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Procedural document: Collaboration with networks of expertise for the revision of the Orphanet nomenclature and classification of rare diseases

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List of abbreviations

ERN: European Reference Network
INSERM: Institut National de la Santé et de la Recherche Médicale (French National Institute of Health and Medical Research)
OMIM: Online Mendelian Inheritance in Man

I. Introduction

1. Purpose/objectives

Orphanet has developed and maintains the Orphanet nomenclature of rare diseases, a unique and multilingual standardised system aimed at providing a specific terminology for rare diseases. Each clinical entity is assigned a unique and time-stable ORPHAcode, around which the rest of the data present in the Orphanet database is structured. This clinical coding system provides a common language across healthcare and research systems for effective monitoring and reporting on rare diseases, thus improving their visibility.

A collaborative effort between Orphanet and various networks for rare diseases has been ongoing with the aim to integrate the most up-to-date available clinical knowledge into the Orphanet nomenclature of rare diseases (ORPHAcodes), among other activities. These networks include the European Reference Networks for rare diseases (ERNs) established by the European Commission in 2017, the French rare diseases Healthcare Networks (Filière de santé maladies rares), and other national, European, or international learned societies.
Many of these networks have built patient registries that integrate ORPHAcodes for the codification of rare disease patients, in order to connect and uniform the information collected either at the national level or across European countries. It is therefore necessary that the information provided by the Orphanet nomenclature reflect the most up-to-date knowledge, so as to enable appropriate coding (and thus identification and follow-up) of patients affected by rare diseases within healthcare and research information systems.

To this end, revision projects for the update and improvement of groups of disorders in Orphanet are conducted with the participation of medical experts representing the expert network they are involved in, and an Orphanet nomenclature manager in charge of the coordination of the project.
The medical experts apport to the collaboration their scientific and clinical knowledge, while the Orphanet nomenclature manager transposes the knowledge provided by the experts (integrated with the scientific literature) into the standardized Orphanet classification system, that organises the nomenclature with consistency and accuracy.

The experience and lessons learned gathered by Orphanet in working with networks of expertise have led to the establishment of a standardised methodology of collaboration.
This methodology aims to structure the revision projects and formalise a set of common steps and tools that allow efficient traceability and homogenous interactions between Orphanet and the networks of expertise, while allowing a flexibility to adapt to the challenges and specific needs of every single project.

This procedural document describes the different steps and tools composing the methodology in use for the collaboration between Orphanet and networks of expertise for the revision of the nomenclature and classification of rare diseases.

2. Range of application

The Orphanet nomenclature includes all disorders, subtypes of disorders, and groups of disorders that organise the Orphanet classification.

The nomenclature and classification of rare diseases are produced and updated in English by information scientists of the Orphanet coordinating team and collaborating institutions with a scientific and/or medical background, referred to as Orphanet nomenclature managers.

Medical experts participate in revision projects of the nomenclature and classification together with the Orphanet nomenclature managers in order to provide their scientific and clinical expertise. This joint effort ensures that the actions discussed, validated and implemented in the Orphanet database result in an accurate representation of the current knowledge on rare diseases and meet the needs of professionals involved in rare diseases coding activities.

This procedure applies to all collaborations on the revision of groups of disorders involving networks of expertise, and describes the workflow applied from the initial request to the effective implementation of validated actions in the Orphanet database and finalisation of the revision project.

This procedure does not describe the production and update process of the Orphanet nomenclature and classification of rare diseases, which is detailed in a separate document.

3. Disclaimer

- This publication is part of the Orphanet Data for Rare Diseases project (OD4RD2-101110100), which has received funding from the EU4Health programme.

- The content of this publication represents the views of the author only and is their sole responsibility; it can not be considered to reflect the views of the European Commission and/or the Consumers, Health, Agriculture and Food Executive Agency or any other body of the European Union. The European Commission and the Agency do not accept any responsibility for use that may be made of the information it contains.

4. References

- Regulation (EC) N°141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products

- Orphanet Nomenclature and Classification of Rare Diseases: description of the production, validation and update process of the Orphanet nomenclature and classification of rare

diseases.

- Orphanet Naming Rules for the Rare Disease Nomenclature in English: description of the editorial rules applied for the naming of clinical entities in Orphanet.

5. Availability of data

The Orphanet nomenclature and classification are available on the Orphanet website and in Orphadata in variable formats, according to the intended use, as detailed in the dedicated procedure.

6. Definitions

a. Orphanet nomenclature of rare diseases

Rare disease (RD): a disease that affects less than five in 10,000 persons in Europe, as defined by the European Regulation on orphan medicinal products (*Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products*). In order to be registered in Orphanet, the disease must be described in at least two independent individuals, confirming that it is not an incidental association of clinical signs.

