orphanet

| Version 05 | June 2023

Procedural document: Orphanet nomenclature and classification of rare diseases

www.orpha.net www.orphadata.org

Inserm
La science pour la santé
From science to health

Co-funded by
the Health Programme
of the European Union

Table of contents

List of abbreviations

ERN: European Reference Network
GARD: Genetic and Rare Diseases Information Center
ICD-10: International Classification of Diseases, 10th revision
INSERM: Institut national de la santé et de la recherche médicale
MedDRA: Medical Dictionary for Regulatory Activities
MeSH: Medical Subject Headings
OMIM: Online Mendelian Inheritance in Man
ORDO: Orphanet Rare Disease Ontology
SNOMED-CT: Systematized Nomenclature of Human and Veterinary Medicine - Clinical Terms
UMLS: Unified Medical Language System

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.
The Orphanet nomenclature is cross-referenced with other international terminologies and reference databases (including OMIM, ICD-10, ICD-11, SNOMED-CT, MedDRA, UMLS, MeSH, and GARD) in order to enable interoperability between different information systems.
Orphanet also maintains the Orphanet classification of rare diseases, a multi-hierarchical and polyparental structure built on the Orphanet nomenclature and organised by medical specialty according to diagnostic and therapeutic relevance. This structure reflects the multidimensional nature of rare diseases and enables to carry out epidemiological and statistical studies for research purposes.
By providing these services, Orphanet actively contributes to generating knowledge on rare diseases and promotes the improvement of the diagnostic pathway and clinical care provided to affected patients.

This procedural document describes the production, validation and update process of the Orphanet 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 with a scientific and/or medical background.
International experts are consulted to ensure that the nomenclature and classification provide 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 types of modification of the nomenclature, including the creation of new clinical entities and the removal or update of existing entities, and describes the workflow applied from the initial update request to the effective implementation of the modification in the database. It also outlines the maintenance and revision of the Orphanet classification.

3. Disclaimer

- This publication is part of the OrphaNetWork Direct Grant, which has received funding from the European Union's Health Programme (2014-2020).

- 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.

- While the term *disease* technically stands for a narrower clinical concept than *disorder* in the Orphanet database, it is used in its large and widely accepted definition in this procedural document, since *rare disease* is the universally employed term in healthcare and research systems. The term *disorder* is used when necessary in its more technical definition.

4. References

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

- Orphanet Naming Rules for the Rare Disease Nomenclature in English: description of the editorial rules applied for the naming of clinical entities in Orphanet.
- Linearisation Rules for the Orphanet Classification: description of the rules applied for the attribution of a preferential parent to each clinical entity included in the Orphanet nomenclature.
- Creation and Update of Disease Summary Texts for the Orphanet Encyclopaedia for Professionals: description of the editorial rules applied for the production of definitions included in the nomenclature of rare diseases.

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:

Platform	Section/access link	Purpose	Update frequency
Orphanet website	• Rare diseases • Classifications	Information by rare disease: nomenclature(including definitions), classification, textual information and associated activities.	Daily
Orphadata	Orphanet nomenclaturefiles for coding (Nomenclature pack)	Computable files providing data for theimplementation of ORPHAcodes in Health Information Systems.	Annual
	Cross-referencing of rare diseases	Computable file containing all diseases and their cross-referencing with externalterminologies and databases. The relationship between each disease and external reference is qualified in order toindicate if the terms are perfectly equivalent (exact mapping) or not.	Twice a year (July & December)
	Classifications of rare diseases	Computable files incorporating the relationships between diseases that organise the nomenclature into a multi- hierarchical classification structure (onefile for each classification group).	Twice a year (July & December)
	Linearisation of rare diseases	Computable files incorporating the preferential parent attributed to every disorder and subtype of a disorder presentin the nomenclature.	Twice a year (July & December)
	Orphanet Rare Disease Ontology	Integrated and reusable OWL data files provided for computational analysis and integration of the Orphanet nomenclatureinto health and research information systems.	Twice a year (July & December)

Table 1. *Available sources of information for the Orphanet nomenclature and classification*

6. Definitions

a. Orphanet nomenclature of rare diseases

Rare disease: 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.

- **Keywords**: significant clinical terms for a disorder or a group of disorders that do not fit the defining criteria of a preferred term or a synonym. These terms are included when they are particularly likely to be searched for in the database, to ensure appropriate redirection of users towards relevant entities.

- 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	Keywords
ORPHA:73229	HANAC syndrome	Autosomal dominant familial hematuria-retinal arteriolar tortuosity-contractures syndrome Hereditary angiopathy-nephropathy-aneurysms-muscle cramps syndrome	Glomerular basement membrane disease due to a COL4A mutation
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 2**. 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.

