EndoCompass Transversal Area: Rare Diseases

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Background

Despite the inherent rarity of a rare disease, it is far from rare to have a rare disease. The European Commission reported in 2022 that approximately 36 million people in the EU live with a rare condition, and that already more than 6000 different rare diseases have been identified in the EU. So, whilst one rare condition may affect only a handful patients worldwide (being considered ultra-rare conditions), another may touch as many as 250 thousand patients. According to the European Registries for rare Endocrine Conditions[1] there are over 440 distinct rare diseases that affect the endocrine system[2], but to date, the number of patients with rare endocrine conditions in Europe is still not known. To date, around 80% of rare conditions are of genetic origin, and, of those, 70% already start in childhood[3]. While historically, rare conditions have had their key focus in Paediatrics, this has changed recently. Due to advances in care and therapy, many conditions have an extended or even normalized life-span so that age-appropriate care practices in adult medicine are needed. Furthermore, some rare conditions have been overlooked in childhood and may primarily present in adulthood, either due to the time points of certain symptoms. And lastly, adult medicine has realized the importance of acquired rare conditions during adult life. Therefore, the care of patients with rare (endocrine) conditions requires a) knowledge gain across many medical specialist areas, b) a concept of management over the life-time, c) the availability of diagnostic and therapeutic options including the participation in translational and clinical research for all age groups.

The missing experience and scattered knowledge about rare diseases leads to diagnostic delays and requires increased awareness among public and the need for establishment, funding, and sustainability of centers of expertise to enable earlier and correct diagnosis, as well as optimal management, treatment, and care. Many additional hurdles, however, still need to be taken, as there are still no treatment options for the vast majority of cases. Furthermore, there might be smaller interest from pharma companies due to difficulties of appropriate clinical trials and lesser chances for economic success. The phrasing and structuring of research needs, opportunities, and chances in rare diseases is a challenge that is pursued vigorously by the EU.

The development of a research network and platform

What has been realized by the EU and the ERNs to develop the prerequisite framework for rare disease research:

ERNs and ERICA (European Rare Disease Research Coordination and support action)

In 2017, the European Commission installed 24 European Reference Networks (ERNs) under the 2011 EU directive on cross border health care and the EU4Health program. In 2023, the ERNs included more than 1400 expertise centers within 400 health care providers in the EU and Norway, which altogether capture all rare disease domains[2]. The mission of the ERNs is to reduce present health

inequalities across Europe and focusses on the following mile stones: 1) the demonstration of an added value of (cross-border) virtual consultations by multidisciplinary expert boards, 2) the standardization of care for rare conditions (using transparency, guideline conformity, patient involvement), and 3) the development of structural pathways into science. For this purpose, in 2021, an ERN Research Working Group set up the ERICA (European Rare Disease Research Coordination and support Action) project (funded by Horizon 2020), in which all 24 ERNs participate[5].

ERICA has created a platform that integrates all ERN research and innovation capacities with a focus on effective data collection strategies via the ERN registries, on patient reported outcome measures, and on translation and research innovation. A Research Priorities Survey of the ERN Research Working Group mapped the research priorities across all ERNs. The integrated results of this survey formed the basis for the strategic positioning, structure, and actions of the ERICA project (2021-2025). These research priorities were: harmonized data capture, patient centered outcome measures (PCOMs), legal issues, investigator-initiated trial planning and execution, pragmatic (registry based) clinical trials, and advanced experimental therapies (Figure 1A). A pivotal role is given to the ERN Registries, which are regarded as unique platforms linking care to research under the umbrella of and in line with the vision of the European Health Data Space (EHDS)[4]. The registries have developed from assessment of quality of care by numbers and have progressed through standardization of what is collected as assessment of quality by clinical outcomes[5]. Thus, they are benchmarking clinical outcomes and acting as platform for quality improvement with active patient participation (with the patient as co-owner of her/his data).

European Rare Disease Research Infrastructures and Rare Disease Research Programs

