DEL 2.4 Orphanet Network Direct Grant

GENERAL PUBLIC REPORT

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1. INTRODUCTION

Rare diseases (RD) have been considered a challenge for Europe, for they have been identified as one of the paradigmatic fields in which actions conducted at the European level constitute the adequate response to their specific problems: poor recognition leading to diagnostic delay and inappropriate management including adapted social services, poor health outcomes, social burden, limited knowledge on natural history and pathophysiology leading to an insufficient development of new therapies.

Amongst the actions the European Commission has contributed to develop so far is Orphanet, a comprehensive European database dedicated to rare diseases and orphan drugs, accessible for all audiences from the portal www.orpha.net , and providing re-usable data for research and health policy through the platform www.orphadata.org.

Orphanet's aim is to help improve the diagnosis, care and treatment of patients with rare diseases by achieving the following objectives:

- **Improve the visibility of rare diseases** in the field of care and research through the development of the nomenclature on rare diseases (ORPHAcodes) essential to promote interoperability
- **Provide high quality information** and expertise on rare diseases accessible to anyone: ensuring equal access to knowledge for all the stakeholders, and orientating users and actors in the field in the mass of information online.
- **Contribute to improve knowledge** on rare diseases: piecing together the parts of the puzzle to better understand rare diseases from a medical, scientific and organisational point of view.

2. AIMS AND OBJECTIVES OF THE PROJECT

General objectives of the project are:

1. To provide the rare diseases community at large with interoperability tools, in particular around an inventory of rare diseases, to allow for semantic interoperability between countries and between domains (health, research)
2. To provide high-quality information on rare diseases, in particular through an encyclopedia in as many languages as possible,
3. To provide a directory of expert services in the participating countries in order to help patients, physicians and other stakeholders finding the expertise on a particular disease in Europe and beyond, and to produce data necessary to support policy actions.
4. To further develop and sustain Orphanet as the reference database on rare diseases, by establishing and consolidating collaboration within the Orphanet pan-European network and with European Reference Networks (ERNs) for the production, improvement and dissemination of knowledge on rare diseases. It will allow for the creation of a consistent expertise ecosystem for rare diseases in Europe.

The overall outcome is the consolidation of Orphanet as the reference source of information on rare diseases for European citizens.

3. ACHIEVEMENTS

1) Orphanet Nomenclature production and update

Orphanet nomenclature provides a common language between systems and countries to precisely identify each rare disease. It is available in 9 languages and it is at the “core” of the rich Oprhanet Knowledge base which provides knowledge around RD (fig.1). The Orphanet Nomenclature is the only terminology that recognizes the more than 6,000 rare diseases and gives each of them a standardised name, a definition and a unique, traceable code that can be used for the codification of patients in health (patient records) and in research settings (registries and cohorts) and for data sharing and exchange between countries and resources.

During the Direct Grant, this Nomenclature has been kept up-to-date by including all newly described rare diseases in the scientific literature and by consulting with experts, in particular European Reference Networks (fig.2). Moreover, collaboration with European Reference Networks has also been strengthen in order to revise the Orphanet Classification which organizes the Nomenclature into groups (fig2).

This Nomenclature is also aligned with the other main medical terminologies in use, in order to ensure the interoperability, meaning the transfer of data between systems (fig 3.)

