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Orphanet Standard Operating Procedures

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I. Introduction

1. Purpose/objectives

The Orphanet “Standard Operating Procedures” (SOPs) provide Orphanet teams with general information and agreed principles to run the activities related to Orphanet’s missions.

It is structured into six different parts:

1. Introduction;
2. General information on the Orphanet network;
3. Information on the agreed principles to run the network and the activities;
4. Information on the Orphanet knowledge base, the general process to populate it by activity and links to available procedures;
5. Expert directory data collection and update, which are jointly managed by the Orphanet coordinating team and the Orphanet national teams;
6. General processes set up for the translation of all or part of the Orphanet content.

These procedures are agreed on by the Orphanet Management Board, they are reviewed and amended yearly.

2. Range of application

This procedure is intended for Orphanet Network teams and Orphanet users.

3. References

- Orphanet Network agreement (version in force)
- <https://www.orpha.net/en/other-information/procedures>

4. Filing and updates

These procedures are updated annually by the Inserm-based Coordinating team. The most up-to-date version is available on the Orphanet website: <http://www.orpha.net>.

5. Disclaimer

N/A

6. Definitions

Annual Activity Report	Comprehensive report on Orphanet's activities, with statistics, from January to December each year.
Anesthesia guidelines	Recommendations for anesthesiologists, written and revised by experts. They are produced by Orphananesthesia ; exceptionally, other anesthesia guidelines published in peer-reviewed scientific journals can be found under this term.
Clinical practice guidelines (CPGs)	Recommendations or guidelines to standardise the diagnosis and treatment of clinical disorders for clinicians, patients and healthcare administrators. They are produced by learned societies or official organisations and are published either in peer-reviewed scientific journals or in learned societies or on health agencies websites. CPGs are assessed through a methodology based on the AGREE II instrument criteria, before dissemination via Orphanet.
Clinical signs and symptoms/ Clinical features	Rare disorders are currently being annotated with phenotypic abnormalities (clinical features) in the Human Phenotype Ontology (HPO). The alignment is characterised by frequency (obligatory, very frequent, frequent, occasional, very rare or excluded) and whether the annotated HPO term is a major diagnostic criterion, a pathognomonic sign or an exclusion criterion of the rare disease.
Clinical genetics review	Externally produced and peer-reviewed disease descriptions focusing on genetic aspects, of use in the diagnosis, management, and genetic counseling of patients and families with specific inherited conditions. This category comprises mostly GeneReview articles.
Coordinating team (OCT)	French US14 Inserm-based team coordinating the Orphanet Network, producing the English Orphanet nomenclature and its scientific annotations and responsible for coordination of the production of the scientific content and for all Network activities including translation and IT developments.
Data transfer agreement (DTA)	Contract between the data provider and recipient institutions governing legal obligations and restrictions, as well as compliance with applicable laws and regulations, related to the transfer of such data between the parties.
Director of Orphanet	Orphanet's coordinator, meaning the Director of the Coordinating Team (Inserm US14) who chairs the Management Board.
Disabilities	Information on activity limitation/participation restriction (functional consequences) described in rare disorders, using the Orphanet Functioning Thesaurus, derived and adapted from the International Classification of Functioning, Disability and Health – Children and Youth (ICF-CY, WHO 2007). The information provided is derived from an assessment of data from the whole patient population affected by the disease, receiving standard care and management (specific and/or symptomatic management, prevention and prophylaxis, devices and aids, care and support).

Disability factsheets	Factsheet containing information intended to provide a better understand and assess of the needs of people with disabilities associated with a rare disorder and to promote guidance and appropriate support in the French national health care system, as well as in the social support system. Each text contains a description of the disorder (adapted from the corresponding text from the Orphanet Encyclopaedia for professionals) and a focus on disability-related measures and consequences in everyday life. The factsheet can be available in other languages if national funding is available. Translations are coordinated by the relevant Orphanet National Team and they promote guidance and appropriate support in the relevant national health care system, as well as in the social support system
Emergency guidelines	Concise guidelines intended to improve management of patients with a known rare disease in an emergency situation. They are structured in two parts: one for the pre-hospital care environment and one for the hospital emergency department. They are produced in French and can be translated in other languages if national funding is available. Coordination of the translation is carried out by the ONT.
Encyclopaedia for patients	Encyclopaedia intended to the general public that is made up of informative texts either produced by Orphanet and peer-reviewed by disease experts and dedicated patient organisations. Either produced by third parties, with their permission. The latter are quality assessed and published with permission of the copyright holder.
Encyclopaedia for professionals, Health Professional Encyclopaedia	Encyclopaedia intended to professional that is made up of a set of expert-authored and peer-reviewed articles. This encyclopaedia includes: review articles, clinical practice guidelines, diagnostic criteria, guidance for genetic testing, Practical Genetics, clinical genetics review, emergency guidelines, anaesthesia guidelines, disability factsheets, and summary information on the disease in a language other than the 8 languages of Orphanet. A methodology for quality assessment has been developed to assess the articles which are published with permission.
ERNs	Virtual networks 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.
Information scientist (IS)	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.
International Advisory Board (IAB)	Consultative board of the Orphanet Network. Composed of independent representatives of stakeholders in charge of peer reviewing the Orphanet project, it reports to the MB and issues comments and recommendations which will enable the MB to define changes to be introduced to the project. The members are nominated by the MB.

National Advisory Board (NAB)	A consultative group for the ONT. Its members can be nominated by the appropriate legitimate institutions (learned societies, national authorities, etc.), which are defined at country level. National Advisory Board members contribute their expertise to Orphanet at country level and validate any database content concerning resources listed for the country in question as well as translation of the Rare Disease Nomenclature and of the Encyclopaedia in the national language, if relevant.
National Coordinator	Designated by the Institution having signed the Network Agreement. He /She has the duty to set up a National team and coordinate it. He/She participates in the Orphanet MB, organises the governance of the project at national level, including liaison with learned societies, National authorities and patient organisations. He/She is responsible for all the data production (either core-data or national data) and data quality management, and translation carried out within the ONT
National websites	The national website are tools to communicate at national level on the activities of the ONT, on events, and on the rare diseases policy in the country. National teams are responsible for the content published on their national website. Only one national entry point is foreseen in any one country, even in federalised countries. The national website provides access to the Orphanet portal in one or two of the 10 available languages (Czech,Dutch, English, French, German, Italian, Spanish, Polish and Portuguese and Russian).
Network Agreement (NA)	Agreement specifying binding commitments among members of the Orphanet Network
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 Advisory Board on Genetics (GAB)	Consultative board of the Orphanet network that advises Orphanet on topics related to the database of genes and the database of medical laboratories and genetic tests. It is composed of geneticists (belonging or not to the MB).
Orphanet Contact Point (OCP)	Applies to the person who has accepted to be a Orphanet spokesperson in the country where there is no active team (having not signed the Network Agreement). All national contact points are located in high-profile institutions. In these countries no dedicated funding is allocated to Orphanet activities, therefore there is no active data collection on expert resources by OCP. Translation of the Orphanet content may be carried out provided that a specific DTA is signed.
Orphanet Knowledge base	Orphanet is the International Rare Diseases and Orphan Drugs knowledge base, an organised and dynamic collection of information about rare diseases and orphan drugs where data from multiple sources are archived, reviewed, distilled and manually annotated by experts and quality controlled according to published procedures.

