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Final report on ERN- Orphanet nomenclature and classification collaborations
Report

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Content summary

Introduction

The main scope of OD4RD2 Work Package 2 (WP2) is to update the Orphanet Nomenclature and Classification of Rare Diseases (RD) in collaboration with European Reference Networks (ERNs), to reflect the evolution of scientific and clinical knowledge and provide the most up-to-date possible terminology to code RD patients. The methodology used for the collaborations to revise the Orphanet nomenclature and classification of RD followed the Procedural document: Collaboration between Orphanet and ERNs (link).
This final report will provide an overview of completed and ongoing collaborations with ERNs from April 2023 to March 2026. For every collaboration the following elements will be specified:

- The ERN involved and the composition of the working group;
- The group of diseases covered and the scope of the revision;
- A brief overview of the rationale and guiding principles of the collaboration;
- For finalized collaborations: the list of clinical entities that have been treated/revised (Annex 1, OD4RD2_ERN_ORPHAcodes_collab);
- For ongoing collaborations: an estimation of how many groups/clinical entities will be revised during the follow-up project OD4RD3.

A final chapter will assess the lessons learned from the collaboration experiences. A brief conclusion will also summarize the analysis of the feedback from the satisfaction surveys sent at the end of each finalized collaboration. Annex 1 includes the lists of clinical entities revised by activity.
In addition, past and current collaborations with ERNs are regularly published in the OD4RD GitHub for transparency.

Methodology

A collaboration project is usually initiated when Orphanet receives a request from an ERN to update the nomenclature and classification of a certain group of disorders. A collaboration can also be initiated by Orphanet if, during internal quality control, the necessity for an update of the classification is identified. In this case Orphanet contacts the ERN(s) to ask experts' availability to begin a revision process.
Generally speaking, any collaboration project established for the revision of a group of disorders involves the following roles:

- **Experts**: medical doctors contributing their knowledge and validating the scientific accuracy of the information provided by the Orphanet nomenclature; when updates are proposed, they help determine if these will appropriately answer the needs of clinicians dealing with patients suspected/confirmed to have a RD.
- **Orphanet**: transposes the clinical knowledge provided by the experts and the scientific literature into a standardized terminological structure; prevents the introduction of inter- and intra-classification inconsistencies; anticipates any issue that may arise as a result of the proposed updates regarding disease coding/data sharing, and in such case, finds and suggests alternatives.

Collaborations usually follow these main steps:

- Assessment of the work necessary:

  (i) the type of revision needed: only at the diagnosis level (ORPHAcodes missing, outdated, wrongly named, or misclassified); only at the structural level (classification to reorganize, subgroups missing or outdated); or both;

  (ii) a quantitative assessment: how many clinical entities need to be analyzed, and the level of complexity of the issues at hand. A « weight » value is attributed to each project according to its scale and complexity among these values: 0.5 - 1 - 1.5 - 2 (from smallest size/lowest complexity to larger size/highest complexity).

- Prioritization between different ERNs, or between different thematic groups within the same ERN, guided by the above-mentioned assessment and the criticality of the revision for ERN activities (e.g. registries, publications, etc.).
- Definition of the methodology: experts to be involved, working group(s) to be created, tools for the revision, timeline.
- Training of the involved experts on the Orphanet nomenclature standards and update process.
- Review of the nomenclature by ERN experts.
- Review by Orphanet of the updates proposed by experts, to ensure compliance with the nomenclature standards and state-of-the-art publications.
- Discussion to clarify scientific issues, solve problems, find alternatives, and reach a consensus.
- Validation of actions to be implemented by Orphanet and implementation of all validated decisions in the Orphanet database.
- Finalization of the project: a project summary report and a master file listing all clinical entities discussed (with the associated validated actions) are sent to the ERN representatives.
- Possible validation of the disease definition for each newly included entity by ERN experts.
- Evaluation of satisfaction with the revision of the Orphanet classification through a short survey sent to ERN experts once the project is completed.

This methodology has been progressively established since 2017 and draws directly from past and ongoing experiences with ERNs. In particular, the last two steps were introduced only recently as part of our ongoing effort to improve the collaboration process. While it outlines a general structure and requirements for the collaboration, this methodology, formalized and published on the Orphanet website (link), is flexible enough to adapt to the specific challenges and scale of each project.

Finalized ERN collaborations

1. ERN-EuroBloodNet: Rare paediatric thrombosis

The goal of this low complexity collaboration (weight = 0.5) was to evaluate the inclusion in the nomenclature of 5 clinical entities, without changes to the classification structure, based on a request from ERN-EuroBloodNet experts.

Based on coding needs in their clinical practice, the experts provided a Word document with a brief description of the entities and recommended several references for the documentation of the requests. After discussion in the Orphanet medical and scientific committee, some issues required the input of the epidemiology manager to evaluate the rarity. The final decision was to create 2 of the 5 requested ORPHAcodes. The 3 remaining requests did not fulfil the Orphanet's definition of disease. Indeed, rejected requests were intended to represent manifestations of diseases but not to code the main diagnosis of the patient. Complementing ORPHAcodes with different terminologies such as HPO codes was recommended in these cases.

2. MetabERN: Porphyria

The goal of this low complexity collaboration (weight = 0.5) was to revise the Porphyria group, ORPHA:657, and update its classification based on physiopathology following the scientific literature and MetabERN expert's guidance. This revision resulted in a new classification axis based on the physiopathology, and as a result, several changes were applied, including: the creation of 3 new groups of disorders and one disorder, and the obsolescence of 'Chronic hepatic porphyria' ORPHA: 95161, to be referred to the new created group 'Hepatic porphyria', ORPHA:659694.

3. ERN-EYE: Isolated optic neuritis

The goal of this low complexity collaboration (weight = 0.5) was to revise the group of disorders 'Isolated optic neuritis', ORPHA:499096, following a consensus paper transmitted by ERN-EYE medical experts (PMID: 36179757). Some entities already existed in Orphanet and others required an update of the terminology. As a result of the revision process, the classification level and nomenclature of one entity was modified (ORPHA:499085 from disorder to subtype and located under 'Isolated optic neuritis', ORPHA:499096)2 entities were obsoleted since experts confirmed their only difference was the positivity of a specific autoantibody with no difference in terms of clinical picture. For these cases, complementing with HPO terms to specify the autoantibody of interest can be a solution for a more specific diagnosis. Alsoto better reflect the current clinical practice, 2 new ORPHAcodes were created to represent the solitary and recurrent clinical subtypes of 'Isolated optic neuritis', ORPHA:499096.