Figure 1 The Orphanet Nomenclature is the core of the Orphanet Knowledge base

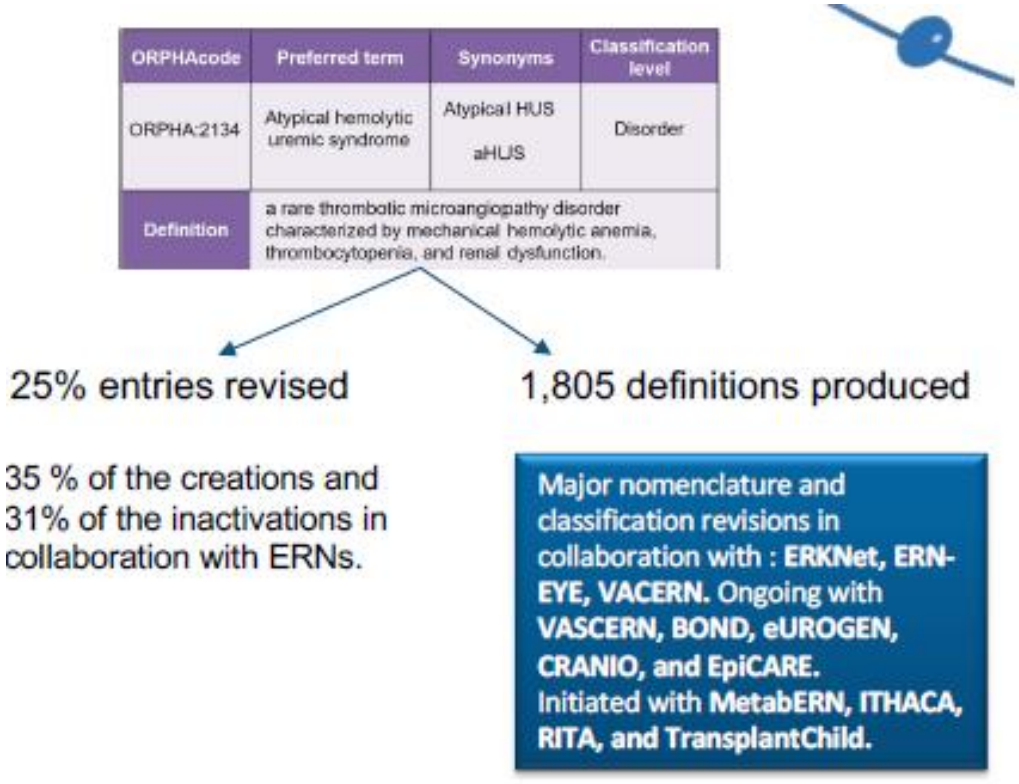

Figure 2 Figures on updates of the Orphanet Nomenclature carried out during the Direct Grant with detail on ERNs collaboration

Terminologies	Orphanet RD Coverage
ICD10	93%
OMIM	62%
SNOMED CT	83%
UMLS	70%
MeSH	24%
MedDra	15%
ICD11	ongoing

Figure 3 Orphanet Nomenclature alignments with other medical terminologies as of 15 June 2021

Orphanet Nomenclature data is accessible by disease on the www.orpha.net website in 9 languages, for massive data extraction on www.orphadata.org and as pdf files in the Orphanet Report series published annually in 9 languages here. .

2) Orphanet Knowledge base

During the Direct Grant the Orphanet Knowledge base has also been expanded, annotating rare diseases with information on Epidemiological data, Orphan drugs and genetic information.thanks to the survey of the scientific literature.