Orphanet Management Board (MB)	Decision-making body of the Orphanet Network. It is composed of the National Coordinators (one per member of the Orphanet Network). The MB is in charge of identifying funding opportunities, of guiding the project to provide an optimum service for the end-users, and of considering the inclusion of new teams as well as ensuring the continuity of Orphanet. It is chaired by the Orphanet coordinator at the Inserm. The Board is coordinated by Inserm.
Orphanet National Teams (ONT)	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 and validation of data collected at national level. 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 (French, German, Italian, Spanish, Portuguese, Polish, Czech and Dutch).
Orphanet Network	Means the ONTs contributing to the Orphanet database in the framework of the signed Network Agreement and DTAs.
Orphanet Nomenclature National Hubs	National support teams for the implementation of ORPHAcodes at the national level, conducted by the ONT. ONT interact with HCPs' managers and identified target stakeholders in order to promote the nomenclature, assess their needs, organize the capacity building at the national level (by delivering trainings, organizing workshops), and act as the first-level helpdesk (using the RD-CODE GitHub as a tool). Local teams also provide feedback to the coordination level both on the supporting tools and on ORPHAcodes improvement needs (if funding available).
Orphanet online registration service	Service allowing the professionals to register and/or update their activities related to rare diseases in the Orphanet database.
OrphaNetWork internal newsletter	Internal newsletter that aims to improve the management of the network by communicating on MB, OCT and ONT activities, recommendations, suggestions and achievements, providing information on Orphanet's evolution and tools. It is published bi-monthly and sent within the Orphanet Network to ONT by the OCT. National Advisory Board members, scientific board members and IAB members can also subscribe.
OrphaNetWork website	The internal website dedicated to Orphanet national teams and works as a repository for common tools and documents. It is only accessible to ONT through a login and password.
OrphaNews	A newsletter dedicated to bringing the latest political and scientific news in the field of rare diseases to stakeholders. OrphaNews International is the newsletter in English. OrphaNews national editions are translations/adaptations of OrphaNews International, produced when national funding is identified. The newsletter is also available in French and Italian.
Practical genetic articles	Articles on clinical genetics produced by the European Journal of Human Genetics (EJHG), which is an Orphanet partner.
Project manager	In an ONT, he/she ensures that the missions of the Orphanet team are met and coordinates information scientists' activities in accordance with the strategy established by the National Coordinator. He/she is under the supervision of the national coordinator to whom he/she reports.

Review articles	Articles that provide a comprehensive, clinically-oriented and up-to-date description of a rare disorder (or of a group of rare disorders, a sub-type, etc.). They are intended for health professionals and scientists ; generally published in a peer-reviewed medical or scientific journal
Scientific annotations	Orphanet scientific annotations comprise clinical signs and symptoms (phenotypes), epidemiological data, natural history, disabilities related to a rare disorder, associated genes. Information reported in the literature are collected, selected, reviewed and annotated. Sources are available. Data collection is manually curated and a validation status is available.
Translation report	Report containing Orphanet content to be translated in languages other than English by the ONT.
Translation staff	Staff in charge of translation of the relevant material sent through the Translation Report and according to the relevant procedures (either within the ONT or appointed by it or within the Third Party if relevant). He/she is under the supervision of the country National Coordinator to whom he/she should report.
Medical Validation Staff	Staff in charge of the medical validation of the summary information and of the translation of (medical) Orphanet content in national language.

II. General information on the Orphanet Network

Orphanet was established in France by the INSERM (French National Institute for Health and Medical Research) at the initiative of the French Ministry of Health in 1997. This initiative became a European endeavour from 2000, supported by grants from the European Commission: Orphanet has gradually grown to a network, within Europe and across the globe.

The Orphanet Network is composed of 31 members (endorsed by national authorities) in countries¹ bound by a Network Agreement (in place since 2018), plus a member in temporary suspension, as well as 6 contact points (Fig.1). The network is coordinated by the Orphanet Coordinating team (Inserm US14) according to the principles agreed in the Network Agreement and the present Standard Operating Procedures (SOPs). Each Institution member nominates a National Coordinator who agrees to advance the goals of the project (please refer to paragraph 3) and to be responsible for their Orphanet National Team’s work according to the present SOPs.

¹ NB. This figure is correct as of December 2024, figure evolves as new countries join regularly. To have the most up to date figure please refer to the https://www.orpha.net/orphacom/cahiers/docs/GB/Orphanet_Network_MB_members.pdf

The Orphanet Network’s mission is to increase awareness and knowledge on rare disorders (RD) and ultimately contribute to improve the diagnosis, care and treatment of patients with rare diseases by making available the Orphanet knowledge base, an organised and dynamic collection of information and data about RD and orphan drugs. Orphanet is intended to serve the following communities: health care professionals, patients and their relatives, patient organisations, researchers, biotech and pharmaceutical companies, public health and research institutions, and public authorities.

