Deliverable 1.1
OD4RD Kick Off Meeting Executive Report
March 2022

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Content summary

Introduction

The Orphanet Data for Rare Diseases Direct Grant is a one year project co-funded by the European Commision's EU4Health programme. The project kicked-off with a meeting gathering the Orphanet network and the ERN representatives on the 21st of March. It gathered 68 participants from 19 countries, including 18 representatives of 13 ERNs.
The meeting was opened by European Commission's Deputy Head of Unit of the Unit B.3, European Reference Networks and Digital Health.

Project Overview

The discussions revolved around how the Orphanet Data for Rare Disease project will build on Orphanet's specific expertise, and on its organisation as a long-lasting, well-established network, to fulfil the following general objectives:

- To contribute to the generation of standardised, interoperable data on RD diagnosis for primary and secondary use, through maintenance of the Orphanet nomenclature of RD in collaboration with ERNs, and active support for its implementation in hospitals hosting ERNs,

- To contribute to the harmonisation of data collection amongst various settings (health records, registries) and amongst countries, through dissemination of coding good practices at the source (health records, registries, etc).

- To support evidence-based decision-making in the frame of the European strategy around ERNs, by providing an exploitable reference corpus of data and information on RD.

To achieve these, interaction with all relevant initiatives and stakeholders will be ensured in order to have a coherent approach and avoid duplication of effort (fig.1).

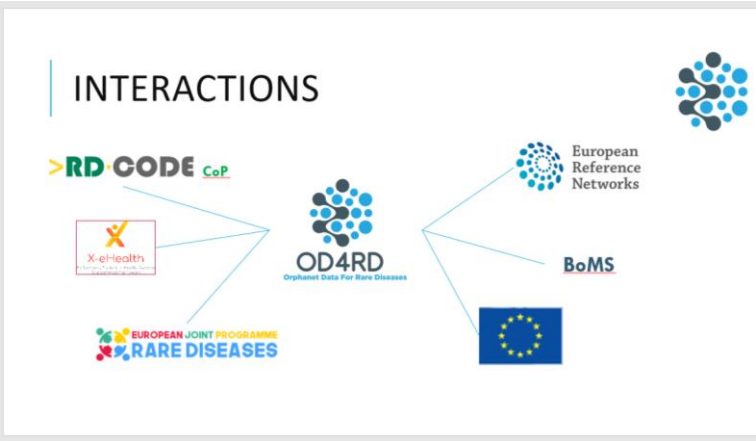

Fig1. Interactions with relevant initiatives and stakeholders

The action plan proposed was presented by the Orphanet Network. It has been organised into the 5 different workpackages[1] (WP) that were presented and discussed with the audience.

Workpackage 2 : Orphanet nomenclature and classification of RD update and maintenance

The audience was reminded that Orphanet maintains a comprehensive RD nomenclature system aligned with several non-RD specific terminology resources, allowing for semantic interoperability in a context of heterogeneity of coding systems used in different countries. The nomenclature is also annotated with curated information (see WP3).

ERNs are end-users of the Orphanet nomenclature, but also active contributors to its development, since they concentrate clinical and scientific expertise as knowledge evolves. For this reason, a methodology was established to address ERNs' needs in terms of revision of the nomenclature during the OrphaNetwork Direct Grant (2018-2021), based on the collaboration with a number of ERNs. With this new grant, the Orphanet Nomenclature team increases its capacity to work with ERNs on improving the Orphanet nomenclature, upon ERNs' requests or on Orphanet request (for instance, linked to an upcoming paper publication).

The priorisation of ERNs requests was also explained. Obviously many factors will contribute to this exercice, the major would be wether the coding activity is blocked until an action is done on the nomenclature. For each request, the complexity and scale will be analysed and a weight (score) will be assigned to it so as to allow for a transparent planification in regards to the available staff resources in the team.

[1] Within WP1 are to be found all the Administative and project coordinating tasks.