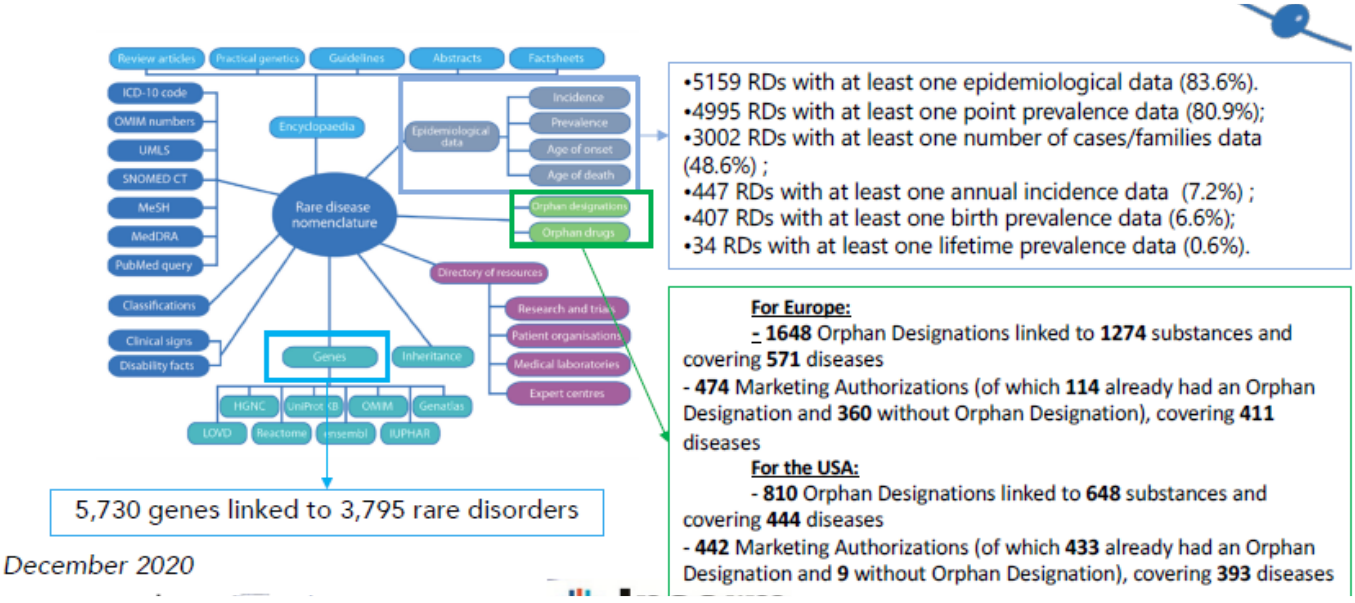

Figure 4 Orphanet KNOWLEDGE base DATA as per December 2020

Orphanet data is accessible by disease on the www.orpha.net website in 9 languages, for massive data extraction on www.orphadata.org, epidemiological data by disease is also available as an Orphanet Report series published annually in 9 languages here.

3) Orphanet Encyclopaedia of RD

During the Direct Grant the Orphanet encyclopaedia of RD available in 13 languages has been updated and expanded (fig.5).

Rare disease summaries in 13 languages	
6,603	English
4,079	French
5,358	Spanish
4,472	Italian
3,558	German
4,709	Dutch
1,160	Portuguese
1,248	Polish
420	Greek
253	Russian
166	Finnish
113	Japanese
103	Slovak

Figure 5 Rare Diseases Summaries available by language as per December 2020

Moreover, collaboration with European Reference Network have been organised in order to avoid duplication of work (fig.6).

ERN	Disease abstracts		Defintion quality control
	Ongoing	Completed	Completed
ERKNet	24	47	7
ITHACA	11	83	16
EpiCARE	4	10	0
ERN-SKIN	4	18	15
TOTAL	**43**	**158**	**36**

Figure 6 Detail of collaboration with ERNs per number of RD summaries/abstracts and for Quality Control of definitions

4) Orphanet catalogue of Expert Resources

Orphanet provides a catalogue of expert resources in the countries belonging to the Oprhanet Network. During the Direct Grant it has been updated and expanded including centres of

expertise, clinical laboratories, patient organisations, (fig.7) N.B. Research-related expert resources data are collected in the frame of a different EU-funded project the EJP-RD

- **37,923** Professionals referenced in the database
- **2,773** Patient organisations
- **8,318** Expert centres
- **1,621** Medical laboratories dedicated to diagnosis
- **44,127** Diagnostic tests linked to **4,904** diseases a(**5,541** genes and **2,537** panels of genes)
- **1,828** Sites conducting **3,686** ongoing research projects (**536** multinational+**2,993** national + **157** subprojects**) on **1,552** diseases
- **2,878** Sites conducting **4,516** ongoing clinical trials for **1,024** diseases
- **917** Patient registries
- **202** Variants databases
- **187** Biobanks

Figure 7Number of available resources per type of resource, as of 30 May 2021.

A dedicated section for European reference networks is available online (fig.8). It allows to have a one-stop shop where all the expert resources by ERN can be found.