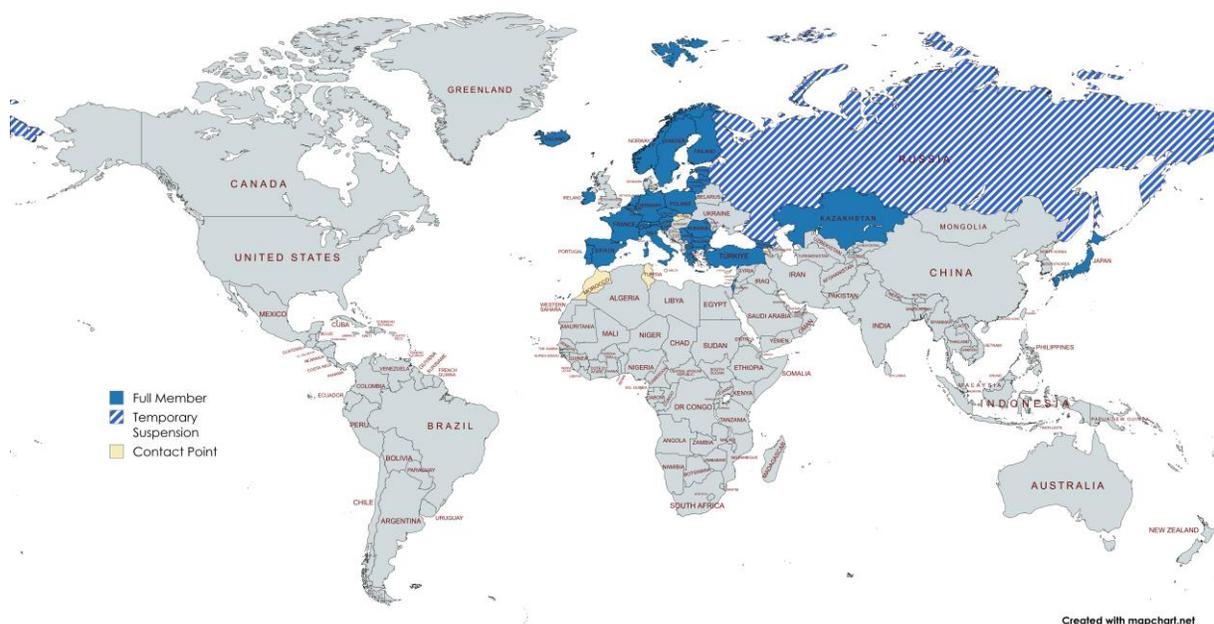


Figure 1 Orphanet Network as of December 2024

1. Goals

To achieve its missions the Orphanet Network works towards meeting the **three main goals** listed below, by populating the Orphanet knowledge base, an organised and dynamic collection of information and data about RD and orphan drugs (for detailed information on the knowledge base and data population please refer to chapter 3).

i) Improve the visibility of rare diseases in the fields of healthcare and research by maintaining the Orphanet rare disease nomenclature (ORPHAcodes) which provides a common language to understand each other across the RD field. The nomenclature is unique and multi-lingual and the additional data in our relational database is structured around it. Each disease is assigned a unique ORPHAcode: integrating this nomenclature in health and research information systems is essential in ensuring that rare diseases are visible and that different systems can work together. This nomenclature is aligned with other terminologies: OMIM, ICD-10, ICD11, SNOMED-CT, MedDRA, UMLS, MeSH, GARD. These alignments constitute a key step towards the interoperability of databases and the

Orphanet nomenclature acts as an interoperability vector² between healthcare and research. Please refer to section 3 for additional info on the nomenclature.

ii) Provide high-quality information on rare diseases and expertise, ensuring equal access to knowledge for all stakeholders thus orientating users and actors in the field in the mass of information online. Orphanet provides visibility to experts and for patients by providing access to a catalogue of expert resources in member countries by disease, such as ERNs, centres of expertise, laboratories and diagnostic tests, patient organisations, research projects, biobanks, variant databases, patient registries, infrastructures and clinical trials. This data promotes networking, tackles isolation and helps foster appropriate referrals. Orphanet draws on the expertise of professionals from across the world to provide scientific data on rare diseases (gene-disease relationships, epidemiology, phenotypic features, functional consequences of diseases, etc.). In addition, Orphanet produces a multi-lingual encyclopaedia of rare diseases. Orphanet also integrates and provides access to high quality information produced around the world, such as clinical practice guidelines and information geared to the general public.

iii) Contribute to generating knowledge on rare diseases thus piecing together the parts of the puzzle to better understand rare diseases. To develop and curate the scientific data, Orphanet works with experts from around the globe, from health care professionals and researchers (including ERNs), to patient representatives and professionals from the medical-social sector. The wealth of data in Orphanet and the way this data is structured allows additional knowledge to be generated, helping to piece together data that at times can resemble pieces of an irresolvable puzzle. Integration of this data adds value and renders it interpretable. Orphanet provides standards for rare disease identification, notably via the Orphanet nomenclature, an essential key for interoperability as is the production of links to other agreed standards, such as the Human Phenotype Ontology (HPO). Orphanet provides integrated, re-usable data essential for research on the Orphadata platform (www.orphadata.com) and as a structured vocabulary for RD, the [Orphanet Ontology of Rare Diseases \(ORDO\)](#) and [as HPO – ORDO Ontological Module \(HOOM\)](#). These resources are being integrated in several bioinformatics projects and infrastructures around the world in order to improve diagnosis and treatment. Orphanet is committed to networking with partners across the globe order to help contribute to generating new knowledge on RD.

2. History

Orphanet was established in 1997 as an Inserm (French National Institute for Health and Medical Research) service, at the request of the French Ministry of Health, and was developed thanks to financial support from several French institutions and organisations: the Ministry of Health, Inserm, CNAM (French public health insurance fund), AFM-Téléthon (French neuromuscular organisation) and the FNMF (Federation of non-profit health insurers).

This initiative became a European endeavour from 2000, supported by grants from the European

² ELIXIR Excelsior: Report on disease mappings and added value of Orphanet and ORDO for the project with contribution of rare disease linked data and models from Orphanet as interoperability backbone components for rare diseases (October 2016) <https://drive.google.com/file/d/1dsfAAdxF4USmsKK9YQ4lpDW44OqNIZ--/view?usp=sharing>

Commission (DG Santé and DG Research & Innovation)³. Thus, the database and the website were progressively translated, and are now available in 8 languages: English, Dutch, French, German, Italian, Polish, Portuguese and Spanish. The Network has evolved as described below:

- Belgium, Germany, Italy, Switzerland (2001)
- Austria, Spain (2002)
- Portugal (2003)
- Bulgaria, Cyprus*, Denmark**, Estonia, Finland, Greece**, Hungary**, Ireland, Lithuania, Netherlands, Romania, United Kingdom** (2004)
- Croatia **, Czech Republic, Latvia, Lebanon**, Malta*, Morocco*, Norway, Poland, Slovakia*, Slovenia, Serbia, Sweden, Turkey** (2006)
- Israel, Armenia* (2007)
- Canada* (2011)
- Western Australia *(2012)
- Georgia and Tunisia* (2014)
- Argentina* (2015)
- Japan (2017)
- Luxembourg, North Macedonia, Turkey***** (2019)
- Russia***, Kazakhstan (2020)
- Greece***** (2023)
- Iceland (2024)

*: Orphanet contact points

** Now withdrawn from the Network

*** Temporary suspended in 2022 and until further notice

**** reintegration into the Network after an interruption of activity

3. Description of the Application process to join the network

The institution wishing to join the network expresses its will to become a member of Orphanet by sending a letter to the Coordinating team's (Inserm US14) Director, demonstrating its capacity to run Orphanet activities (see paragraph 6.2). The application must be endorsed by the National Health Authorities of the country or its Ministry of Science/Research, by a letter of support. This is of paramount importance as the data on national expert resources made available has a direct impact on referrals to these resources. Any application of a new Institution will be subject to a vote of the Management Board (see paragraph 4).