4. ERN SKIN: Ectodermal dysplasia syndrome (step 1)

In 2025, ERN SKIN experts contacted Orphanet requesting the evaluation of the inclusion of six clinical entities in the group of 'Ectodermal dysplasia syndrome', ORPHA:79373. This low complexity projet (weight = 0.5) led to the creation of 4 new ORPHAcodes for disorders to complete the representation of the ectodermal dysplasias in the nomenclature. the 2 remaining asked creations were not validated since they referred to existing ORPHAcodes, However, their associated genetic information was updated. This collaboration evidenced the need for a deep revision of the entire group to be aligned to the current medical practice, and therefore, a step 2-project was programed to address nomenclature update and classification completeness and rearrangement (see page 16).

5. ERN EURO-NMD: Acquired skeletal muscle disease

The goal of this low complexity collaboration (weight = 0.5) was to revise the group of 'Acquired skeletal muscle disease', ORPHA:206638, and to specifically complete the group 'Idiopathic inflammatory myopathy', ORPHA:98482. The revision process ended with the creation of an ORPHAcode for 'Immune checkpoint inhibitor-induced myositis', ORPHA:714829as a disorder.

6. ERN EURO-NMD: Neuromuscular junction disorders

The goal of this medium-low complexity collaboration (weight = 1) was to complete the 'Neuromuscular junction disease' group, ORPHA: 98491. This work involved the creation of 16 new subtypes of 'Congenital myasthenic syndrome', ORPHA:590. The addition of greater granularity is intended to facilitate diagnosis and improve targeted treatment. The genes related to each new entity were also linked in the context of this revision.

7. ERN PaedCan/SIOPE: High-grade gliomas

The revision of high-grade gliomas with expert input from the High-Grade Glioma (HGG) working group, was defined as a medium-low complexity collaboration (weight = 1) within a broader revision of paediatric Central Nervous System (CNS) neoplasms.

Part of the project involved a substantial reorganisation of the structure of the Orphanet pediatric tumor classification (available so far, only for internal use, and not published). As a result of this revision, the group 'Pediatric gliomas, glioneuronal tumors, and neuronal tumors' ORPHA:715717, was created to organise the gliomas in the 'Orphanet classification of pediatric tumors' as well in the 'Orphanet classification of rare neoplastic disease'. Underneath ORPHA:715717, two other groups were created: 'Pediatric circumscribed astrocytic gliomas', ORPHA:715713, and 'Pediatric-type diffuse high-grade gliomas', ORPHA:715707, to organise circumscribed astrocytic gliomas and diffuse high-grade gliomas, respectively.

The revision highlighted the need of several creations in order to represent the diffuse high-grade gliomas. Consequently, 3 groups of disorders, 5 disorders, and 4 subtypes of disorder have been included in the Orphanet nomenclature, adding the necessary granularity to better reflect different prognosis and therapeutic options.. Moreover, 'Pediatric cancer of neuroepithelial tissue', ORPHA: 602695 was obsoleted because the entity does not reflect the current clinical practice; and 'Diffuse intrinsic pontine glioma', ORPHA: 497188 deprecated since it was substantial overlap with one of the created ORPHAcodes for 'Diffuse Midline Glioma, H3 K27-altered'. Therefore, ORPHA: 497188 was moved towards the new disorder, which definition will mention that this new code also encompasses the pontine region.

8. ERN EURO-NMD: Distal myopathy

The goal of this medium-low complexity collaboration (weight = 1) was to revise and complete the group of 'Distal myopathy', ORPHA:599. This work involved the creation of a new group of distal myopathies, 'X-linked distal myopathy' ORPHA: 700143, to accommodate the recently identified disorder 'SMPX-related distal myopathy', ORPHA:700163. The previous axis of classification of the distal myopathies was respected and follows the mode of inheritance of the causal genes. Also in the context of this revision, the position in the classification of 'BAG3-related myofrillar myopathy', ORPHA:199340, and 'Autosomal dominant distal axonal motor neuropathy-myofibrillar myopathy syndrome', ORPHA:476093, was changed, and are now included to the 'Distal myopathy', ORPHA:599 group. Converserly, and 'Asymptomatic hyperCKemia-myalgia-rhabdomyolysis syndrome', ORPHA:689021 has been removed from the group because it is not considered as a distal myopathy in current practice. 'Oculopharyngodistal myopathy', ORPHA:98897 has been removed from 'Autosomal recessive distal myopathy' group because this disorder is autosomal dominant. The genetic information was also reviewed and updated for each entity of this group.

9. ERN GENTURIS: Intestinal polyposis syndrome

The goal of this medium-low complexity collaboration (weight = 1) was the update of the group of 'Intestinal polyposis syndrome', ORPHA: 104010 with the help of the ERN GENTURIS experts. This revision ended up with the deprecation of 'Gardner syndrome' ORPHA:79665, and 'Turcot syndrome with polyposis', ORPHA: 99818 currently recognized as clinical presentations within 'Familial adenomatous polyposis', ORPHA:733. 'Oligodontia-cancer predisposition syndrome' ORPHA:300576, initially described as an independent diagnosis, was deprecated and moved to 'AXIN2-related attenuated familial adenomatous', ORPHA:401911. 'APC-related attenuated familial adenomatous polyposis', ORPHA:247806 was obsoleted since the entity was an exact duplicate of another Orphanet entity ('Attenuated familial adenomatous polyposis', ORPHA:220460).

The level in the classification of 6 ORPHAcodes was adjusted to better reflect the phenotype. As an example, '5q22.2 microdeletion syndrome', ORPHA: 261584, have changed the classification level from subtype of disorder to a disorder, while retaining it within the 'Intestinal polyposis syndrome' group. Also, 5 entities (ORPHA:247798, ORPHA:447877, ORPHA:454840, ORPHA:480536, and ORPHA:401911) previously classified as subtypes of 'Attenuated familial adenomatous polyposis', ORPHA:220460 were revised and no longer considered as subtypes but as independent disorder clinical entities based on their differences in genetic etiology, clinical presentation, and cancer risk.