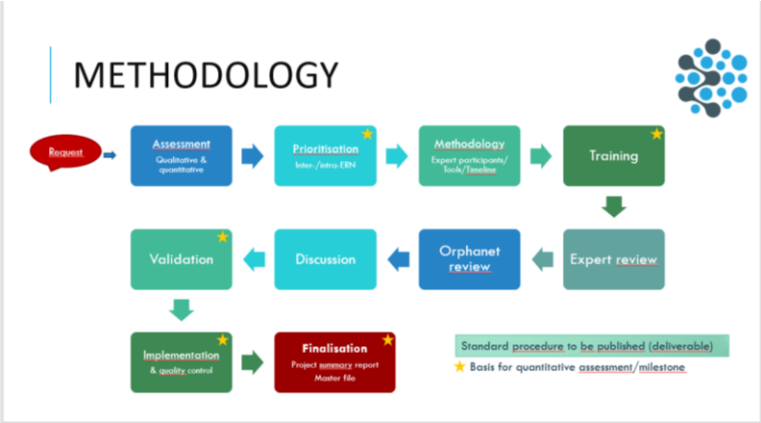

Fig.2 Methodology of Collaboration projects for ERNs Nomenclature requests

The general methodology of the collaboration projects for ERNs Nomenclature requests was presented (fig.2). This methodology has been progressively established since 2017 and draws directly from past and ongoing experiences with ERNs. While it outlines a general structure and requirements for the collaboration, it is flexible enough to adapt to the specific challenges and scale of each project.

As it emerged form the discussion, one of the essential steps is the training of the experts on the Orphanet nomenclature standards and update process which is key in ensuring a constructive and efficient dialog. Thus the final project summary result is a consensus and become fully expoitable by the users. A detailed procedure detailing this methodology will be made available online in June 2022.

A state of play of the Collaboration projects for ERNs Nomenclature requests was presented as below.

ERN	Diseases group	Status
ERN-EYE	Rare ophtalmic diseases (first Orphanet-ERN collaboration)	Finalized
ERKNet	Global revision with focus on Thrombotic microangiopathies, Glomerular diseases, and Rare causes of hypertension	Finalized
	Renal tubular diseases & ciliopathies	Ongoing
ERN-SKIN	Epidermolysis bullosas	Finalized
eUROGEN	Anorectal malformations	Finalized
ERN-BOND	Primary skeletal dysplasias & Dysostoses (in collaboration with the ISDS)	Ongoing
VASCERN	Primary lymphedema	Finalized
	Vascular anomalies	Ongoing
ERN CRANIO	Cranial malformations	Ongoing
RARE-LIVER	Vascular liver diseases	Finalized
MetabERN	Inborn errors of metabolism	Initiated
EpiCARE	Rare epilepsies	Initiated
ENDO-ERN	Pseudohypoparathyroidism (PTH/PTHrp signaling pathway)	Ongoing
ITHACA	Intellectual disabilities	Ongoing

Fig.3 State of Play of Collaboration projects for ERNs Nomenclature requests

The conservative objective for this first pilot year considering that the team is being built and trained is a cumulative projects' score of 4.5(projects being weighted from 0.5 for the simpler ones to 2 for the more complex ones). Also to assess the impact of this activity we will determine the number (%) of finalised ERN collaboration projects, after which the related ERNs/ERN thematic group(s) have expressed their intention to effectively implement and use the revised ORPHAcodes in their activities including, for instance, monitoring, coding activities, publications, registries, etc. All this information will be available in a global report on completed and ongoing ERN collaborations which is planned for delivery in December 2022.

During the discussion it was clarified that ERNs could submit their requests at any time and these will be prioritized according to the methodology presented.

Workpackage 3 : Develop Orphanet Knowledge and information base around RD in collaboration with ERNs

The audience was reminded that the Orphanet RD nomenclature is also annotated with curated information on genes, epidemiological data, phenotypic traits, and functional consequences. This unique body of knowledge, completed by textual information, is delivered in both computable and human-readable formats.