A new Institution becomes a Member of the Orphanet Network upon signature of the Accession document in Attachment 4 of the Orphanet Network Agreement.

4. Structure

The Orphanet Network governance is defined in the **Network Agreement** signed by all members.

³ for detailed information on funding please refer to the online [Orphanet activity report](#)

The **Orphanet Network** is composed by several institutions and it is managed by several boards, which oversee the project independently of specific projects and grants, in order to ensure the coherence of Orphanet's activities, their evolution in relation to technological developments and the needs of its end-users, as well as their sustainability (fig.2).



Figure 2 Orphanet governance

4.1 Governance

The Decision-making body of the Network is the Management Board (MB). It is in charge of guiding the project to provide an optimum service for the end-users, and of considering the inclusion of new members as well as ensuring the continuity of Orphanet. It is composed of the National Coordinators (one per member of the Orphanet Network). It is chaired by the Director of the Coordinating team at the Inserm. The list of members is available [here](#) (refer to section II for more info).

Several Consultative Boards are in place (please refer to section II for more info)

The OrphaNetWork Operating Committee. This internal consultative committee is in charge of defining a strategy so that the Orphanet 'culture' is consolidated within the network and to improve effective communication within the network. It reports to the Management Board.

The International Advisory Board, composed of international experts, is in charge of advising the Management Board regarding the overall strategy of the project. Rules of procedures available [here](#).

The Genetic Advisory Board, composed of international experts, is in charge of advising Orphanet on topics related to the gene database and the database of genetic tests and laboratories. Rules of procedures available [here](#).

The National Advisory Board(s) is/are composed by members nominated by the appropriate legitimate institutions, defined at country level by the ONT. The board members contribute with their expertise to

Orphanet at country level.

Terms of reference for each Board are indicated in section II.

4.2 Teams

4.2.1 Orphanet coordinating team (OCT)

The Orphanet Coordinating Team (OCT) is located at the Inserm (the French National Institute of Health and Medical Research), service Unit 14. Coordination activities and Database core activities are carried out by the Inserm US14 since the creation of Orphanet in 1997. [\(Please refer to section 6 for more info\).](#)

4.2.2 Orphanet National teams (ONT)

Orphanet National Teams (ONT) are located in each participating country of the Orphanet Network. A ONT is composed, at least, of a National Coordinator who is responsible for the national Orphanet activities (at minimum data collection on expert resources at national level, refer to section 6 for more info). It can also include a project manager, one or several information scientists, translation staff and a Orphanet Nomenclature National Hub project manager.

4.2.3 Orphanet Contact Point

All national contact points are located in high-profile institutions. In these countries no dedicated funding is allocated to Orphanet activities, therefore there is no active data collection concerning expert resources. Translation of the Orphanet content may be carried out provided that a specific DTA is signed.

5. Orphanet Teams activities and their impact

Orphanet activities are divided into three categories: (1) Network coordination activities and core activities (blue nucleus in the figure below) performed by the OCT, (2) shared core activities (grey layer in the figure below) which can be performed both by the OCT or the ONT, both (1) and (2) are transnational activities, and (3) national activities (blue external layer in the figure below) performed by ONT. An impact analysis of these activities is presented in the Table below.