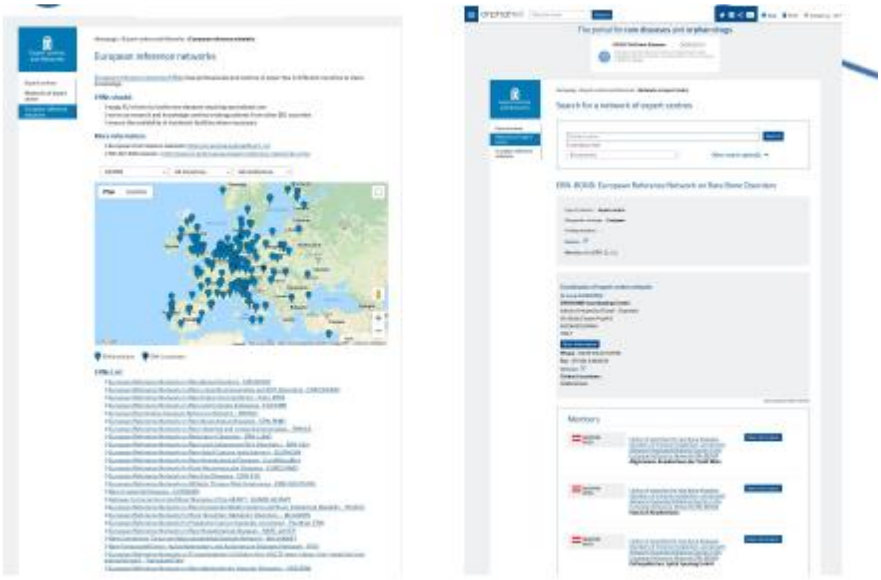

Figure 8 ERNs Specific section on the www.orpha.net website

5) Consolidate Orphanet position in Member States

During this Grant a series of effort have been carried out in order to consolidate Orphanet position in Member States.

Empowering of the National Teams has been organised through Trainings and coaching on several topics. Particular efforts were made to increase the capacity of the teams to populate the database to produce database content according to the Orphanet standards of quality, thus improving Orphanet's transparency and traceability. Based on the principles of the quality

management system (ISO9001), Orphanet decided to act on three most important axes:

1) have clear written procedures explaining how and why to produce data:
   Procedures are available online here. A list of Experts having contributed to the database are published annually here. Finally sources for decisions are traced internally and available in Orphadata files.

2) regularly train the information scientists producing the data in order for them to be as efficient as possible: during the Grant 1 F2F session and 2 full programme of at distance training sessions have been held.

3) Set up a quality control strategy in order to detect and correct non-compliant products present in the database.

Moreover, a strategic communication pack has been developed in order to ensure a common and coherent communication strategy by the network.
In the frame of this pack, a short video describing Orphanet activities and their impact in an easy to understand language has been made available and it is available on the Orphanet YouTube channel: https://www.youtube.com/channel/UCKMLSL9hlrxz6zKFod5IlnA

6) Consolidate cooperation with European Reference Networks

As stated in the paragraphs above, during this Direct Grant collaboration with many ERNs have been strengthen and Orphanet ambition is to develop collaboration with all ERNs. Indeed, we believe ERNs and Orphanet belong to the same RD ecosytem carrying out complementary actions. ERNs bring the scientific and clinical expertise while Orphanet brings the experience on databasing, standardisation and terminologies. These complementary skills will improve the knowledge on RDs by making available standardised, consistent, accurate data which is adapted to ERNs needs and compatible with the EJP-RD virtual platform (a RD platform developed in the frame of the EJP-RD project aimed at making resources and data sources relevant for RD research findable and queyrable ina federated, standardised and structured way.

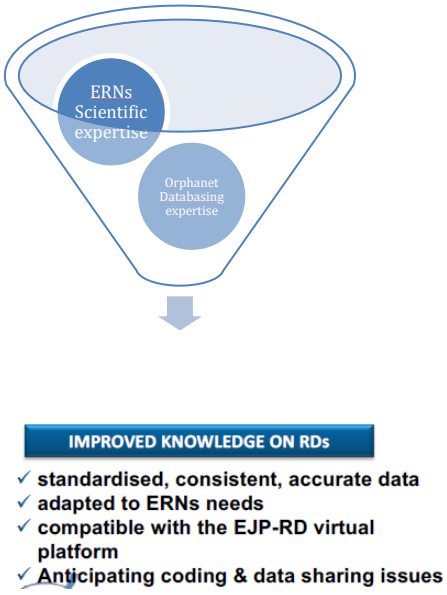

Figure 9Improved Knowledge on RD thanks to Orphanet/ERNs collaboration

7) Towards a Sustainability model for Orphanet

Finally, Orphanet has worked in order to solve the problem of its non-sustainable funding mode which has been project-based since the creation of the Network. The project based model is not compatible with the ground work that Orphanet provides as an essential brick/infrastructure of the RD ecosystem.

The timeline of the Sustainability work, with indication of the major milestones of the process is provided in the figure below (fig.10).