The **Orphanet nomenclature** is a multilingual, standardised, controlled medical terminology specific to rare diseases, that includes all clinical entities registered in the Orphanet database. Each clinical entity is defined by the following elements:

- An **ORPHAcode**: a unique and time-stable numerical identifier attributed randomly by the database upon creation of the entity.
- A **preferred term**: the most generally accepted name according to the literature, and as adopted by the medical community.
  As no international consensus is available for the naming of rare diseases, Orphanet has defined a set of editorial rules in order to ensure that the nomenclature is consistent and accurate.
- **Synonyms**: terms that are perfectly equivalent to the preferred term they are attached to. As many synonyms as necessary are added to a preferred term. Acronyms are included only when they are consistently used in the literature. Some acronyms are used for convenience in the Orphanet summary texts without having a particular use in the scientific community, and are therefore not included. Several entities can share the same acronym.
- **A classification level**: a level of precision attributed to each clinical entity: *Group of disorders*, *Disorder*, or *Subtype of a disorder*. These three levels organise the relational structure of the Orphanet classification.

- A **definition**: a short text stating the group of disorders that the clinical entity belongs to, and listing the major clinical characteristics (e.g. clinical, pathological, radiological, etc.) that define the entity and differentiate it from other entities classified within the same clinical group.

ORPHAcode	Preferred term	Synonyms	Classification level
ORPHA:73229	HANAC syndrome	Autosomal dominant familial hematuria-retinal arteriolar tortuosity-contractures syndrome Hereditary angiopathy-nephropathy-aneurysms-muscle cramps syndrome	Disorder
Definition: A rare multisystemic disease characterized by small-vessel brain disease, cerebral aneurysm, and extracerebral findings involving the kidney, muscle, and small vessels of the eye.			

Table 1. *Representation of the nomenclature of a rare disease.*

b. Orphanet classification of rare diseases

The Orphanet nomenclature is organised in a **multi-hierarchical and polyparental classification system**, structured around the major medical specialties and based on **clinical criteria** according to diagnostic and therapeutic relevance.

The Orphanet classification is organised according to three hierarchical levels: *Group of disorders*, *Disorder*, and *Subtype of a disorder*, that determine the level of precision of each diagnosis included in the nomenclature. This **classification level** is indicated on the respective Orphanet website page of each clinical entity.
The *Disorder* level is designated as the main typological level for data sharing and statistical reporting across the European Union. It is used to establish the total number of rare diseases that exist.

c. Other definitions

Clinical entity: a generic technical term used to describe the clinical items included in the nomenclature of rare diseases.

European Reference Network (ERN): a cross-border virtual network that bring together European hospital centres of expertise and reference to tackle rare, low prevalence and complex diseases and conditions requiring highly specialised healthcare. ERNs enable specialists in Europe to discuss cases of patients affected by rare, low-prevalence and complex diseases, providing advice on the most appropriate diagnosis and the best treatment available.

Expert: a medical doctor or researcher with prominent experience in a rare disease or a group of rare diseases, and identified by Orphanet based on published articles (particularly reviews and guidelines), involvement in expert centers, expert networks, and/or in dedicated research activities including clinical trials.

Information scientist: a member of the Orphanet team with a scientific and/or medical background in charge of collecting, producing and updating information provided in the Orphanet database.

Network of expert centers: a virtual network aiming to connect medical experts for the discussion of rare diseases and coordination of activities and services dedicated to RD patients and healthcare professionals, including RD diagnosis and management, production of guidelines, data sharing, clinical trials, consensus publications, coordination of expert centers, interaction with patient organisations, and trainings.

Orphanet coordinating team: based at the French National Institute of Health and Medical Research (INSERM-US14, Paris, France), the coordinating team is responsible for the coordination of the Orphanet Network, the production of the Orphanet database, the elaboration of procedures and trainings, and the coordination of quality control activities, enabling the production of the knowledge base and the catalogue of expert resources by the Orphanet national teams. The coordinating team is in charge of producing the Orphanet nomenclature in English.

Orphanet nomenclature manager: an information scientist of the Orphanet coordinating team or a collaborative institution in charge of producing and updating the nomenclature and classification of rare diseases. Orphanet nomenclature managers collectively form the **Orphanet nomenclature team**.

7. Filing and updates

This document is updated by an Orphanet nomenclature manager as often as necessary and at least once a year. The most up-to-date version is available on the Orphanet website.