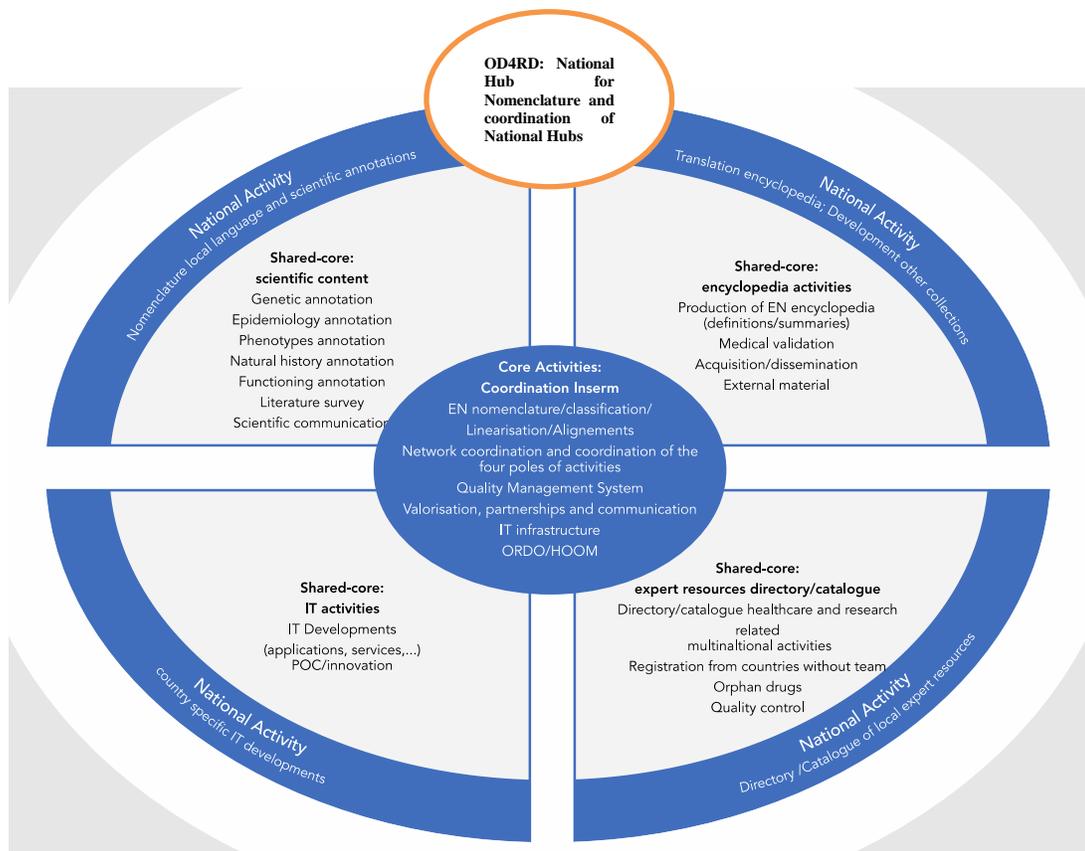


Figure 3 Modular representation of Orphanet activities

Activity	Impact
<p>Nomenclature and alignments Core nomenclature in English (coordination activity)</p> <p>Alignments</p>	<p><i>For patients:</i> increased visibility/recognition in health pathways <i>For healthcare/social care professionals:</i> facilitated identification of RD patients <i>For policy-makers:</i> estimation of prevalence and burden of RD for policy planning <i>For researchers:</i> facilitated data sharing and patient recruitment</p>
<p>Nomenclature in local languages (per country)</p>	<p><i>For industry:</i> facilitated estimation of the market size; facilitated recruitment</p>
<p>National Nomenclature Hubs</p>	<p><i>For patients: better identification in HIS by clinicians</i> <i>For Healthcare professionals: easier use of the ORPHAcodes and decreased codification burden</i> <i>For ERNs: better interoperability of the hospital data with CPMS and with registries, facilitated activity indicators</i> <i>For hospital managers: better control on the process of</i></p>

Activity	Impact
	<i>integrating a new terminology in hospital's medical information systems, support and facilitation of implementation, capacity building for their personnel, better control on rare disease related activity</i>
Scientific Annotations (epidemiology, phenotype, genotype, natural history, disabilities)	<p><i>For patients:</i> know the manifestations and disabilities of their disease</p> <p><i>For professionals:</i> facilitated examination, diagnosis and evaluation of patients</p> <p><i>For policy-makers:</i> reliable figures on epidemiology for policy planning</p> <p><i>For researchers:</i> re-use of combinations of data for hypothesis making</p> <p><i>For industry:</i> facilitated knowledge of market size; re-use of combinations of data for hypothesis making in R&D (pre-competitive)</p>
Encyclopedia in English	<p><i>For patients:</i> understanding of diseases; support for communication with professionals/institutions on their or their relative's disease</p> <p><i>For professionals:</i> increased knowledge, support for diagnosis and referral, access to best practice guidelines</p> <p><i>For researchers:</i> rapid access to the literature and state of the art of knowledge</p> <p><i>For policy-makers:</i> facilitated access to state of the art per disease and to guidelines (standards of care)</p>
Encyclopaedia translated in local languages (per country)	
Orphan Drugs	<p><i>For patients and professionals:</i> identification of possible treatments</p> <p><i>For decision-makers:</i> facilitation of analysis, anticipation of costs and follow-up of the therapies to be provided; gap analysis</p> <p><i>For researchers:</i> facilitated analysis and hypothesis-generation together with other elements of the knowledge base; gap analysis;</p> <p><i>For industry:</i> facilitated market surveillance and analysis per disease/groups/domains</p>
International/trans-national expert resources catalogue	<p><i>For patients:</i> identification of expertise in their country and across borders; tackling isolation</p> <p><i>For professionals:</i> facilitated referrals including cross-border services</p> <p><i>For decision-makers:</i> follow-up of the allocation of resources, analysis of coverage of patients' needs and gap analysis for healthcare planning and elaboration of research agenda</p> <p><i>For researchers:</i> facilitated networking by identification of experts and groups</p>

Activity	Impact
National expert resources catalogue	<i>For industry:</i> facilitated identification of experts, researchers, patient organisations for collaboration and recruitment (i.e. for clinical research)
IT developments	<i>All stakeholders:</i> availability of information in dedicated formats (query facilities; re-use formats)

Table 1 *Impact of Core and national activities performed by the whole network (excluding coordination activities, unless otherwise indicated)*

5.1 Resources required

- ❖ The resources necessary to run the coordination and core activities are dependent on the scope of activities which are considered and are ideally not less than 22 FTE (table 2). In addition to staff costs, all costs associated to the IT infrastructure and its maintenance should be added.

Activity	Min. Staff needed (Full Time Equivalents)
Network Coordination activities	4 FTE
Coordination of four poles of activities (including IT development, translations and QoD); SMQ and National hubs Coordination	11.5 FTE
Nomenclature Production and Maintenance	3.5 FTE
Valorisation, Partnerships and Communication	3 FTE

Table 2 *Minimum staff needed per coordination and core activity*

- ❖ The resources necessary to run the shared core activities are ideally not less than 18 FTE (table 3).

Activity	Min. Staff needed (Full Time Equivalents)
Scientific annotations	7.5 FTE
Encyclopaedia	6.5 FTE
International/transnational ER catalogue	2.5 FTE
Orphan Drugs	0.5 FTE
IT project specific developments	1 FTE

Table 3 Minimum staff needed per shared core activity

- ❖ The resources necessary to run Orphanet at national level, are dependent on the scope of activities which are considered, the size of the country and the level of development of expert services in the country.

Activity	Min Staff needed
National coordinator	20 days/year
Expert resources catalogue documentation	0.5 FTE (~1 FTE/ 30 million inhabitants)
National Hub project manager	1 FTE
Nomenclature Translation	0.5 FTE
Database and website content translation	1 FTE/6 months (one shot)
Encyclopaedia translation	1 FTE

Table 4 Minimum staff needed for National Team activities

- The workload to document the expert resources and edit the national web pages is roughly 1 full time equivalent for 30 million inhabitants; this role requires a profile with training or experience in documentation in the field of health/biology (Master's degree level or PhD).
- The workload for translation activities varies according to the content translated (see chapter V). For translation of the whole database content and its updates, roughly a full-time equivalent is needed for approx. 6 months. For translation of the encyclopaedia roughly a full-time equivalent is needed. For translation of the nomenclature roughly a half-time equivalent is needed.
- The workload for a National Hub project manager should be of min. 1 Full Time equivalent for the first year of setting up the National hub, but can vary later according to the number of HCPs present in the country.
- The National Coordinator should be able to dedicate at least 20 days per year to Orphanet, depending on the level of development of the expert resources/services in the country and the scope of the envisaged activities of the team.