10. ERN TransplantChild: Rare disorder potentially indicated for transplant

This collaboration was intended to revise the classification of the group of disorders in relation to kidney, liver, lung, heart, intestine and hematopoietic stem cell transplantation. The project was initiated by Orphanet following an internal quality control that revealed several diseases classified as 'Rare disorder potentially indicated for transplantation', ORPHA:506207, even if their risk of transplantation is very low or inexistent. The final aim of the collaboration is to exclude entities that

do not have an indication for transplantation from the 'Rare disorder potentially indicated for transplantation', ORPHA:506207 classification, and to include entities present in Orphanet that are potentially missing in the transplant classification, following the expert's guidance. No creation of codes was foreseen in this project.

Due to the differences among each working group and to the number of entities to be revised, the original collaboration was split up into 6 parallel revisions according to medical specialty. The collaboration began with the assemblage of the working groups made up of experts from the 6 organ-related domains. The Orphanet manager prepared and shared a file containing the clinical entities related to each organ to each working group. The clinicians evaluated the ORPHAcodes for the clinical entities on the lists, deciding whether or not to include them in the classification based on their risk of transplantation. They were also asked to add missing entities to the Excel file.

Once the files revised, a virtual meeting was scheduled for all the working groups to decide on actions for a few cases with contradictory expert recommendations. Following these final discussions, Orphanet prepared a corrected list to be implemented in the database.

The revision of the following groups were completed and implemented to date:

- *Rare disorder potentially indicated for liver transplant, ORPHA:506210* (medium-low complexity, weight = 1)

As a result of this revision process, 53 clinical entities (30 disorders and 23 subtypes of disorders) have been removed from this group, 142 kept (1 groups of disorders, 58 disorders and 27 subtypes of disorders), and 4 disorders previously not included in this group were added.

- *Rare disorder potentially indicated for kidney transplant, ORPHA:506213* (medium-high complexity, weight = 1.5)

As a result of this revision process, 197 clinical entities (16 groups of disorders, 127 disorders and 54 subtypes of disorders) have been removed from this group, 247 kept (8 groups of disorders, 153 disorders and 86 subtypes of disorder), and 1 disorder previously not included in this group was added.

Rare disorder potentially indicated for lung transplant, ORPHA:506222 (medium-low complexity, weight = 1)

As a result of this revision process, 49 clinical entities (35 disorders and 14 subtypes of disorder) have been removed from this group, 50 keptpreviously not included in this list were added.

- *Rare disorder potentially indicated for heart transplant, ORPHA:506225* (medium-low complexity, weight = 1)

As a result of this revision process, 74 clinical entities (43 disorders and 31 subtypes of disorders) have been removed from this group, 69 (58 disorders and 11 subtypes of disorders) kept, and 2 disorders previously not included in this list were added'*Rare disorder potentially indicated for HSC transplant, ORPHA:506219'* (medium-high complexity, weight = 1.5)

As a result of this revision process, 81 clinical entities (56 disorders and 25 subtypes of disorders) have been removed from this group, and 396 (315 disorders and 81 subtypes of disorders) were kept.

Only the revision of 'Rare disorder potentially indicated for bowel transplant, ORPHA:506216' is pending (medium-low complexity, weight =1). This is because the working group aimed at revising the clinical entities has not yet been formed due to lack of sufficient experts. The project is scheduled for re-launch in 2026, following the identification of the relevant experts with the assistance of the ERN TransplantChild project manager.

11. ERN ERNICA: Rare inflammatory bowel disease

The goal of this medium-high complexity collaboration (weight = 1.5) was to update the classification of 'Rare monogenic inflammatory bowel disease', ORPHA:104012. The revision followed the latest integrated taxonomy for monogenic inflammatory bowel disease publication (PMID: 34780721, 2022).

The revision resulted in 114 classification changes including changes of the position of groups of disorders, disorders and subtypes of disorders within the group, and outside the revised group. One group of disorders and 1 disorder were obsoleted to align with the current clinical practice. Moreover, 6 disorders and 8 groups of disorders were created to allocate the existing and the new ORPHAcodes in the group 'Rare monogenic inflammatory bowel disease', ORPHA:104012

12. ERN EuroBloodNet: Hemoglobinopathies

The goal of this medium-high complexity weight collaboration (weight = 1.5) was to restructure part of the Orphanet classification of 'Hemoglobinopathies', ORPHA:68364, with the support of ERN EuroBloodNet experts, to better reflect the clinical and phenotypic characteristics of these hematological disorders. Specifically, this work focused on the representation and coding of different forms of thalassemia and rare combined hemoglobinopathies. The revision highlighted the absence of several disorder and subtype ORPHAcodes, especially within sickle cell disease. A major gap concerned the representation of combined hemoglobinopathies. To ensure adequate coverage of patients with these rare hemoglobinopathies, 'Sickle cell disease due to hemoglobin S and a non-S/non-C hemoglobin variant', ORPHA:700085, was created. This disorder covers patients presenting rare combinations involving Hemoglobin S and another variant that is neither HbS nor HbC. Under this disorder, five subtypes were added, four of which cover the more frequent combinations, along with 'Sickle cell S-other specified hemoglobin variant disease', ORPHA:700107, which can be used for any other rare combination.

Also, the clinical entities were reorganized within the classification with some changes of the classification level to better fit coding purposes. As an illustrative example of this restructuration, a group 'Thalassemia' ORPHA:707786, was created to bring together disorders and groups representing distinct forms of thalassemia.

Some experts' requests could not be implemented since they did not meet Orphanet criteria, for example "Symptomatic sickle cell trait," which is not rare in Europe and therefore cannot be included in the Orphanet nomenclature.

13. ERN-ITHACA + eUROGEN: Spina Bifida and other spinal Dysraphisms

The goal of this high complexity collaboration (weight = 2) was to revise the nomenclature and classification structure of the group 'Spina bifida and other spinal dysraphisms', ORPHA:823, and update the group according to the clinical practice and expert's advice. This work was performed in collaboration with inter-ERN Working Group "Spina Bifida and other spinal Dysraphisms" (SBoD) constituted by experts from ERN ITHACA and ERN eUROGEN.