II. Methodology

1. Flowchart

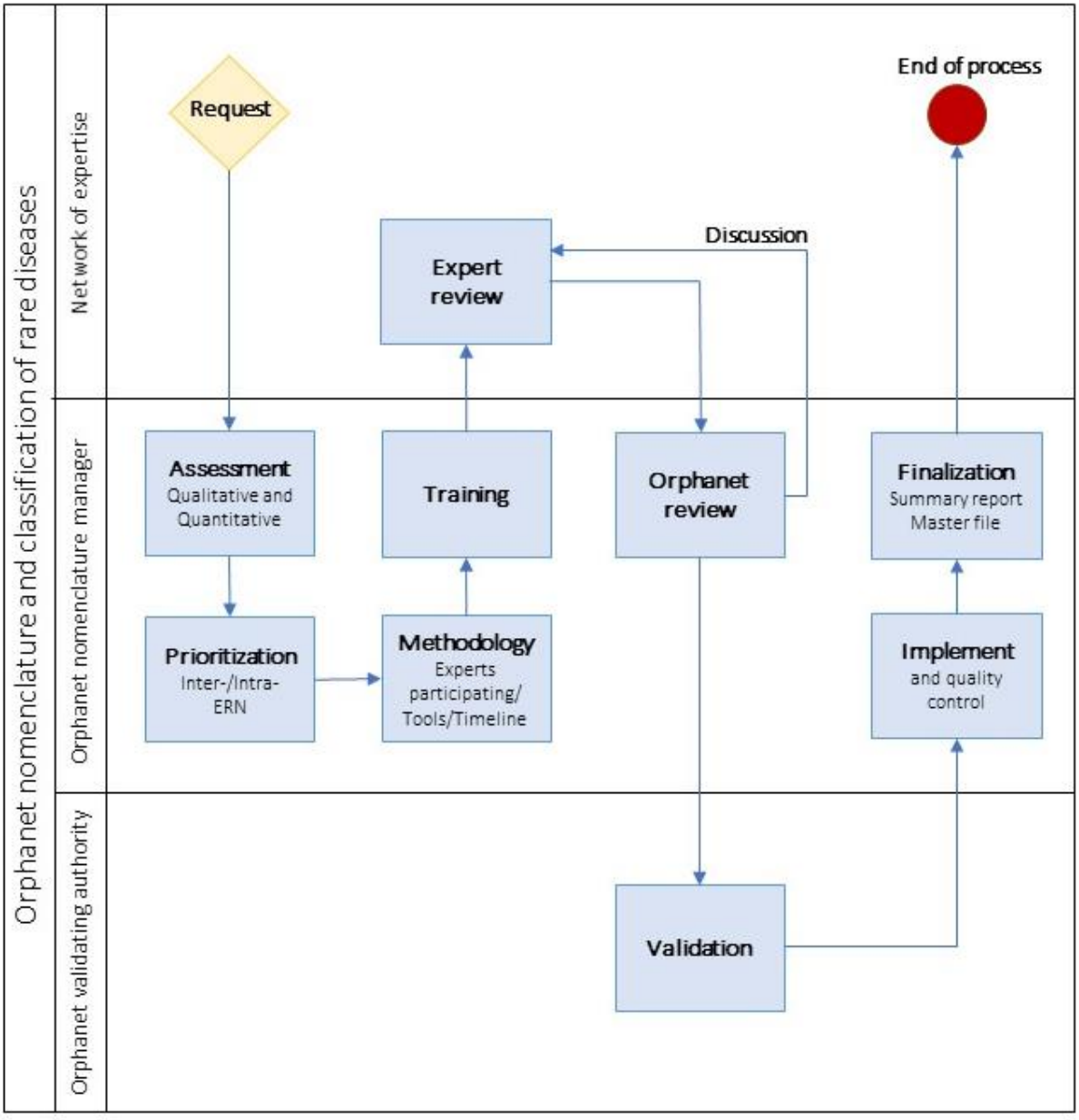

Figure 1. *Workflow of the collaboration between Orphanet and a network of expertise for the revision of a RD classification group.*

2. Description

A collaboration between Orphanet and a network of expertise can be initiated in two possible contexts:

- Request submitted by the network of expertise for the revision of an Orphanet classification group, for the appropriate use of ORPHAcodes in their registries allowing for efficient patient identification and follow-up as well as RD data exploitation.
- Publication of a consensus classification in the literature, calling for the update of the Orphanet nomenclature in order to reflect the current knowledge as accurately as possible, and thus invitation of a network of expertise to participate to a revision project.

Every request received by the Orphanet nomenclature team must first be **assessed** in order to estimate the amount of work needed to complete the project. This evaluation takes into consideration both quantitative and qualitative aspects, as it depends on the size of the classification group considered as well as the complexity of the issue at hand. The main elements considered by the Orphanet nomenclature manager are:

- The identification of the main issue: whether the requested revision mainly focuses on the diagnostic level (disorders and subtypes that are missing, wrong, or outdated), on the classification structure, or both.
- The number of clinical entities that need to be reviewed.
- Specific issues that may arise for the classification group to be revised.