The institution hosting the team should provide the office, the computer(s), Internet connection and other necessary supplies, it also should seek additional funding to run the considered activities.

The institutions can also contribute to the shared core activities. The contribution will be

discussed by the MB when reviewing the application.

6. Termination Process

The Orphanet Network has agreed on a series of Indicators and threshold to be reached in order to assess the activity/inactivity of a team (list is available in the Annex of this document). One red indicator tolerance could be applied but mitigating actions should be discussed with the ONT.

- ✓ More than 1 red indicator should require an urgent meeting with the team in order to assess the difficulties and set up an action plan to address them
- ✓ All indicators in red: team should be contacted by the OCT announcing termination process launch as per network Agreement (N.B. it is always possible to find a solution and/or remain part of the Network as a contact point)

The following step-wise approach is to be put in place in order to make sure that the termination process is launched only after every mitigating action are evaluated.

- 1) After 6 months of inactivity (database wise and contact wise according to the Indicators and thresholds available in annex 1): OCT tries to reach out to all the contacts within the party in order to present a mitigating solution and warning about the step-wise approach to the termination process.
- 2) After additional 3 months if still no news, contact the designating Authority in order to help find a solution in the country
- 3) After 12 months in total: if no mitigating action plan can be set up, launch vote for termination as per Network Agreement [according to results of Discussion with National authorities]

7. Orphanet in the health and research policy landscape

7.1 Orphanet in Europe

Orphanet has become a backbone for the European rare disease community, with the substantial quantity of data developed being not only essential as leverage for scientific projects, but also for the elaboration of national and European policies related to RD, and for increasing the awareness and the dissemination of knowledge on RD. Over the past 20 years, a virtuous, symbiotic cycle has evolved, connecting Orphanet's data and RD policy: Orphanet informs policy by providing aggregated data (Orphanet Report Series⁴), and data for annual reports on the State of the Art of RD policies in Europe⁵, and the State of Play of RD research⁶. Orphanet data has proved indispensable in implementing policy measures, such as the official designation of centres of expertise for RD at national level by identifying where experts and expertise is located in a country. Orphanet data can respond to policy needs (for example, data on laboratories carrying out diagnostic tests for rare diseases in Orphanet has evolved in order to facilitate cross-border testing).

⁴ <https://www.orpha.net/consor/cgi-bin/Education.php?lng=EN>

⁵ <http://www.rd-action.eu/rare-disease-policies-in-europe/>

⁶ <http://www.irdirc.org/research/state-of-play-of-research/>

Every European Union text published to date concerning rare diseases highlights the essential role played by Orphanet in the RD landscape, starting with the Commission Communication “Rare diseases: Europe’s challenges”⁷ (11 November 2008) that set the direction of the Community policy as regards the rare disease field. In 2009, the Council of the European Union recommended that all EU MS develop national plans or strategies to structure their response to the challenges presented by RD (Council Recommendation on Action in the field of rare diseases, 8 June 2009⁸). National contribution to the Orphanet network was recommended, and as a result many national plans or strategies developed to date mention Orphanet and ORPHA codification as key measures. Orphanet is also cited in the Directive on the application of patients’ rights in cross-border healthcare (9 March 2011)⁹ as a key resource to assist « *health professionals [...] in correct diagnosis of rare diseases*».

Orphanet’s activities and resources are also supported by a number of key policy recommendations issued by expert committees at the European Commission, on topics such as codification of RD¹⁰, centres of expertise¹¹, European Reference Networks¹² and cross-border genetic testing¹³.

In 2017, Orphanet was recognised as having a *de facto* monopoly in its field in the 2018 Work Plan¹⁴ of the European Union’s Third Health Programme (2014-2020), notably for its unique nomenclature of RD. This recognition has been reconducted in the EU4Health Programme.

7.2 Orphanet in Member States’ national plans/strategies for rare diseases

To date, 25 Member States have adopted a national plan/strategy for rare diseases¹⁵, as recommended by the Council in 2009. The scope and the means accorded to the implementation of these plans/strategies are highly heterogeneous. Active participation by Orphanet National Teams in the preparation of many of those has been sought, as they are recognised as experts at the national level. In the majority of these plans/strategies, Orphanet is mentioned either as the reference site for RD, or as the main source of information on RD, in the recommendations and proposed measures of the majority of national plans or strategies adopted to date¹⁶. Some plans provide explicit and funded support to Orphanet’s national activities, as well as the integration of ORPHA codes into health information systems, some do not foresee specific support to Orphanet teams and their activities, but these countries have Orphanet teams

⁷ https://ec.europa.eu/health/ph_threats/non_com/docs/rare_com_en.pdf

⁸ http://ec.europa.eu/chafea/documents/health/prague-rd-council-recommendation_en.pdf

⁹ <https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32011L0024>

¹⁰ Commission Expert Group on Rare Diseases, Recommendation on ways to improve codification for rare diseases in health information systems (2014),

https://ec.europa.eu/health/sites/health/files/rare_diseases/docs/recommendation_coding_cegrd_en.pdf

¹¹ EUCERD Recommendations on Quality Criteria for Centres of Expertise for Rare Diseases in Member States (2011), http://www.eucerd.eu/?post_type=document&p=1224

¹² EUCERD Recommendations on European Reference Networks for Rare Diseases (2013)

http://www.eucerd.eu/?post_type=document&p=2207

¹³ Commission Expert Group on Rare Diseases, Recommendation on cross-border genetic testing of rare diseases in the European Union (2015)

https://ec.europa.eu/health/sites/health/files/rare_diseases/docs/2015_recommendation_crossbordergeneticstesting_en.pdf

¹⁴ https://ec.europa.eu/health/sites/health/files/programme/docs/wp2018_annex_en.pdf

¹⁵ <http://www.rd-action.eu/rare-disease-policies-in-europe/>

¹⁶ <https://www.eurordis.org/content/rare-disease-plan-and-strategies-european-countries>

<http://www.euoplanproject.eu/NationalPlans?idMap=1>

<http://www.rd-action.eu/rare-disease-policies-in-europe/>

https://ec.europa.eu/health/non_communicable_diseases/overview_en

designated by their competent authorities.

In addition to the prominent position of Orphanet in national plans/strategies for RD in MS, the Italian Health Ministry has included Orphanet as a reference in the new version (July 2016) of the Ministerial Decree of 9 December 2015¹⁷, on Prescription Appropriateness that requires laboratories performing genetic tests in Italy to refer to genes reported in the Orphanet database with their diagnostic value.