The revision of the spina bifida group was guided by the following elements:

- The group should include all the other dysraphisms described and not just restricted to the concept of spina bidifa.
- The new classification is based on the medical practice and the diagnostic process.
- The revision is based on dividing the disorders in 3 main classification groups of disorders: 'Closed spinal dysraphism', 'Open spinal dysraphisms', and 'Spinal dysraphism with a posterior meningocele'.

The revision of the classification was presented during a trans-ERN meeting in June 2023 for final validation in presence of all experts. The experts contribute also to the validation of the medical texts in French and English. The new classification with the new and updated ORPHAcodes, and definitions was implemented for the Nomenclature pack 2023 and was published in 2025 (PMID: 40629359).

14. ERN BOND/ISDS: Primary bone dysplasia and Dysostosis (step1)

The goal of this high complexity collaboration (weight = 2) was to update the classification of Rare bone disease, and in particular the 'Primary bone dysplasia', ORPHA: 364526 and 'Dysostosis', OPRHA:364559 groups in collaboration with ERN BOND and the International Skeletal Dysplasia Society (ISDS). The revision was guided by experts' feedback and based on the Nosology and classification of genetic skeletal disorders published by the ISDS (2019 edition, PMID: 31633310 and 2023 edition, PMID: 36779427).

Due to the high number of entities to be revised and of changes to be applied, concerning both the nomenclature and structure of the classification, the collaboration was divided in 2 steps: a first phase focused on the confirmation of the completeness of the Orphanet classification and correctness of the terminology of the nomenclature as compared to the ISDS Nosology. A second phase concerns the classification structure.

The first phase involved 38 experts from ERN BOND/ISDS, and consisted in reviewing the clinical manifestations considered as 'Primary bone dysplasia' and 'Dysostosis', and their representation of the aforementioned groups in the Orphanet classification. Orphanet compared the content of the Orphanet classification (containing more than 250 clinical entities) with the list of genetic skeletal disorders considered by ISDS. This comparison revealed discrepancies between the two classifications in terms of representation and terminology. As a result, the collaboration led to the following changes: inclusion of 18 new clinical entities (1 group of disorders, 16 disorders, and 1 subtype of disorder), the deprecation of 13 disorders, the obsolescence of 21 ORPHAcodes (1 group of disorders, 16 disorders, and 4 subtypes of disorder) and one inactivation because non-rare in EU ('Buschke-Ollendorff syndrome', ORPHA:1306). Twenty disorders have been identified as historical entities, and 31 modifications concerning nomenclature or classification changes have been applied to 18ORPHAcodes, concerning groups of the disorder (2), disorders (44) and subtypes of the disorder (1).

The second phase, which concerns the revision of the classification structure, was not addressed during the course of this project and will be the subject of a future independent project (see page 18).

15. VASCERN: Rare vascular anomaly

The goal of this collaboration was to revise the group of 'Rare vascular anomaly', ORPHA:68419 in the classification of Rare circulatory diseases, ORPHA:98028. Due to the number of entities and changes to be applied, concerning both the nomenclature and structure of the classification, the collaboration was divided in 2 independent projects. The first one focused on the vascular tumors, and the second one comprises the revision of the simple and complex vascular malformations. Each project was a high complexity collaboration (weight = 2).

In May 2023, Orphanet started working with experts from the VASCERN-Vascular anomalies (VASCA) working group to revise the classification of the group 'Rare vascular tumors', ORPHA: 211237. This revision followed the International Society for the Study of Vascular Anomalies (ISSVA) classification from 2018 and the WHO Classification of Tumors. This project resulted in the inclusion of 18 clinical entities (4 groups of disorders and 14 disorders) in the Orphanet nomenclature, and in a new axis of classification where all the rare vascular tumors entities are reorganized in three newly created groups, according to their behavior as 'benign', 'borderline', or 'malignant'. The changes were implemented before the release of the Nomenclature pack 2024 providing timely access for coders to the revised group now aligned with the ISSVA classification and the current clinical practice.

At the end of this project, Orphanet and VASCA experts worked on the revision of the group of the 'Rare vascular malformation', ORPHA: 723256. The previous classification presented the malformations grouped as 'simple' or 'complex'. The new ISSVA classification considers instead the individual characteristics of each vascular anomaly, grouping together lesions with similar key features. The axes of the new Orphanet classification follows the ISSVA classification, and the clinical entities are reorganized according to the type of flow, body location and/or type of regional distribution (unique or multiple). Moreover, the revision process identified missing clinical entities and led to the inclusion of 73 ORPHAcodes in the nomenclature (24 groups of disorder, and 49 disorders). Fifteen ORPHAcodes were inactivated (1 deprecated, 14 obsoleted); 17 ORPHAcodes followed classification changes and 11 ORPHAcodes needed nomenclature updates.

16. ERN EpiCARE: Rare epilepsy syndromes

The goal of this high complexity collaboration (weight = 2) was to revise the nomenclature and classification of the group of 'Epilepsy syndrome', ORPHA: 166463. The work was guided by the recent consensus papers (PMID: 35490361, 35503712, 3550371, 35503717, 35503725, among others) of the Epileptic Syndromes of the International League Against Epilepsy (ILAE) and the ERN EpiCARE expert advice. In parallel, ERN EpiCARE has also been collaborating with Orphanet's edition team on writing the summaries and disease definitions.

Following the ILAE position papers, the group of the Orphanet 'Epilepsy syndromes', ORPHA: 166463 is grouped by age of onset, and the clinical entities distributed into (1) syndromes with onset in neonates and infants (up to age two years), (2) syndromes that onset in childhood, and (3) syndromes that may begin at a variable age (meaning in both pediatric and adult patients). The entities present under the group of 'Adolescent-onset epilepsy syndrome', ORPHA:98260 from the past Orphanet classification, have been distributed into the current groups or have been Inactivated when applicable, according to the evolution of knowledge.

The clinical entities belonging to the group of 'Variable age-onset epilepsy syndrome', were reviewed and validated by experts with the exception of the group of 'Progressive myoclonic epilepsy', (PME) ORPHA:98261. PME includes clinical conditions under the umbrella of epilepsy and metabolic disorders. For this reason, a future collaboration will be proposed to review this group with the help of experts from ERN EpiCARE and MetabERN ensuring full expertise coverage.