In addition to the classification level, each clinical entity is assigned a **typology** defined by the purpose and clinical concept that it entails (**Table 3**). The typology of each entity is indicated in the Orphadata nomenclature files and in ORDO.

Classification level	Typology	Definition
Group of disorders A collection of clinical entities sharing a set of common features.	**Category**	A group of clinically heterogeneous disorders sharing one general feature, used to organise the classification. Example: ORPHA:68385 Neurometabolic disease
	Clinical group	A group of clinically homogeneous disorders that share a similar etiology, course, outcome, and/or management. Example: ORPHA:216 Neuronal ceroid lipofuscinosis
Disorder A clinical entity characterised by a set of homogeneous phenotypic abnormalities and evolution allowing a definitive clinical diagnosis.	**Disease**	A disorder with homogeneous therapeutic possibilities and an identified pathophysiological mechanism. Developmental anomalies are excluded. Example: ORPHA:848 Beta-thalassemia
	Clinical syndrome	A disorder with homogeneous therapeutic possibilities, regardless of the pathophysiological mechanism involved. Example: ORPHA:529799 Acute bilirubin encephalopathy
	Malformation syndrome	A disorder resulting from a developmental anomaly involving more than one morphogenetic field. Malformative sequences and associations are included. Example: ORPHA:648 Noonan syndrome
	Morphological anomaly	A disorder characterised by a morphological alteration resulting from a development anomaly involving a single morphogenetic field. Example: ORPHA:617 Congenital primary megaureter

	Biological anomaly	A disorder defined by a set of physiological abnormalities without clearly associated clinical manifestations. Example: ORPHA:440731 L-ferritin deficiency
	Particular clinical situation in a disease or syndrome	A set of phenotypic abnormalities presenting in a subset of patients under particular circumstances. Example: ORPHA:567983 Parenteral nutrition-associated cholestasis
Subtype of a disorder Subdivision of a disorder according to a positive criterion.	**Clinical subtype**	Subdivision of a disorder according to distinct clinical characteristics (severity, age of onset, particular clinical signs, etc.). Example: - Mild Canavan disease (ORPHA:314918) - Severe Canavan disease (ORPHA:314911) are subtypes of Canavan disease (ORPHA:141).
	Etiological subtype	Subdivision of a disorder according to distinct causes resulting in a similar clinical presentation. Example: - Cystinuria type A (ORPHA:93612) - Cystinuria type B (ORPHA:93613) are subtypes of Cystinuria (ORPHA:214), caused by mutations in SLC3A1 and SLC7A9 respectively.
	Histopathological subtype	Subdivision of a disorder according to characteristic histological patterns. Example: - Protoplasmic astrocytoma (ORPHA:251598) - Fibrillary astrocytoma (ORPHA:251601) - Gemistocytic astrocytoma (ORPHA:251604) are subtypes of Diffuse astrocytoma (ORPHA:251595).

***Table 3**. Representation of the typological components of the Orphanet classification*

This relational characterisation of clinical entities translates into the following structure:

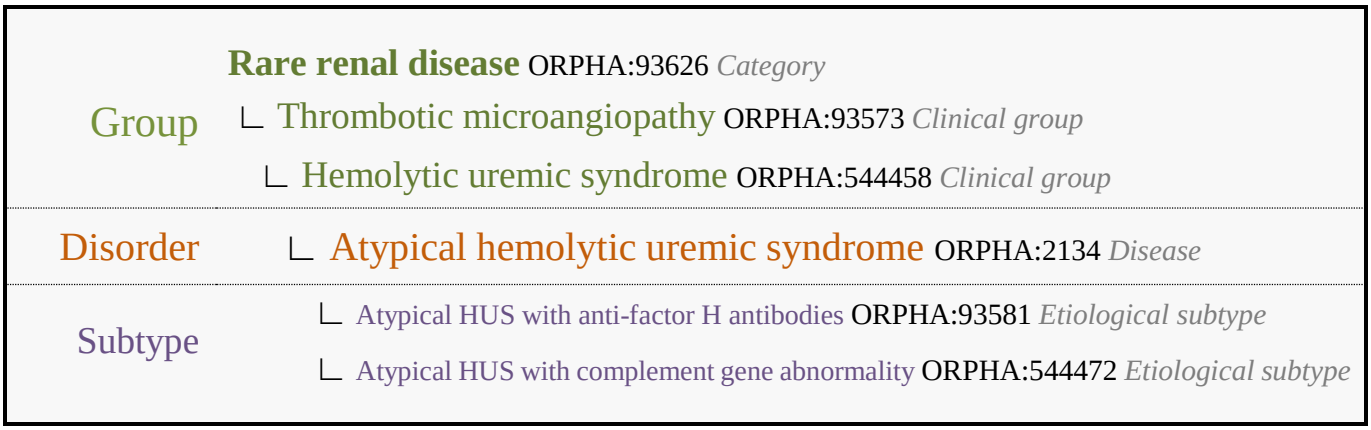

***Figure 1**. Representation of classification levels in the Orphanet classification system*

Each clinical entity is included in as many classification groups as necessary depending on its clinical presentation and the medical specialties to which it is relevant, reflecting the current state of knowledge and the multidimensional nature of rare diseases.

However, each entity is assigned one classification group (called *preferential parent*) in order to enable the sorting out of all clinical entities by medical specialty and avoid multiple counting of multiclassified entities in statistical analysis. This "linearisation" process is described in a separate procedure.

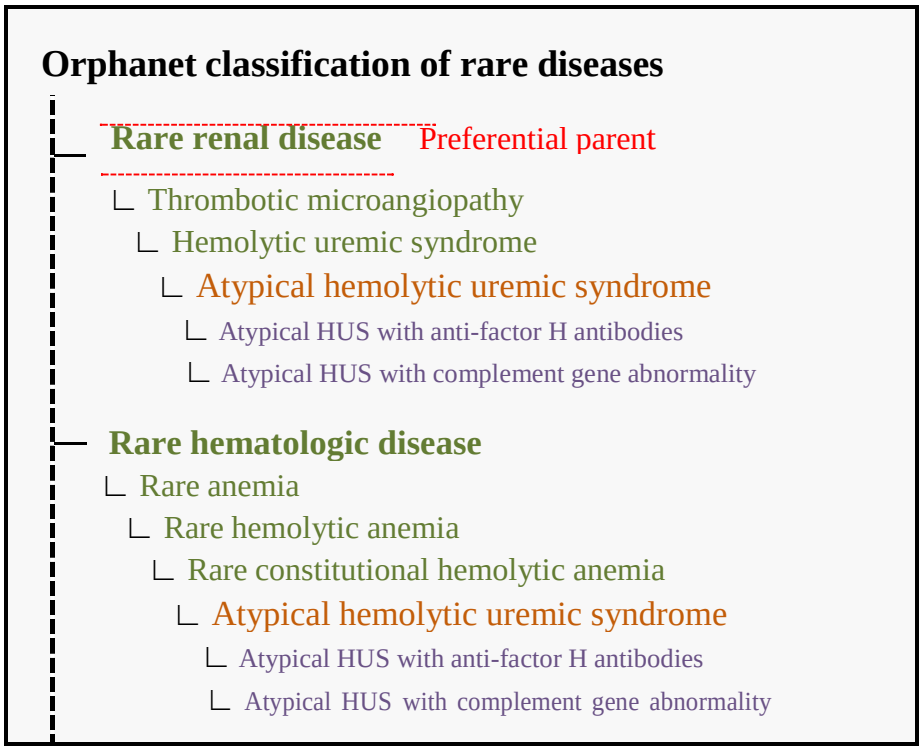

***Figure 2.** Polyparental structure of the Orphanet classification*

In this example, Atypical hemolytic uremic syndrome (HUS) is present in several classification

groups, including rare hematologic diseases and rare renal diseases. Since it is typically diagnosed and managed by nephrology specialists, the rare renal diseases group is designated as the preferential parent of Atypical HUS and its subtypes.

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 virtual network involving healthcare providers across Europe, aiming to facilitate discussion on complex or rare diseases and conditions that require highly specialised treatment, and concentrated knowledge and resources.

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.

Expert resource: a resource specific to rare diseases, including patient-centered services (medical laboratories and diagnostic tests, expert centers, and patient organisations) and research-related activities (research projects, clinical trials, patient registries, biobanks, and networks of experts) collected in member countries of the Orphanet Network, and constituting the Orphanet catalogue of expert resources.

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.

Orphadata: a platform developed by Orphanet to provide the scientific community with comprehensive, high-quality and freely accessible datasets related to rare diseases and orphan drugs, in a reusable format.

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 national team: an Orphanet team based in one of the member countries of the Orphanet Network as per the Orphanet Network Agreement, and responsible for the collection of data on national expert resources. Some of the national teams are also in charge of the translation of the Orphanet nomenclature into one of the languages of translation of the database (German, Italian, Spanish, Portuguese, Polish, Czech and Dutch).