Also as of 1 April 2023 in Germany the "Digital-Care-and-Nursing-Modernisation Act"(the DVPMG) will come into force: RD coding by using the Alpha-ID-SE file is legally mandatory in the inpatient sector in all German hospitals. The Alpha-ID-SE file contains ORPHAcodes in addition the key number of the ICD-10-GM is produced by the Orphanet Germany team to provide a RD coding system in the German health-care area offering a simplified, uniform and standardised coding of rare diseases.

7.3 Recognition

Orphanet, and its nomenclature are now an internationally recognised standard: Orphadata, the data download platform from Orphanet, has been recognised as an [ELIXIR Core Data Resource in 2019](#). This acknowledges the critical importance of the data Orphanet makes available to the life science research community, the International Rare Disease Research Consortium (IRDIRC) awarded Orphanet and its ontology *Orphanet Rare Diseases Ontology* (ORDO) [IRDIRC Recognized Resource](#) status in 2015. These two resources were also named [Human Variome Project Recommended Systems](#) in 2017.

The European Commission Expert Group on Rare Diseases has also promoted the inclusion of ORPHAcodes in health information systems ("[Recommendation on Ways to Improve Codification for Rare Diseases in Health Information Systems](#)" 2014). Many EU MS are implementing ORPHAcodes into their health information systems, and rely now on this central resource. A survey of Member States¹⁸ was carried out in May 2017 in the context of the RD-Action Joint Action, demonstrating that 10 Member States have already started implementing ORPHAcodes in health information systems: the level and scope of this integration is heterogeneous with, in some cases, ORPHAcodes used in addition to existing coding systems for rare disease patients.

The use of ORPHAcodes for the codification of RD patients in Europe has been recognised as a Best Practice by the Steering Group on Health Promotion, Disease Prevention and Management of Non-Communicable Diseases (the Steering Group on Promotion and Prevention (SPGG) in 2017¹⁹. The Orphanet Nomenclature of RD was seen as instrumental to implement the 2011 Cross Border Health-care Directive as far as RD are concerned. So, ORPHAcodes are the recommended code to trace RD diagnoses in the European Common Semantic Strategy 2019 & in the Guidelines on Patient Summary, Release 3.2, Mar 2022 ²⁰, as such ORPHAcodes (aggregation level-disorder level and subtypes) are included in the Code Systems used in the MVC - My Health @ EU - eHealth Digital Service

¹⁷ <http://www.trovanorme.salute.gov.it/norme/dettaglioAtto?id=53949>;

https://www.gazzettaufficiale.it/do/atto/serie_generale/caricaPdf?cdimg=16A0039800100010110001&dgu=2016-01-20&art.dataPubblicazioneGazzetta=2016-01-20&art.codiceRedazionale=16A00398&art.num=1&art.tiposerie=SG

¹⁸ RD-Action report: Implementation of rare disease patient coding across member states http://www.rd-action.eu/wp-content/uploads/2017/09/2017-09_RD-ACTION-implementation-coding-survey2.pdf

¹⁹ https://ec.europa.eu/health/sites/health/files/major_chronic_diseases/docs/ev_20180411_flash_en.pdf

²⁰ https://ec.europa.eu/health/sites/health/files/ehealth/docs/ehn_guidelines_patientsummary_en.pdf

Infrastructure (eHDSI). The functional specifications issued by the X-eHealth project also included ORPHAcodes in the MDS required for the ePS ^{21,22}

As a codification and interoperability tool, the RD nomenclature and ontology (ORDO) are central resources in other structuring projects: RD-CODE²³, as the core nomenclature is delivered in an adapted format to fit patient codification needs, and EJP-RD²⁴, using ORDO as a core interoperability resource for research.

The Orphanet catalogue of expert resources and ORDO constitute the basis of the virtual platform for resources in the European Joint Co-fund Programme for RD (EJP-RD).

Since December 2022, Orphadata Science, the Orphanet scientific knowledge base including ORPHAcodes and ontologies, is a Global Core Biodata Resource (GCBRs) as recognized by the Global Biodata Coalition. This recognition identifies resources whose long-term funding and sustainability is deemed to be critical to life science and biomedical research worldwide.

7.4 Orphanet and European Reference Networks

ERNs and Orphanet are the components of a European ecosystem dedicated to rare diseases with complementary roles: ERNs have the clinical and scientific expertise on RDs and Orphanet has the expertise on databasing and standardization. Furthermore, Orphanet's national anchorage (through the national teams) is contributing to the integration of the ERNs at the Member State level, in particular by assisting the ORPHAcodes implementation in HCPs hosting ERNs. Supporting this complementarity will result in avoiding a "silo" approach, thus avoiding of duplication of efforts, and *in fine*, a better use of scarce resources. Collaborations with several ERNs are ongoing with the aim at improving the Orphanet classifications, at producing summaries for selected diseases and at improving the representation of ERN-related expert resources as well as working on PROMs and PCOMs. In particular, trainings to improve the implementation and use of the ORPHAcodes are provided to ERN centers at the national level (see www.OD4RD.eu).

III. Agreed principles to run the network and the activities

Principles governing the Orphanet network are established in the Network Agreement signed by all members. Network governance and organisation are described here. Definitions of each Board are provided at the beginning of this document.

²¹ https://health.ec.europa.eu/system/files/2023-04/ehn_guidelines_patientsummary_en.pdf

²² <https://www.x-ehealth.eu/wp-content/uploads/2022/11/D5.6-Refine-PS-functional-specifications-to-account-for-eHN-Guidelines-and-rare-diseases.pdf>

²³ www.rd-code.eu

²⁴ <http://www.ejprarediseases.org/>

1. Governance: terms of reference

1.1 The Management Board terms of reference

The Management Board (MB) is composed of the National Coordinators (one per member of the Orphanet Network). It is chaired by the Director of the Coordinating team at the Inserm. The list of members is available [here](#).

The Management Board meet by conference calls every two months and face-to-face during an annual meeting. Annual meetings can be organised by partner institutions in turn.

A report is issued after each meeting (at distance and *de visu*) and made available in the intranet.

1.2 Consultative Boards terms of reference:

1.2.1 Orphanetwork Operating Committee (OOC) terms of reference

The OOC was established in the context of the evolution of Orphanet organisational model into a more flexible and distributed model (see section II), to ensure consolidation of the Orphanet ‘culture’ amongst the network and to improve effective communication within the network (a two-way information sharing process). This Board was established in the context of the evolution of Orphanet organisational model into a more flexible and distributed model, in the context of the joint action RD-ACTION 2015-2018. It is organised into 8 groups, each group is composed of two members and represents 3 to 6 National teams. The final composition is agreed by the MB. It meets every two months by conference call and annually *de visu* if funding available.