This revision has introduced extensive updates to the nomenclature to reflect current expert consensus guidelines. In total, more than 32 modifications of the main name were applied, and 9 classification changes (including rearrangement in the recently created groups, of inclusion in the group of 'Epilepsy syndromes' for some clinical entities already present in the Orphanet classification but in a different group or classification).

The revision has also led to the inclusion of 5 new ORPHAcodes (3 groups of disorders and 2 disorders) to fill existing coding gaps and to allow better structuration of the group.

Finally, resulting of this revision, 11 disorders were deprecated and 8 ORPHAcodes (5 groups of disorder, 3 disorders) were obsoleted as a result of the evolution of knowledge and/or inconsistency with the current clinical practice, respectively.

17. ERN EYE: Rare disorder of the posterior segment of the eye

The goal of this high complexity weight collaboration (weight = 2) was to revise and update the classification of 'Rare disorder of the posterior segment of the eye', ORPHA:519311, following a request from ERN-EYE.

The group 'Rare retinal disorder' ORPHA:519315, was remodeled to better reflect the clinical practice by obsolete of the group of 'Inherited retinal disorder', ORPHA:71862 and the creation of two new groups of disorders: 'Rare predominantly chorioretinal disorder', ORPHA:716290 and 'Rare generalized retinal disorder', ORPHA:716358.

The new axis of classification distinguishes between progressive disorders and non-progressive disorders providing a better alignment with the current medical practice and scientific literature. Finally, in each category the disorders are distributed in groups depending if they only affect the eye ('Isolated') or if other organs besides the eye are affected (e.g. 'Rare disorder with corneal involvement as a major feature', ORPHA:519288).

In total, the revision process resulted in the inactivation by deprecation of 1 disorder, inactivation because not rare in EU for 1 disorder, and inactivation by obsolescence of 13 groups of disorders and 6 disorders. Moreover, 1 disorder was removed and another included in the new classification, 12 ORPHAcodes followed nomenclature modifications, and 6 entities were categorized as historic.

Table 1. Summary of the finalized collaborations in the context of OD4RD2 project.

ERN	ORPHA	Group Revised	Collaboration weight
ERN-EuroBloodNet	**NA**	Pediatric thrombotic diseases	0.5
MetabERN	738	Porphyria	0.5
ERN-EYE	499047	Isolated optic neuritis	0.5
ERN SKIN	79373	Ectodermal dysplasia syndrome	0.5
ERN EURO-NMD	98482	Acquired skeletal muscle disease	0.5
ERN EURO-NMD	98491	Neuromuscular junction disease	1
ERN PaedCan/SIOPE	715717	Pediatric gliomas, glioneuronal tumours, and neuronal tumours	1
ERN EURO-NMD	599	Distal myopathy	1
ERN GENTURIS	104010	Intestinal polyposis syndrome	1
ERN-Transplantchild	506210	Rare disorder potentially indicated for liver transplant	1
ERN-Transplantchild	506222	Rare disorder potentially indicated for lung transplant	1
ERN-Transplantchild	506225	Rare disorder potentially indicated for heart transplant	1
ERN-Transplantchild	506219	Rare disorder potentially indicated for HSC transplant	1.5
ERN-Transplantchild	506213	Rare disorder potentially indicated for kidney transplant	1.5
ERN ERNICA	104012	Rare inflammatory bowel disease	1.5
ERN EuroBloodNet	68364	Hemoglobinopathies	1.5
ITHACA-eUROGEN / Spina Bifida and other dysraphisms	268357	Neural tube closure defect	2
ERN BOND/ISDD	364526 364559	Primary bone dysplasia and Dysostosis	2
VASCERN	211237	Rare vascular tumor	2
VASCERN	211243	Rare vascular malformation: simple	2
VASCERN	211277	Rare vascular malformation: complex	2
ERN EpiCARE	166463	Epilepsy syndromes	2
ERN-EYE	519311	Rare disorder of the posterior segment of the eye	2
			TOTAL = 29.5

Ongoing ERN collaborations

Some of the collaborations started in the context of the OD4RD2 project are ongoing as of today. Moreover, Orphanet has already detected and/or has been contacted by ERNs willing to start new revision projects with us. In order to ensure the production and delivery of the Orphanet nomenclature of RD (ORPHAcodes), in a way it is updated and adapted to evolution of knowledge and coding needs, we plan to finalize the ongoing projects and to start new ones under the umbrella of the OD4RD3 project. In addition to the ongoing collaboration detailed in the following paragraphs, Orphanet plans to work with experts from ERN EuroBloodNet to revise the group of 'Polycythemia', ORPHA: 98427, and 'Rare hemolytic anemia', ORPHA98363, and with ERN RARE-LIVER to revise the group of 'Sclerosing cholangitis', ORPHA:447771, and the structure of the Orphanet classification of 'Rare hepatic disease', ORPHA:57146. The goal is to better reflect the ERN thematic groups, which might improve coding gaps and anticipate RD coverage issues.

Please note that the following collaborations started during the period of OD4RD2 project and will be pursued in the context of OD4RD3 project. They have not been counted in the final indicator count, as they are not yet completed.

18. ERN PaedCan/SIOPE: Classification of pediatric cancers

The goal of this collaboration is to release the Orphanet classification of pediatric cancers, so far incomplete and not yet published. This classification will follow the pediatric oncology clinical practice recommendations, and the WHO classification of tumors (5th edition) structure. The goal standard for the pediatric cancer diagnosis (the ICCC guidelines) will also be considered during the revision process.

The collaboration was officially launched with a meeting between Orphanet and the coordinator and the project manager of the ERN PaedCan, and a project manager of SIOPE. Since then, several meetings have been held to determine the priorities and constitute the working groups.

This collaboration is highly complex requiring the involvement of multiple pediatric oncologists to review a high number of clinical entities. For this reason, the revision will be partitioned in several projects with specific working groups of experts from each specific domain, and each project will be considered as an independent collaboration as the scale, weight and experts involved are different. Currently, the Renal Tumors Study Group (RTSG), Very Rare Tumors (VRT), and Central Nervous system Tumors (CNS) working groups have been created and the experts from each group have been trained and provided with a first version working file from Orphanet.

