TOOL 1

The Importance of Public Private Partnerships in Rare Disease

Together4RD
RARE DISEASES

Together4RD RARE DISEASES
Together4RD Toolkit to foster ERN and Industry Collaborations

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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'

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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/

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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/

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

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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."

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

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