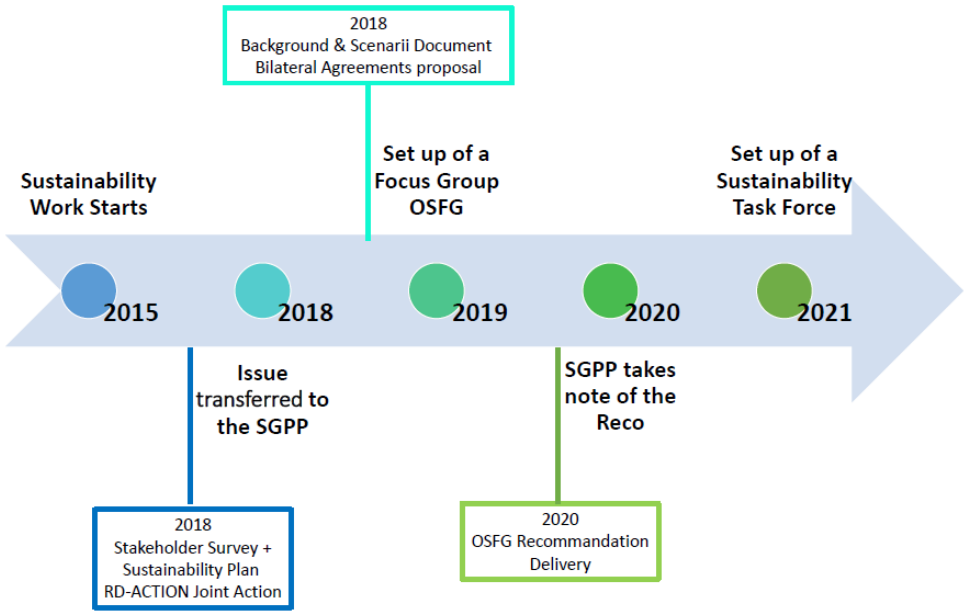

Figure 10 *Orphanet Sustainability work timeline*

Sustainability work started during the previous Joint action (www.rd-action.eu) and continued in the Direct Grant. In 2018, the issue was transferred to the Steering Group of Promotion and Prevention of communicable diseases (SGPP).

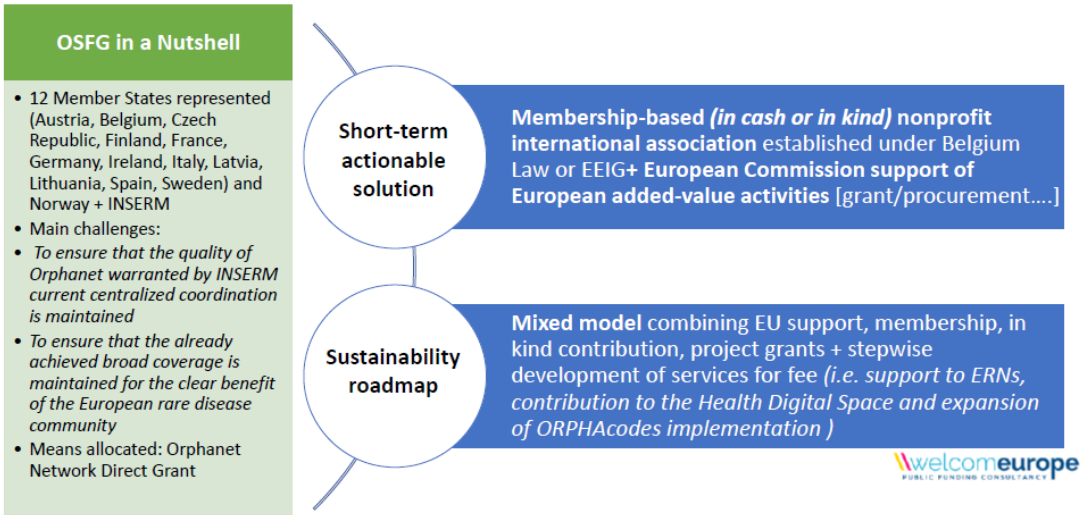

Figure 11 *Orphanet Sustainability Focus Group: Basic info and Main Recommendation*

This group, considering the granularity of the subject decided to set up a Focus Group. The Orphanet Sustainability Focus Group kicked off its activities early 2020 and delivered a Recommendation in November 2020 (fig.11) with the main aim of maintain and develop further the already achieved broad coverage and services for the clear benefit of the European RD community.
In order to analyse the feasibility of this model and the willingness of MS in contributing to it a Sustainability Task Force has been set up within the Orphanet Network and it is operating since January 2021. The compatibility of the AISBL model with the Network expectations was assessed through benchmarking and interviews with existing AISBL and lobbying with National funders has been organised by setting up a common Communication strategy and by making available a Strategic Communication pack (see paragraph above) and coaching of National Coordinators.