19. ERN EURO-NMD

Metabolic myopathies, ORPHA:98486

The goal of this collaboration is to review the content and structure of this group, and complete the group by creating missing ORPHAcodes if necessary. The project is part of a larger effort to update the

nomenclature and classification of the 'Mitochondrial diseases', ORPHA:68380, within the Inter-ERN working group. As to date, the revision process has not started yet, the ERN is looking for experts willing to participate.

Dystrophic myopathy, ORPHA: 98473

The goal of this collaboration is to review the content and structure of this group, and complete the group by creating missing ORPHAcodes if necessary. As to date, one training session has been already assessed with the ERN experts. Future steps planned for the following months, are to start organizing the plan of the revision, and define the priorities and deadlines.

Congenital myopathy, ORPHA:97245

The goal of this collaboration is to review the content and structure of this group, and complete the group by creating missing ORPHAcodes if necessary. The requests are being documented and will start to be treated during the present year.

20. ERN RND

Leukodystrophy ORPHA:68356

The goal of this collaboration is to review the content and structure of this group, and complete the group by creating missing ORPHAcodes if necessary. As of to day only one meeting took place, but the collaboration has not formally started yet.

Hereditary spastic paraplegia, ORPHA:685

The goal of this collaboration is to review the content and structure of this group, and complete the group by creating missing ORPHAcodes if necessary, with a specific focus on the group of ataxias (ORPHA:102002), as a first step of the project. At this stage, the ERN is forming the working group of experts.

Frontotemporal dementia, ORPHA:98535

The goal of this collaboration is to review the content and structure of this group, and complete the group by creating missing ORPHAcodes if necessary. Experts were trained and a first Orphanet proposal was shared with them. A consensus meeting to discuss these proposals will be addressed in the following months.

21. ERN SKIN

In 2025, Orphanet and ERN-SKIN launched a collaboration to update the nomenclature and classification of rare skin diseases. Currently, we have three group-specific revision projects in parallel with the ERN SKIN experts:

Ectodermal dysplasia syndrome, ORPHA:79373

Currently, a new project is ongoing intended to revise the completeness of the classification, and the nomenclature adequacy of the clinical entities constituting the group 'Ectodermal dysplasia syndrome', ORPHA:79373, in order to reflect the current and latest classification and the clinical practice. In December 2025 the working group was already constituted, and the experts were trained and provided with a working document to start the revision process.

Ichthyosis, ORPHA:79354

The goal of this collaboration is to revise the completeness of the classification, and the nomenclature adequacy of the clinical entities in the group 'Ichthyosis, ORPHA:79354, since according to latest classification and the clinical practice the definition of the ichthyosis and terminology has evolved. This revision will follow classification papers (PMID: 40308026, PMID: 40184496), and ERN-SKIN experts validation. In December 2025 the experts followed the training and received the first working file with Orphanet comments.

Hereditary palmoplantar keratoderma, ORPHA:79357

In parallel, the ERN SKIN reported another need concerning the revision of the group of 'Hereditary palmoplantar keratoderma, ORPHA:79357. This revision will follow the 'Palmoplantar epidermal differentiation disorders: a new classification toward pathogenesis-based therapy' paper (PMID: 40106577). In March 2026 the experts followed the training and received the first working file with Orphanet comments.

22. ERN GUARD-Heart: Rare cardiac rhythm disease

The goal of this collaboration is to revise and update the group of 'Rare cardiac rhythm disease', ORPHA:218436. ERN GUARD-Heart experts were trained and sent a proposal that is being progressively documented and presented for validation to the medical and scientific committee in Orphanet. The revision is ongoing and is focused first on the group 'Congenital long QT syndrome', ORPHA:768.

In March the 19th this work will be presented at the ERN board meeting in Bucharest, and the Orphanet manager in charge of this revision will join the discussion and exchange with other ERN working groups to assess the needs and plan future revision projects within the network.

23. ERN CRANIO: Rare orofacial cleft

The goal of this collaboration consists in homogenizing the terminology and completing the coverage of the rare orofacial clefts in the Orphanet nomenclature. In November 2024, Orphanet trained the experts from ERN-CRANIO, and since then, several proposals have been shared by Orphanet and commented by the experts. The project requires the readjustment of the structure of the classification and the confirmation of the rarity of some of the requested inclusions. A meeting is scheduled in March 2026 to discuss a consensual proposal, considering the experts' suggestions and the Orphanet rules.

24. ERN BOND: Primary bone dysplasias and Dysostoses (step 2)

The goals of this collaboration are 1/consider the remining issues from the finalized project concerning revision of the Nosology and classification of genetic skeletal disorders, and 2/complete the classification revision by confirming the final structure of the classification and the clinical entities contained in each of the accepted groups. Orphanet held a discussion in July 2025 with ERN-BOND/ISDS, and it was decided to complete first 54 pending minor revisions. Specifically, it concerns: 1 ORPHAcode creation, 19 ORPHAcodes inactivations, 7 ORPHAcodes annotated as historical entities, 18 classification issues, and changes in the nomenclature terms. In July 2025, Orphanet contacted and sent an working document containing the current Orphanet classification of rare bone disease, with the pending issues.

Orphanet participated in the ERN BOND plenary meeting held in Leiden, the Netherlands, in September 2025. Further contacts were intended by Orphanet since, that are awaiting follow-up. Orphanet plan to reactivate this collaboration throughout the year.

25. ERN MetabERN: Rare inborn errors of metabolism

The goal of this collaboration is to align the group of 'Rare inborn error of metabolism', ORPHA:68367, with the classification provided by ERN MetabERN experts, reflected in a consensus paper (PMID: 33340416). Orphanet is currently analyzing and comparing the two classifications in order to identify and complete the gaps (clinical entities not yet present in the Orphanet classification), proceed to classification changes (e.g for those existing ORPHA codes but currently rearranged under different groups or classifications), and update the nomenclature and genetic information if this is in line with the current literature and clinical practice. At the end of this revision process, MetabERN experts will be contacted for a final validation of the Orphanet proposal before the implementation of the changes, along 2026-2027.

