TOOL 8

Summary of areas or activities for potential ERN and Industry collaboration

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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.

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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 Sanoffi 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."	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

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		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.	

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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.

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	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.

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