to have goals and vision to improve the wider rare disease ecosystem, beyond simply developing and selling a product.

Do not underestimate the organisational and cultural differences and plan to take the time to understand what each other *desires and needs* from this collaboration.

Take time to discuss the expertise and skills each partner can bring to the collaboration – this is important, in order to build a fruitful collaboration in which all slides appreciate what the others can *bring* and to assess the skills across the full consortium (also allowing the identification of any gaps).

Think carefully about a realistic scope of work, depending on the timelines for completion: it may be helpful to view initial interactions between a given ERN and Industry as a proof-of-concept, starting relatively small but still meaningful, as an entry point for more elaborate projects down the line, e.g. once institutions have experience of forging these collaborations.

- Define small quick wins, achievable in a reasonable timeframe.

If it is the first foray into working with Industry for an ERN, accept that there may be setbacks and things may not develop as efficiently as one would wish – focus on the achievement of delving into a new area of activity, and plan for smoother progress on the next collaboration.

ERNs – accept that the Industry partner(s) will wish to have input to the scientific

development of the project plan, and should be viewed as an equal partner. Indeed, this should be welcomed, as it will bring significant advantages to the research, as it will give you access to the vast in-house scientific expertise but also expertise in medicines development, HTA, data science, and much more.

ERNs – be prepared to be vocal in co-developing a concrete project plan. Share your expert perspectives at every stage, as the industry partner will be seeking an active partnership with robust input.

Be prepared, in initial discussions especially, to ask challenging questions of the partners in your project – each party should understand the motivations and drivers of the other, and this means all should be willing to state what they would most like to achieve. This is important to build trust.

Managing Resource Discussions

Do not postpone resource discussions, as uncertainty can cause delays and misalignment in project planning.

ERNs – it is important to have realistic expectation of both the level of resources industry can contribute to projects, and the way in which it does this. Avoid thinking of companies as purely funders of research. Companies are generally unable to dedicate large sums of money, for the subsequent definition of a detailed project plan – in fact it is the reverse: funding can only be found, internally, based on the contents of a proposed plan. Companies do not award funds as unrestricted grants, without any direct involvement.

Developing a concrete project plan as early as possible supports more efficient negotiations around budget and resources widely.

Identify project owners from both industry and ERNs who are sufficiently senior and have budget decision making power.

Keeping the project-planning phase on track

Agree who will be the key drivers for each stage of the proposal initiation phase and project plan development.

It is highly recommended that dedicated project management time be allocated, to keep all partners on track. Standard progress tracking tools should be used, to agree timelines for each activity, and the project manager should be willing and able to follow-up when deadlines lapse, to keep the project moving forwards. It may be useful to involve external stakeholders (a third party) to support with this.

Regular virtual meeting should be established, to develop the more specific plan and drive the project forwards. However, these should be supplemented by at least one in-person meeting, across a day or two, ideally, to accelerate progress and address any uncertainties and make decisions.

Where projects involve more than one ERN centre, consider how those teams will work together most efficiently, making best use of everyone's expertise but also helping to keep a project on track. Consider focusing most of the administrative and bureaucratic and legal activity through one centre, for instance, but agree when and how individual experts and HCPs might take the lead to advance elements of the project.

Appreciate that delays can occur, on both side, and that these can cause major inconveniences (indeed jeopardize the project entirely) – both ERN and industry parties should therefore seek to avoid timelines becoming too long, by closely monitoring their progress and considering whether those working on a project are prioritizing it appropriately. In unavoidable periods of delay, it is imperative to maintain robust communication and inform each other of the situation, to manage expectations.

Companies should attempt to maintain key contacts working on any engagements with ERNs – although some staff turnover is normal, it is important for the rest of the consortium to have sight of who they are working with within each company.

Involve legal departments, from both/all sides, as early as possible.

Ensure that when entering into legal discussions, key project personnel are present at initial meetings of respective legal departments, to avoid misunderstandings.

TOOL 11: QUESTIONS PEOPLE SHOULD CONSIDER WHEN APPROACHING A NEW COLLABORATION BETWEEN ERNS AND INDUSTRY

Questions people should consider when approaching a new collaboration between ERNs and Industry

This resource consists of a list of key questions which should be considered by anyone contemplating a collaborative activity between an ERN (or ERNs) and Industry (whether single company or multiple). The questions stem from the survey initially used to support the selection of the Together4RD pilot projects, updated in light of the the lessons learned from the pilot initiation process.

It is intended as merely a guide, for all parties (public and private), to help stakeholders ensure they enter into co-creation and negotiations with the best chance of success. Specific and realistic expectations are important, to maximise the efficiency of those early discussions, and hopefully avoid some of the pitfalls that can occur and delay or even jeopardize a public-private collaboration. This should be viewed in connection with Tool 9 **Lessons Report on the Experiences and Learnings from the first ERN-Industry pilots supported by Together4RD** and Tool 10 **Key recommendations for both ERNs and industry from the experiences of the first ERN-Industry pilots**.

Objectives / expected outcomes of the collaboration

- What are the overall and specific objectives of the project/collaboration?
- How does the proposal link to wider priorities (for the ERN(s), industry, patients, or the broader policy/Research & Development ecosystem)?
- When would you be ready to start?
- What would a reasonable timeline be for this project to be delivered?
- Would it be a one-off distinct project or do you envisage it as the first step in a longer collaboration?
- Would this project be suitable for multiple ERNs and/or multiple companies to embark upon together? Or is it a single ERN-single company collaboration?

involved?

- How would you ensure the ERN(s) supports and shapes this, beyond a single researcher or centre (e.g. has this been discussed in the relevant governance boards? Or research working groups or networks?)
- Are there any areas or outcomes of the project which are non-negotiable?

Expertise and Resources

- Is there already any established infrastructure or data on which this project could/ should build?
- If so, who owns this/how can you access or use it?
- If a registry or registries are involved, who owns the data, what kind of data access agreements are already in place, etc.
- What types of expertise and *non-financial* resources would be needed? (thinking in terms of technical expertise, scientific expertise, training, etc)
- Who, within the planned consortium, can bring each kind of expertise and resource?
- How do you plan to involve patients/ a relevant patient organisation?

Funding

- What level of budget would be required to meet the project goals you have in mind at this stage?
- What would be the key milestones in this project, and what kind of budget would each require?

Process Considerations

- Would one party drive this forward overall, or lead on particular stages/areas of work?
  - Who is ultimately responsible for keeping the project planning, and the implementation, on track?
- Do you have commitment from senior leadership in all respective parties, for project sign-off and for financial issues?
- Who would provide dedicated project management time for the project, and how?
- Would the project involve accessing or collecting patient data (and is it retrospective

or prospective data)?

- Do you need to engage/access data for a minimum or maximum number of patients?

- Would the project require ethics approval?
- Have you involved legal and compliance teams in all prospective partner institutions? How will you ensure the smoothest possible approvals process?
- What risks would you foresee?
  - And what actions could you envisage to mitigate these?

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