The specific objective of this WP is to develop and continuously maintain the data associated with RD, and in particular genetic data and the alignments of ORPHAcodes with the main terminologies in use in health information systems and registries (including ICD-10 & 11, SNOMED CT and OMIM); and to create and update the textual information associated with RD; to ultimately ensure better comparability and interoperability in the RD domain and to provide up-to-date information on RD validated by ERN RD experts, as a mean to aid accurate assignment of ORPHAcodes.

Thus, WP2 and WP3 are closely interrelated since updates performed on the Orphanet Nomenclature naturally lead to quality control and updates on associated information (texts, genes, alignments), and vice-versa.

The audience was reminded of the methodologies associated with these tasks and they were provided with the relevant links to the published procedures (here).

Also the ongoing collaborations linked to these tasks were presented :

- An Intellectual disabilities gene curation in being carried out in collaboration with ERN ITHACA. The aim of this collaboration is to avoid duplication of effort and to be able to go from one database to the other as they contain complementary information.
- Mappings with ICD-11 will be released in July 2022, in the frame of the participation of Inserm, US14-Orphanet to the French WHO collaborating centre. Also the overall strategy is to be able to incorporate new RD terms in ICD11 and to insert backlinks from ICD11 to Orphanet so that all the up-to-date RD knowledge available in Orphanet is also accessible to ICD 11 users.
- Mappings with SNOMED CT are produced in the frame of the collaboration agreement in place between Orphanet and SNOMED International. SNOMED will release this mapping file in a machine-readable format for its subscribers, while Orphanet will make freely available the human readable format of this file. Release notes will also be provided to facilitate exploitation of this mapping file.
- Regarding the Orphanet textual information there are several ongoing structured collaborations with ERKNet ; ITHACA ; EpiCARE ; ERN-Skin and MetabERN. As well as punctual collaborations have been carried on with Endo-ERN, EURO-NMD, EuroBloodNet, ERN RARE-LIVER, ERN-LUNG, ERN-Skin, eUROGEN, ERNICA, ERN-RND, ERN-EYE.

The audience was reminded that further collaborations are open for discussion, especially in the frame of the Nomenclature revision in harmonization with WP2.

Workpackage 4 : Develop national Orphanet nomenclature hubs

The objective of this WP, co-led by the Orphanet Germany team and the Orphanet Coordinating team, is to ensure support for local implementation of ORPHAcodes in national HCPs hosting ERNs and national HCPs linked to ERNs by establishing Orphanet national nomenclature support hubs. In this pilot year, 13 Orphanet teams will participate (AT, BE, CZ, DE , FI, ES, IT, NL, NO, PL, PT, SE and SI).

In order to ensure that local support is provided consistently across participating countries, a national hubs network coordination is being set up. Coordination activities consist of providing material and scientific and technical back-up, ensuring same service quality level in each country. Also the coordination will ensure that the network mutualizes the efforts as well as the lessons learned, shares all the relevant information, approaches common stakeholders in a coordinated manner, and streamlines the needs expressed by local ERN hubs back to the Orphanet nomenclature coordinating team regarding ORPHAcodes.

As a kick-off of its activity a questionnaire to assess the situation and needs of end users in regards to ORPHAcodes implementation was prepared.

At the local level, Orphanet national teams will interact with HCPs' managers and national decision-makers (e.g. Ministry of Health, Directorate of Health, hospital managers, etc.) in order to promote the nomenclature use and assess their needs. National hubs will also organise the capacity building at the national level, by delivering trainings in national language for example. They will act as helpdesks in local languages (see WP5 for details on the tool) in order to provide support to ensure the Nomenclature correct implementation and use, based on RD-CODE guidelines and, when appropriate, on good practice coding guidelines produced by ERNs; and to provide prompt and reactive guidance for implementing and using the nomenclature and classification for statistical aggregation analysis for coded data. Helpdesks will also provide feedback to the coordination level both on the supporting tools and on ORPHAcodes improvement national needs.

To kick-off this task, each National hub will deliver its yearly action plan.