Orphanet nomenclature manager: an information scientist of the Orphanet coordinating team in charge of producing and updating the nomenclature and classification of rare diseases.

Orphanet Rare Disease Ontology (ORDO): an open access, structured, and machine-readable vocabulary for rare diseases derived from the Orphanet database, capturing relationships between diseases, genes and other relevant features, and forming a useful resource for the computational analysis of rare diseases. ORDO was jointly developed by Orphanet and the European Bioinformatics Institute (EMBL-EBI).

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:

https://www.orpha.net/orphacom/cahiers/docs/GB/eproc_disease_inventory_R1_Nom_Dis_EP_04.pdf

II. Methodology

1. Flowchart

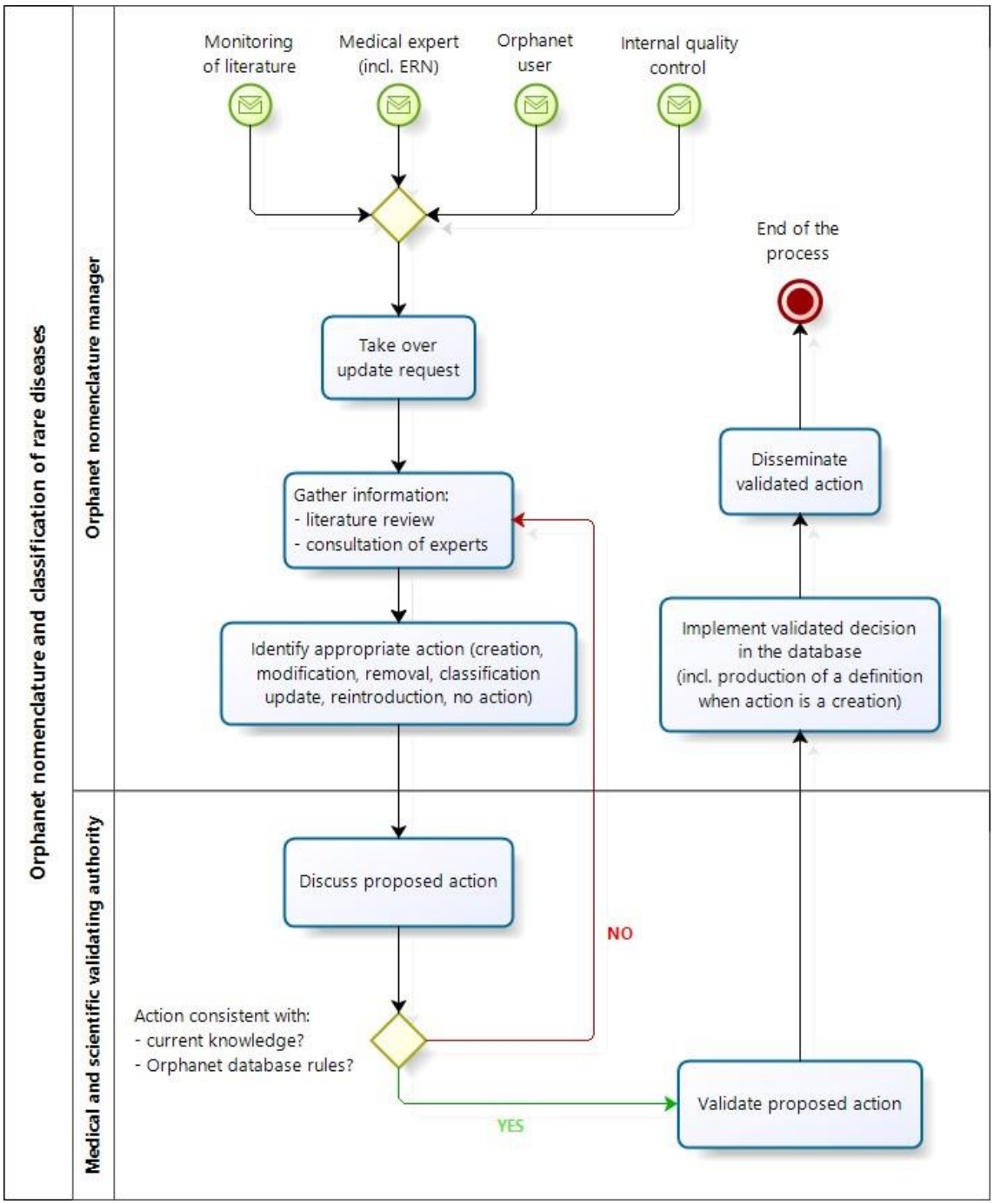

***Figure 3**. Workflow of the production and update process of the Orphanet nomenclature and classification of rare diseases* (powered by Bizagi modeler)

2. Description

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.