Despite the enormous availability of expertise on rare disease research, the RD research landscape in Europe has been scattered until recently. Multiple European research infrastructures harboring specific RD expertise have been launched, such as Connect for Children (C4C), ECRIN , European Clinical Research Infrastructure Network, EATRIS (European infrastructure for translational medicine) , biobanks, such as BBMRI, in the presence of the European Medicines Agency (EMA), industry partnerships, the European Commission (DG Research and +DG Sante), and the Board of Member States. In 2019, the European Joint Program on Rare Diseases (EJP-RD) was launched as the first overarching RD research consortium bringing together 130 institutions (including the 24 ERNs) from 35 countries to create a comprehensive and sustainable eco-system, allowing a virtuous circle between research, care, and medical innovation[6]. The successor of EJP-RD under Horizon Europe is even more ambitious and will run from 2024-2034. It is called ERDERA (European Rare Disease Research Alliance). ERDERA aims to be maximally inclusive by supporting robust patient need-led research, by utilising and maximising the power of health and research data, by engaging and coordinating regional, national, EU and international alignment, to accelerate the development of new treatments and diagnostic pathways[7]. ERDERA includes 171 organisations from 36 countries (26 EU, 7 associated countries, 3 non-EU), and its structure encompasses, in addition to funding (such as Joint transnational calls), a European Clinical Research Network (CRN). This CRN will implement research activities targeting clinical trial readiness of rare conditions around 4 pillars: 1) Diagnostic research (data readiness, genome re-analysis research pipeline, genomic innovation to shorten time to diagnosis), 2) Outcome Research (real world data, clinical outcome assessment), 3) Innovative therapies (advanced therapeutic medicinal products (ATMPs), trial methodologies for number of few approach, and 4) Task Forces (drug trials, non-pharmacological interventions).

Expectations from patients and society

The development of a well-structured rare disease research eco-system requires that all rare disease research stakeholders can participate. Identification of the right partners for coordinated research initiatives, including initiation of new public-private-partnerships, alignment of research strategies with professional societies, as well as with international networks such as the ERNs that represent both academia and patients, will be key. Partners will need to be prepared and equipped to demonstrate readiness for the initiation of, and partnering in international and translational clinical trials, ranging from phase 1-4.

The expectations from patients and society with regard to research on rare endocrine conditions have already recently been mapped[8]. In this survey-based study, the specific themes related to rare endocrine conditions were prioritized by patients and highlighted in particular the need for more research on the ability to work and to participate in social activities (figure 1B). The study provided clear recommendations for clinical experts on how to incorporate the results of the study into the design of future studies on rare endocrine conditions, and in particular, the utilization of the results in designing patient-reported outcome measures for the disease areas covered by Endo-ERN. This is exemplary for many chronic conditions requiring life-long therapy with an overall good life expectancy, and thus maybe relevant for all ERNs.

Overall, the now established framework will allow to propel health care provision for complex and rare conditions to a new expertise-driven quality, based on knowledge generation, transparency and networking. Furthermore, the connection to a combined research environment will open possibilities for exponential and competitive science in human biology and medicine and will provide the European partnership with a world leading role. For many rare conditions, networking activities are mandatory in research, be it the reliance on adequate patient cohorts, modern techniques and methodology, as well as the exchange of experts in robust consortia that allow for transparent albeit competitive scientific activities. Similarly, only transparency of a two-sided model for optimal management of complex and rare conditions, meaning knowledge on as well as benchmarking of best practice in health care provision, can lead to optimization of health management. Ultimately, the connection of both, research and health care, will provide the basis for the European success in a world-wide competitive environment.

Focus areas for research in rare conditions

Specific topic examples within such Focus Areas that should consider when deciding on a research grant, as has been incorporated in the Endo-ERN Quality of Care Improvement & Research Counsel:

1. Diagnostic research readiness:
    a. Assessment of data readiness, standardization & harmonisation
    b. Genome re-analysis pipeline application, variant interpretation, translation to endocrinology departments/clinics
    c. Genomic innovation to shorten time to diagnosis
2. Clinical trial readiness :
    a. Multinational patient inclusion and collaboration
    b. Disease progression modelling
3. Clinical outcome assessment:
    a. Estimating the Socioeconomic Impact of Rare Endocrine Diseases
    b. Digital tool/ pathway development
    c. Develop/Implement disease specific Clinical Outcome Assessment Tools
4. Innovative therapies :
    a. Advanced Therapeutic Medicinal Products needs assessment/ mapping in Endo-ERN

    b. Analysis of specific therapy / treatment availability across EU member states
5. Unique clinical resource development/pilot
    a. Disease specific patient journey development
    b. Rare endocrine disease patient pathway development/ application
    c. Mapping of European patient referral pathways/channels in Endo-ERN

The overall research framework needs to be used specifically for rare conditions, due to for example the importance of sharing of data, especially from genomics, the specifics for clinical trials and development of novel therapeutic approaches, as well as overall new care models. The latter have been developed through the ERNs and will be introduced into the different member states via the JARDIN programme. JARDIN is a Joint Action of the EU to increase the effective integration of the ERN process into national health care system. This in turn will then proposedly lead to effective future research strategies as outlined above.

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