Ultimately, the network of hubs will serve as a consensus building network for questions and problems arising with the implementation of the ORPHAcodes and related coding questions. Thus the final delivery of this WP will consists in a report on « lesson learned » . This report will contain all questions on coding and on implementation [Results, hurdles, improvements…], that have arisen over the year in the network hubs and standardised, agreed answers will be made available.

During the discussion it was clarified that all ERNs will be included , also those not represented in the 13 pilot countries.

Also the importance of not to extra-burden the coders with avoidable work was stressed : the Nomenclature pack dellivered every July and in particular the Master file where ORPHAcodes are mapped to the relevant ICD10 codes was cited as a succesful example of material facilitating the task. Also in Norway, a shortlist of useful ORPHAcodes by group of diseases was considered very useful by the users.

Finally, the importance of incentive for ORPHAcoding was stressed. It is a mandatory data element for the third version of the ePatient Summary as well as in ERNs registries as part of the Common Data Elements (CDE). In some countries it is becoming mandatory by law to register ORPHAcodes in health records. The audience was reminded that material for disseminating the benefits of ORPHAcoding targeted to different public was produced in the frame of the RD-CODE project and it is available online (www.rd-code.eu).

Workpackage 5 : Support to the EC in its ERN strategy including dedicated IT systems

This workpackage revolves around the two specific objectives below :

a. To put in place the necessary mechanisms to deliver and update the Orphanet nomenclature and knowledge base (as reference body of data) in the European Commission Information system for ERNs.

The overall objective of the different developments is to :

- Improve the curation & implementation of RD nomenclature throught a « feedback & issues tracking system » at the National hub level, this will increase the transparence and tracking of all requests.
- Help the implementation of codes throught technical tooling and documentations (APIs) for the users in general, developped according to users needs.
- Ensure the proper integration of Orphanet's Knowledge base datasets to EC IT systems and provide services to the ERNs community in a coordinated and users-oriented manner.

A ticketing system is already in place to support the workflow processing needed by WP4 activities; access management is being defined and the system should be finalized in one-month time.

Regarding the "Data exchange tool development" according to specifications to address EC IT system's needs, 2 meetings have already been held to clarify the needs. What can be done is to develop the exchange workflow and tools (i.e. APIs, FAIR data point, dedicated web services and databases) to feed the EC IT system for ERNs, including CPMS, with the necessary Orphanet content. It could not be limited to the nomenclature, classifications and alignments, but could also include disease-phenotype relationships (using HPO), gene-disease relationships, and other data necessary to support ERNs in their clinical work by facilitating diagnostic and care decisions about RD patients. By June functional and technical specifications will be provided for data exchange according to discussions. By October a first API release will be delivered, to be tested in November for a final delivery in December.

b. To analyse and produce reports on RD coverage, identifying overlaps and gaps amongst ERNs in order to support evidence-based decisions in the context of ERN coordination, Board of Member States (BoMS) and European Commission activities.

The project aims to cover the following analysis :

- Coverage analysis (within and across ERNs)
- Complementarities (overlaps) between ERNs/HCPs
- Insufficient disease coverage (just one HCP offering expertise for certain diseases or groups of diseases, or one HCP for one age group only)
- Complete gaps (lack of expertise for certain diseases or groups of diseases at all).
- Free room for other topics of help for the coordination of ERNs development

The methodology to achieve this was explained :

- Regarding data sources :
  - Network application forms (2016), which are only full members and paper based.
  - Network/HCP application forms (2019) which consist of electronic data
  - Data from the ERNs monitoring process (Full members AND associated National centres electronic data).
  - Targeted surveys to HCPs

It was pointed out that despite the fact that there are many data sources, these are very diverse in terms of data granularity and the first two do not include Associated National Centres. Also regarding the monitoring data, it has been observed that there is a wide range of diverse granularity in terms of data collected amongst the different ERNs.

The suggested working concept, considering the different data sources and the diverse data granularity will be to :

- make available a general analysis based on Network and HCPs application
- complement this with the development of a technical framework for a future more detailed and more robust analysis based on the monitoring data (done with a pilot ERN). This will allow to compare reports obtained from low granularity data to those obtained with more granular data source.
- For insufficent coverage analysis target surveys will be adressed to HCPs.