26. Inter ERN Mito-WG: Mitochondrial disease

The revision of the classification of the group of 'Mitochondrial diseases, ORPHA:68380' is complex (around 200 ORPHAcodes) and involves several disciplines. For this reason, Orphanet asked the Inter-ERN Working Group of Mitochondrial Diseases made up of 5 ERNs, to bring together the efforts of different medical fields to update the nomenclature and classification. In 2024, the project was officially launched with the following ERNs: MetabERN, Euro-NMD, ERN RND, EpiCARE, and ERN-EYE. However, in the end only MetabERN, Euro-NMD and EpiCARE were able to allocate experts to participate in the meetings. The group agreed to continue the discussions with the available expertise.. Following the two training sessions (held on 29 April and 5 May 2025) and the sharing of the working document, some feedback has already been provided.

Dissemination activities

In an effort to enhance the visibility and awareness of the co-constructive work with the ERNs, Orphanet contributes to the following with ERN meetings, congresses and scientific publications. This section provides a detailed account of the dissemination activities that have been undertaken within the OD4RD2 framework.

1. ERN PaedCan/SIOPE

On line presentation in the ERN PaedCan General Assembly 29-30 June 2023.

2. ERN-ITHACA + eUROGEN

The revision of the Orphanet Nomenclature and Classification for spina bifida and other spinal dysraphisms, conducted in collaboration with two European Rare Disease Networks: ERN ITHACA and ERN eUROGEN resulted in the production of a publication. (PMID: 40629359).

3. ERN BOND/ISDS

Several presentations of the ongoing and updated work have been delivered during the course of the collaboration:

- ERN BOND Conference, 8 February 2022 (remote)
- ERN BOND/ePAG plenary meeting 26-27 September 2022 (remote)
- ERN BOND/ePAG plenary meeting 4-5 May 2023, Bologna, Italy (in person)
- 16th International Skeletal Dysplasia Society Meeting Workshop 18th September 2024, Madrid, Spain (in person)
- ERN BOND plenary meeting, 15-16 October 2024, Milan, Italy (remote)
- ERN BOND plenary meeting, 11-12 September 2025, Leiden, the Netherlands (in person)

4. VASCERN

The revision of the classification of vascular anomalies has been presented in an oral communication in VAC2025, in Berlin on the 14 February 2025 and has been sent as an abstract for a poster in ECRD2026, 6 June Prague, and a possible publication is under discussion.

Lessons learned

Drawing from past and ongoing collaboration projects, Orphanet has been able to improve its collaboration methodology and gain experience and knowledge that will help continuously improve the collaboration process. The following points are the most relevant lessons learned.

1. **Importance of regular interactions with ERN experts**

The dynamic of the revision process effectively relies on the reactivity of the two sides of the collaboration: the projects that Orphanet can absorb in terms of workload (given by the availability of

Nomenclature project managers and the ongoing revision projects) and the ERN reactivity to Orphanet requests for expertise.

It is sometimes difficult to efficiently communicate and interact with ERN experts. Experts are usually medical doctors that are extremely busy with their clinical and research practice and ERN activities. This can generate a delay in the starting of the collaboration (in particular if several different experts are needed at the same time), or a bottleneck during the revision process.

A reactive ERN contact point is essential and it has proven effective when there is an ERN project manager (or contact point) in charge of soliciting experts' responses and organizing meetings with several participants, or an ERN medical doctor that acts as spokesman for all expert participants of the revision and is fully implicated in the revision process.

A revision is only initiated after full commitment of the ERN. A fluid communication with the project manager or ERN person contact point, is an essential brick for a successful collaboration.

It should be noted that, in the event that the ERN is unable to guarantee prompt follow-up due to a number of constraints, it may be possible to suspend the collaboration until the necessary experts and/or time for the project's advancement are available.

2. **Importance of providing an adapted training to ERN experts**

Training ERN experts on the general Orphanet concepts (definition of the nomenclature and structure of the classification) and on the nomenclature update process facilitates the collaborative work.

Adapted training, along with frequent discussions provide experts with a full understanding of the different types of actions applicable in the Orphanet knowledge base. Experts are also shown how to compile their suggestions in the provided supports in a standardized and easy format. Globally, this makes the ERN-Orphanet communication clearer and more efficient.

The training needs are generally assessed by the Orphanet nomenclature project manager, taking into consideration the eventual previous collaborations of the experts with Orphanet and the proportions of the revision. They usually take place at the beginning of the collaborative process; however, further trainings can be proposed even at later stages of the collaboration, especially for complex projects (implicating several expert fields or ERNs, or the ones that were hold on for a while).

3. **Importance of defining the priorities and a precise methodology**

To achieve the objectives of the revision and meet the planned deadlines, it is necessary to establish the priorities of the project at a very early stage of the collaboration. This is especially relevant for high complexity revisions, that usually rely on the contribution of large groups of experts, that complicate the process and the timeline.

In order to reduce the delivery time of the nomenclature updates as much as possible there are some solutions that seem to work to speed up the process and render it more efficient:

- Subdividing the workload by identifying smaller clinical blocs of entities/groups to be revised in a subsequent way during the collaboration;
- Subdividing the workload by separating the ORPHAcodes revision process (namely, creation or inactivation of disorders and subtypes of disorders) from the restructuring of the classification process in two consecutive phases;

- Avoiding working with large groups of clinical experts at the same time. A better approach is to work with a restricted group of 2/3 experts and submit the final proposition for commentary and approval at the end to the entire ERN working group.

4. Importance of maintaining a certain flexibility in the initial assessment of scale and complexity

The initial assessment of the scale and complexity of a collaboration is an important step to anticipate the workload on Orphanet's and the ERN side. However, experience from previous collaborations has shown that this assessment is not always straightforward. The complexity of a project cannot always be fully anticipated at its starting point, as the depth of the classification revisions required may become clearer only once the collaborative work has started.

In some cases, projects initially estimated as low complexity, or medium-low have required more extensive work than expected. This has highlighted the need for maintaining a flexible approach to project evaluation and for allowing the possibility of reassessing the scope and complexity of a collaboration when necessary.

To address this issue, the methodology used to estimate the weight of collaborative projects has been refined in the framework of the new OD4RD3 project. A simplified scale of collaboration complexity has been introduced to facilitate the planning of projects and allow more flexibility when estimating the expected workload. At the same time, the possibility of splitting particularly large or complex revisions into smaller and more manageable projects has been incorporated into the methodology.

5. Integrating the validation of disorder definitions into the revision process

Experience from collaborations lead in 2025 has shown that involving experts in the validation of disease textual definitions improves both the coherence and the efficiency of the updated classification.