A **prioritisation** effort must be performed regularly by the Orphanet nomenclature team: in view of the large number of requests, a long-term planning of collaborations has to be established.
The following criteria are factored in this prioritisation:

- The complexity and scale of the requested revision, as assessed in the previous step;
- Whether the revision is needed to unblock the network's coding activities (missing ORPHAcodes);
- The availability of a consensus publication providing a guiding thread for the collaboration;
- The resources available for the collaboration: every revision project requires the coordination of an Orphanet nomenclature manager and the presence of a "main contact" within the network of expertise, to serve as a reference point for appropriate follow-up, and to provide support to the Orphanet nomenclature manager in organisational and communication aspects (plan meetings, conduct working sessions, motivate participants, identify experts within the network for specific scientific issues, etc.).

The preparation of a revision project also necessitates the delineation of a **detailed and practical methodology** of collaboration, including:

- A clear identification of the experts willing to participate to the project;
- The tools to be used:
    - the working document that will allow the experts to provide their suggestions. This document should be carefully designed in order to integrate any information associated with the revised clinical entities that may be useful for the experts (genes, OMIM references, synonyms, etc.), and must be easy to use;
    - Any additional document that may be of help in the revision, such as training material or relevant publications;
- The timeline of the collaboration, including the estimated date of finalization, and the dates and frequency of the follow-up meetings.

The Orphanet nomenclature manager provides the participating experts **with training on the general concepts of Orphanet** (definition of the nomenclature and structure of the classification) and on the nomenclature update process, in order to ensure that the experts have a good understanding of the different types of actions applicable to the Orphanet database. The training needs will be assessed by the Orphanet nomenclature manager, considering any previous collaboration of the experts with Orphanet and the scope of the revision. Orphanet training is proposed at the beginning of each project, but the nomenclature manager remains available throughout the collaboration process to clarify Orphanet rules with the experts.

Following the training phase, the medical experts and the Orphanet nomenclature manager will start the **review** of clinical entities, each of them contributing in the following way:

- the **experts** contribute their medical knowledge and validate the scientific accuracy of the information provided by the Orphanet nomenclature manager. They propose updates and help the Orphanet nomenclature manager determine if the resulting decisions and classification structure will appropriately answer the needs of clinicians dealing with patients suspected/confirmed to have a rare disease.
- the **Orphanet nomenclature manager** reviews the updates suggested by the experts, in order to verify their compliance with the Orphanet standards and database rules. The nomenclature manager has to prevent the introduction of inter- and intra-classification inconsistencies, anticipate any issue that may arise as a result of the proposed updates in regards to disease coding/data sharing, and in such case, find alternatives to discuss with the experts.

The proposed updates are then **discussed** during dedicated meetings (either online or in-person) in order to clarify any issues that may arise throughout the revision and **reach a consensus** on the best course of action to follow for every entity involved in the revision. Minor issues and simple validations can also be discussed and validated by e-mail.

The update process of the Orphanet nomenclature and classification of rare diseases is subject to a validation workflow designed to ensure that the information and data provided by Orphanet have a satisfactory level of exhaustivity, accuracy, pertinence, and reliability. It is described in more detail in the dedicated procedure.
After reaching a consensus with the experts, the Orphanet nomenclature manager must present the suggested updates to the Orphanet medical and scientific committee, which gathers medical doctors and information scientists of the Orphanet coordinating team, in order to collectively **validate** the actions to be implemented in the database. In some cases, it may be necessary for the Orphanet nomenclature manager to rediscuss certain elements with the experts.

The timing of the **implementation** of validated actions in the Orphanet database must be decided case by case: this can be either be done in a "one-shot" step at the end of the revision (when all issues are discussed and solved), or in several successive steps when the validated actions are not co-dependent and there is no risk for an implemented action to be questioned again in further discussions.

When all actions validated during the revision are implemented in the Orphanet database and there are no issues left to be solved, the Orphanet nomenclature manager provides three documents to the expert network, in order to formalise the **finalisation** of the revision project:

- A **collaboration report** that summarises the main elements of the revision project: the initial request and the context surrounding it, the participants, the methodology used, the issues raised (and the decisions made to solve them), and conclusions with possible perspectives for the future.
- A **"master file"** in XLSX format listing all revised clinical entities (created, modified, inactivated or revised with no action), each with their respective ORPHAcode, main name, classification level, suggested action, and validated action. This file is intended for reportings and statistical analysis on the revised clinical entities.
- A **survey** with some questions to assess the satisfaction with the collaborative project and collect feedback on improvements regarding the collaboration process.

At the end of the collaboration, the Orphanet nomenclature manager will propose to the experts to extend the collaboration between the ERN and Orphanet to the updating of the Orphanet content. In particular, they will be asked to contribute to the writing of the abstracts and definitions of the entities related to their clinical specialty.

For any questions or comments, please contact us: contact.orphanet@inserm.fr

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