The general methodology has already been presented to the EC in January and to the BoMS and ERN-Coordinating Group meeting in February.
The suggested working concept will be further discussed during the April's meetings of the BoMS and ERN-Coordinating Group meeting and during the next Monitoring Group meeting.

Governance and Boards
The governance of the project is as follows :

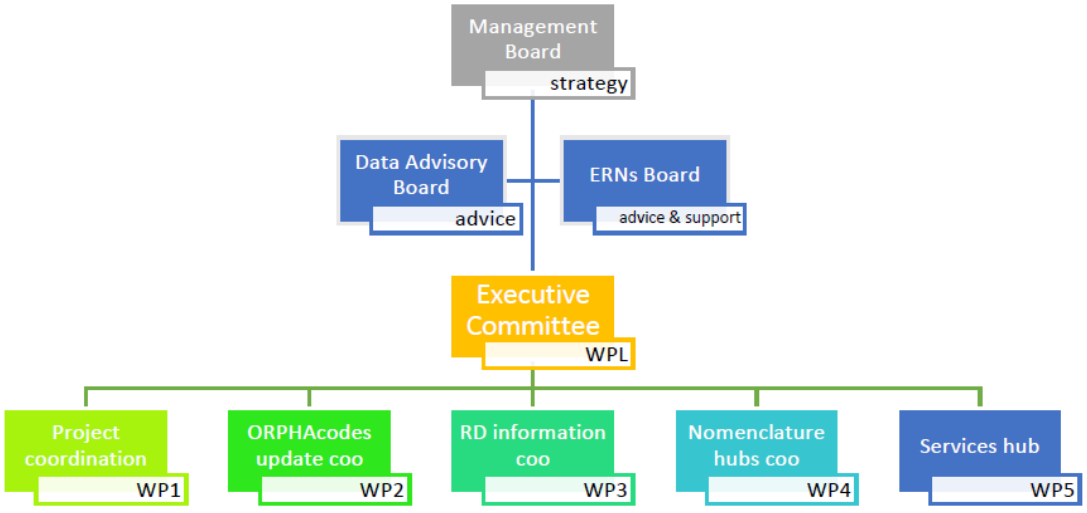

Fig.4 OD4RD Governance

The Orphanet Management Board will be the strategic Board for this project and an Executive commitee will be in charge of monitoring the execution of the project.

In addition two advisory boards will be set up :

The Data Advisory Board (DAB), will be in charge of peer-reviewing the project, in particular of ensuring alignment of this project with the main European data initiatives as well as with ERNs national implementation strategies. The DAB will issue strategic comments and recommendations to the

Executive Committee. It will be composed of all Health data related initiatives, non neceseraly specific to RDs.

The ERNs Board will be in charge of providing advice on the strategy addressing the ORPHAcodification and implementation needs, and of facilitating the collaboration between ERN groups and Orphanet team in improving the Orphanet nomenclature and the production of RD information. The ERN Board will act as the forum in which any new Orphanet-ERNs collaboration will be discussed. This Board will be composed of all ERNs coordinators that have accepted to participate in the project.

During the discussion it emerged that in order to avoid the multiplication of meetings for ERNs coordinators, the meeting of this Board could be merged with an already existing meeting.

Conclusion

The OD4RD project aims at :

- ✓ Increasing the visibility of RD in Health Information Systems by achieving ORPHAcodes real implementation in hospitals
- ✓ Increase the quality of data generated about RD patients by disseminating good ORPHAcodes coding practice
- ✓ Empower ERNs, hospitals and the EC's understanding on RD-related activities by providing means to generate accurate data for exploitation and analysis
- ✓ Contribute to the EU health data strategy by connecting the dots with structuring initiatives around EHR formats and health data spaces (EHDS)
    - For primary use: better diagnosis and care of RD patients, assessment of current practices and results against gold standards of care
    - For secondary use by informing policy decision-making and research