This particularly valuable step can be carried out once the revision of entities and classification has been completed. It allows experts to consolidate the results of the revision by clarifying the concepts underlying the revised entities and ensuring that disorders are clearly defined and consistently described. As a result, revised disorders become more easily and quickly exploitable for coding purposes.

Based on these positive results, the production and validation of disease definitions by the experts involved in the revision process is progressively being integrated into the standard collaborative workflow and will be proposed systematically in future collaborations.

6. Valorization and dissemination of collaborative work

Beyond the primary objective of updating the Orphanet Nomenclature and Classification, collaborative revisions often generate additional scientific value. The work carried out jointly by Orphanet and ERN experts can lead to further communication activities, including presentations at scientific congresses and joint publications.

7. Importance of promoting Orphanet – ERN interactions

Encouraging the valorization of these collaborations contributes to recognizing the efforts of the participating experts and increases the visibility of the performed work by disseminating the results to the wider rare disease community. In the context of the upcoming OD4RD3 project, Orphanet plans to

increase its participation in ERN related events in order to increase the visibility of the collaborative work.

Reinforcing Orphanet's presence in these events will contribute to accelerate and improve the nomenclature revision process, as well as to better anticipate ERN needs, particularly regarding disease coding. Interactions with ERN members in these contexts also provides a valuable opportunity to discuss ongoing projects and validate longstanding issues with all available experts.

To support this new objective, Orphanet aims to be present at ERN's annual member meetings, board meetings or other network-related events that can be a context for discussion and networking.

Results of the satisfaction survey

As part of our ongoing effort to improve the collaboration process, we recently introduced in the methodology a short survey sent to ERNs once the project is completed. We received a total of 10 responses since several ENRs provided more than one feedback (one has 2 projects and in other cases more than one of the experts involved replied).

The feedback is summarized in table 2. The majority of contacted ERNs have expressed a high level of overall satisfaction with the collaboration process, the channels used to communicate, and the regularity of discussion sessions. Satisfaction with the deadlines is slightly lower, and this issue will be examined in more detail. Nevertheless, the feasibility of achieving this objective is contingent upon the availability of experts in the field.

The majority of the respondents intend to use the created ORPHAcodes resulting of the revision: in communications, in patient registries, and in national applications asking for an expertise center on RD. One limitation of the survey is that in some cases the response was provided by the ERN project manager, that explains the 'No', 'Not possible to evaluate' and 'I have no direct say in coding' answers in questions 8 and 10.

The results of this survey suggest that the current workflow has a positive impact on different levels. There was a consensus amongst the respondents regarding the impact of the collaboration on improving the accuracy of the Nomenclature and Classification of the RDs, and the positive effect on coding. The willingness of collaborators to engage in text revision, future follow-up revisions, and the initiation of new projects was also demonstrated. Furthermore, some ERNs have expressed a notable enthusiasm for the dissemination of the co-constructed scientific knowledge through international publications.

Overall, the survey validated the proposed Orphanet methodology for ERN collaborations and revealed the multiple benefits of Orphanet-ERNs scientific interactions.

Table 2. Preliminary results of the survey sent to ERNs to evaluate the satisfaction of the results and steps of the revision process with Orphanet.

	Number of ERNs/ number of feedbacks received	6/10
1.	How do you rate globally the collaboration process?	Excellent (90%)/Acceptable (10%)
2.	How is the level of satisfaction with the channel used to communicate?	Excellent (90%)/Acceptable (10%)
3.	How is the level of satisfaction with the frequency of discussion between the Orphanet Manager and the ERN contact point?	Excellent (90%)/Acceptable (10%)
4.	How is the level of satisfaction with the deadlines?	Excellent (70%)/Acceptable (30%)
5.	If you chose "Not possible to evaluate", please can you briefly explain why?	NA
6.	Has the collaboration improved the accuracy of Nomenclature and Classification of RD?	Yes (100%)
7.	Do you think that the changes will have a positive impact on the coding?	Yes (100%)
8.	Do you intend to use the newly revised codes to code your patients?	Yes (60%)/No (20%)/ Not possible to evaluate (20%)
9.	If you intend to use the newly revised codes to code your patients: in which context do you plan to use the codes?	1/6 "In our national application expertise center for rare disease" 2/6 "In communications" 1/6 "In our hospital and ERN" 1/6 "Out- and inpatient care, registry" 1/6 "Clinical practice and research (national data base for dysraphisms)"
10.	If you chose 'Not possible to evaluate', please can you briefly explain why?	1/3 "Clinically not relevant" 1/3 "Not currently employed in this role" 1/3 "I have no direct say in coding"
11.	Would you be available to contribute to the writing of the abstract of the clinical entities related to your clinical specialty? (That means being available to work again with Orphanet to update the clinical information shown in Orpha.net)	Yes (90%), No (10%)
12.	Would you be available to revise the recently modified classification to help Orphanet in their quality control process? (That means being available to work again with Orphanet to confirm the adequacy and accuracy of the classification in five-year timeline)	Yes (90%), No (10%)
13.	Do you plan to contact Orphanet for other projects in the future?	Yes (80%), No (20%)
14.	If you plan to contact Orphanet for other projects in the future: what would be your request (a revision of the classification, a nomenclature update, ORPHAcode creation, ORPHAcode inactivation…)	1/6 "Not sure yet" 3/6 Yes, revision of a classification 2/6 Nomenclature changes 1/6 "Writing of manuscript about the revision" 1/6 "All"

Conclusions

Since the creation of ERNs in 2017 and the progressive development of their registries from 2019 onwards, the need to harmonize data collection and data sharing across healthcare and research sectors, as well as across ERNs and countries, has become increasingly evident. In this context the OD4RD pilot phase (2022-2023) and the OD4RD2 consolidation phase (2023-2025) have demonstrated the value of closely working with ERN experts for maintaining and updating the Orphanet Nomenclature and Classification, notably in terms of coding accuracy and coverage.

In the framework of the OD4RD2 project, Orphanet has been able to consolidate a robust methodology to initiate and maintain collaborations with ERNs. At the same time, the cumulative scale and

complexity of the revision projects have significantly increased (figure 1). This effort will be maintained and further strengthened in the context of the upcoming OD4RD3 project.

Figure 1 Progression across time of the number of collaboration projects treated and ERNs reached.