Update requests can be submitted to the Orphanet nomenclature managers in different contexts:

- Monitoring of the international scientific literature: identification of a newly described disorder or new phenotypic information impacting the diagnostic scope of an existing disorder,
- Collaboration with a European Expert Network (ERN) on the revision of a group of disorders,
- Consultation of an expert for the update and validation of a disease summary text for the Orphanet Encyclopedia for professionals,
- Collection of data on expert resources by the Orphanet national teams,
- Contributions from users of the Orphanet database,
- Internal quality control performed on a daily basis by the Orphanet nomenclature managers in order to detect and correct inconsistencies in the nomenclature and classifications, such as: missing entities identified while gathering information for another request; entities with an incorrect classification level; discrepant representation of a group of disorders between the different classification groups it is included in; inconsistent nomenclature between similar entities, or categories that are ill-defined, empty or no longer in use, among other cases.

The nomenclature manager in charge of a request gathers information through a review of the scientific literature and/or the consultation of experts, in order to determine the most appropriate action in view of the current state of knowledge and the Orphanet database rules (**Table 4**).

Decisions proposed by the Orphanet nomenclature managers are discussed and validated during meetings held on a monthly basis with the Orphanet Medical and Scientific Committee, which gathers medical doctors and information scientists of the coordinating team.
In certain cases, such as update requests arising from the collaborative revision of a classification with a ERN, proposed actions are validated directly upon discussion with ERN experts.

All validated actions are disseminated within the Orphanet coordinating team after each meeting. Scientific annotations associated with newly created or modified clinical entities (such as genes, epidemiological data, expert resources, etc.) are subsequently controlled and updated in the Orphanet database (when necessary) by the information scientists in charge of these activities.

A definition is produced for each new clinical entity created in the database by an Orphanet nomenclature manager. Conversely, existing definitions associated with removed clinical entities are deleted. The editorial rules and the process applied for the production, the validation, the publication, and the update of definitions included in the Orphanet nomenclature are detailed in a separate procedural document.

Validated decisions are also communicated to the Orphanet national teams, along with a ready-to-translate table listing all the preferred terms, synonyms and keywords of newly created or modified clinical entities, in order to ensure that the terms of the Orphanet nomenclature, which are produced in English and translated in French by the coordinating team, are updated accordingly in all the other languages of translation of the Orphanet database (German, Italian, Spanish, Portuguese, Polish, Czech, and Dutch).

Action	Range of application
Creation	Addition of a newly described or missing clinical entity (disorder, group of disorders or subtype of a disorder) to the Orphanet nomenclature.
Modification	Modification of the nomenclature terms (preferred term, synonyms, keywords) or the typology of a clinical entity.
Removal by **obsolescence**	- Exact duplicate of another existing clinical entity - Unclear entity that cannot be precisely characterised - Only one published case in the literature - Organisational category that is no longer in use The obsolete ORPHAcode is "referred to" an active ORPHAcode.
Removal by **deprecation**	The phenotype was initially considered as an independent diagnosis, but is now considered as part of another diagnosis as a result of the evolution of knowledge. The deprecated ORPHAcode is "moved to" the recognized active ORPHAcode.
Removal as **non rare in Europe**	Current epidemiological knowledge is not consistent with the European definition of a rare disease (less than 5 affected individuals per 10,000).
⚠ ORPHAcodes that are removed from the nomenclature are not reused for different clinical entities.	
Reintroduction	Reintroduction of a previously removed clinical entity into the nomenclature, following the reassessment of all causes of removal in the light of new information available in the literature.
Classification update (disorder or group of disorders)	- Revision of a group of disorders in collaboration with a ERN, and/or following the publication of a new classification scheme by an international medical consortium. - Minor corrections as part of internal quality control.
No action	The request is not consistent with the current knowledge and/or the Orphanet database rules.

***Table 4**. Summary of all types of modification applicable to a clinical entity of the Orphanet nomenclature*

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

Editor of this procedural document: Julie Tahraoui
This procedural document has been approved by: Ana Rath
Quality control (Non Compliant Product): Florence Sauvage
Identification code of the document: R1_Nom_Dis_EP_12.
Version of the document: 05
The correct form when quoting this document is:
Procedural document on the Orphanet nomenclature and classification of rare diseases, Orphanet, June 2023, Number 05
https://www.orpha.net/orphacom/cahiers/docs/GB/eproc_disease_inventory_R1_Nom_Dis_EP_05.pdf