8) Orphanet as an essential Infrastructure of the RD Ecosystem
Orphadata was formally designated as an ELIXIR Core Data Resource at the start of 2019. The ELIXIR Core Data Resources are a set of European data resources of fundamental importance to the wider life-science community and the long-term preservation of biological data. These resources include services such as data platforms and knowledge bases that are authoritative in their field of expertise. Orphadata was added to this list after a detailed study conducted by an independent panel of reviewers following Orphanet's decision to adopt a more open licence, compatible with Open Science principles (Creative Commons BY-4.0). The knowledge bases singled out as Core Resources, to which Orphanet now belongs, work as "conceptual authorities" with a clear role in the standardisation of evolving concepts.
Indeed Orphanet Data and services are essential in many different EuropeanRD projects, such as SOLVE-RD, ERICA, the EJP-RD, RD-CODE but also in non-RD specific projects by providing RD uses cases such as X-eHealth, TEHDaS, WHO's ICD-11 and SNOMED-CT.
At the end of the Direct Grant a Series of seminars aimed at Seminar Aligning major EU structuring projects around data for RD data strategy was set up. During these seminars 15 projects presented their scope and assets and their interaction or potential interactions with the other projects concerning RDs (RARE 2030, ORPHANET, RD-CODE, EU RD Platform - JRC , EJPRD/Pillar 2, EHDS2 Pilot project 2021, TEHDAS, ERN registries/ERICA, B1MG, EOSC Life, RD GO-FAIR, X-eHealth , SolveRD, Darwin EU and the European Semantic Strategy for Health).

4. IMPACT ON TARGET GROUPS

Thanks to Orphanet, patients can find medical experts and contact patient organisations.
As for medical professionals, Orphanet gives them the means to understand rare diseases, to identify their clinical manifestations, and offers guidelines so that they can provide better care.
Turning to the research community, Orphanet grants access to a complete knowledge base on rare diseases and a detailed list of ongoing clinical trials and research projects.

Likewise, companies in the health sector can use the large amounts of data provided by Orphanet. to guidetheir research and development strategies through a better visibility of patient populations and existing orphan drugs.

Finally, policy makers can benefit of the Orphanet Nomenclature into Health and research Information system in order to gain insight to direct investments and make organisational choices to support research and healthcare systems.

5. LIST OF PARTICIPANTS

Applicant No*	Organisation name	Country
1 (Coordinator)	Institut national de la santé et de la recherche médicale (INSERM)	France
2	Medical University of Vienna (MUW)	Austria
3	Sciensano	Belgium
4	Bulgarian Association for Promotion of Education and Science (BAPES)	Bulgaria
5	Charles University, Second Faculty of Medicine (CUNI)	Czech Republic
6	Medizinische Hochschule Hannover (MHH)	Germany
7	University of Tartu (UT)	Estonia
8	Consorcio Centro De Investigacion Biomedica En Red (CIBER)	Spain
9	Rinnekoti Foundation (terminated 31/03/2019)	Finland
10	Public Health England (PHE)	UK
11	Children's Hospital Zagreb, Medical School University of Zagreb (KDB)	Croatia
12	Health Service Executive (HSE)	Ireland
13	Ospedale Pediatrico Bambin Gesù (OPBG)	Italy
14	Vilnius University Hospital Santaros Klinikos (VUHSK)	Lithuania
15	Directorate of Health Information and Research, Department of Health (DHIR)	Malta
16	LUMC (terminated 31-12-2018)	The Netherlands
17	Instytut Pomnick Centrum Zdrowia Driecka (IPCZD)	Poland
18	Directorate-General of Health (DGS)	Portugal
19	Universitatea de Medicina si Farmacie Iasi (UMF)	Romania
20	Institute of molecular genetics and genetic engineering- Belgrade University (IMGGE)	Republic of Serbia
21	Karolinska University Hospital	Sweden
22	University Medical Center Ljubljana (UMCL)	Slovenia
23	Oslo University Hospital Trust, Division of Paediatric and Adolescent Medicine (OUS-BAR)	Norway
24	Ministry of Human Capacities (HU-MHC)	Hungary
25	Children's Clinical University Hospital (CCUH)	Latvia

Applicant No*	Organisation name	Country
26	Radboudumc (RUMC)	the Netherlands
27	Kehitysvammaisten Tukiliitto	Finland
28	Ministry of Health of Luxembourg	Luxembourg