The OOC reports to the MB. A report is issued after each meeting (at distance and *de visu*) and made available via the intranet. Rules of procedures and list of members available [here](#).

The OOC activity has been partially suspended in 2022, only the Nordic group continue its activity.

The mitigating actions in place to ensure consolidation of the Orphanet culture and improve the two-ways communication are the following:

- Coaching sessions are organised to ensure capacity building of junior teams and follow up of teams in difficulties
- a series of open sessions are organised regularly around various topics including the activities of the coordinating team, the new services and tools prior to their public release, the projects in which the coordinating teams is involved
- the training programme has been extended in order to cover additional aspects of the Orphanet Scientific activities (such as Genetic annotations, Alignments, Epidemiologic annotations)
- monthly calls organised in the frame of the OD4RD project to discuss the advances and work of the Orphanet National Hubs as well as a coordinated approach to hubbing.

1.2.2 The International Advisory Board terms of reference

It reports to the MB and issue comments and recommendations which will enable the MB to define changes to be introduced to the project. The members are nominated by the MB. Their expertise covers

the following fields: scientific databases, information technologies, ontologies and nomenclatures, communication and education, R&D, rare diseases and orphan drugs.

A report is issued after each consultation and made available via the intranet.

Rules of procedures and list of members available [here](#).

1.2.3 Genetic Advisory Board terms of reference

Consultative board of the Orphanet network. It is composed of geneticists (belonging or not to the MB). They advise Orphanet on topics related to the database of genes and the database of medical laboratories and genetic tests.

A report is issued after each meeting and made available via the intranet.

Rules of procedures and list of members available [here](#).

1.2.4 National Advisory Board (optional) terms of reference

Orphanet National Teams can decide to set up a National Advisory Board (NAB), its members being nominated by the appropriate legitimate institutions (learned societies, ministries, etc.), defined at country level. NAB members contribute with their expertise to Orphanet at country level: they identify the main sources of information and locate the main expert teams in their country. They also validate any database content concerning resources listed for the country in question and Orphanet nomenclature production in National Language translations, if relevant. Their expertise should cover all medical fields as the study of rare diseases concerns many different disciplines. It is also recommended that the national representative of the Committee of Orphan Medicinal Products is solicited to contribute to the Board. The Board's composition is indicated on the relevant National website.

1.2.5. Boards developed in the frame of the OD4RD project (2022-2025)

[In 2022, a Data Advisory Board was created in the frame of the OD4RD project \(www.od4rd.eu\) in order to advise on the ORPHAcodes and Orphanet knowledge base implementation and exploitation. Terms of reference can be found here.](#)

In 2022, a ERN Board was created in the frame of the OD4RD project. This Board is in charge of providing advice on the strategy addressing the ORPHAcodification and implementation needs, and of facilitating the collaboration between ERN groups and Orphanet team in improving the Orphanet nomenclature and the production of RD information. The ERN Board acts as the forum in which different kinds of Orphanet-ERNs collaboration will be presented to promote synergies across ERNs. Terms of reference can be found [here](#).

2. Principles to run the activities

2.1 Team composition, missions and roles

2.1.1 The Orphanet Coordinating Team composition, missions and roles

Coordination activities are ensured by the Inserm US14 since the creation of Orphanet in 1997. They ensure that the core and network activities are carried out, and oversee the continuous development of Orphanet.

Mission	Responsibility	Contributors
Establish an effective and efficient governance	Director and deputy director	International coordinator
Ensure smooth communication and information exchange amongst network participants & stakeholders	International coordinator/OOC	MB
Enhance the internal cohesion of the Orphanet network	International coordinator/OOC	MB
Support consolidation of Orphanet's position in each participating country at national level	Director, International coordinator/OOC/ Manager/ Nomenclature coordinators	Quality Orphanet network MB
Ensure the smooth development of Orphanet database-related activities and its continuous improvement from a scientific and technical point of view	Director, Scientific Quality Manager, Technical Officer, Project Manager, Annotations Coordinator, Orphanet Encyclopaedia Coordinator, ER Catalogue Coordinator.	Director, Chief Client Scientific Coordinator, MB
Develop a partnership and technology transfer strategy	Partnerships and Technology Transfer Officer	MB
Develop a communication strategy	Communication Officer	MB
Identify, prepare, submit and	Director, International	MB

Mission	Responsibility	Contributors
manage funded projects on behalf of the network	Coordinator and Financial Officer	

Table 5 responsibility and contributors of OCT missions

The coordinating team tasks/contributions are:

❖ Coordination activities:

1) The coordination of the network:

Orphanet coordination support Advise the Coordinator and the MB in the field of contracts (Grant agreement (s) / Network agreement) for international cooperation and in relation to Orphanet scientific policy and Orphanet SOPs including non-scientific international Consultative Boards follow-up. Ensure the management of contractual priorities and arbitrations, anticipate and / or manage risks, and plan and control activities and tasks within the unit and the network.)

Ensure communication and information exchange amongst network participants (see 7.4.1)

Network grant management (see 7.3.2)

2) Partnerships, technology transfer and external communication, (see 7.1.2)

3) Coordination of the four poles of Orphanet database activities, translations, QMS and QoD

Coordination of the Orphanet scientific annotations: The Scientific Content Coordinator ensures the prioritisation and the follow-up of the scientific content of the database linked to the Orphanet nomenclature of rare diseases. These annotations include: epidemiological, genetic, phenotypic, functional consequences, natural history data that are produced by information scientists. He/she also ensures the interaction between the network as end-users and the IT development team and with the quality manager in order to ensure the quality control is achieved. Dedicated internal trainings at distance are also provided to the ONT on regular basis.

Coordination of the Orphanet encyclopedia: The Coordinator of the Orphanet encyclopaedia manages the production and prioritization of textual disease information by the medical writers in different teams, including ERNs and coordinates the medical validation and publication of the content produced. Their role is crucial ensuring the smooth coordination of textual information production with ERNs. They also ensure the interaction between the network as end-users and the IT development team and with the Quality of Data Manager in order to carry out adequate quality control.

Coordination of the catalogue of expert resources: The Expert Resources Coordinator establishes the data collection strategy its prioritisation, supports national teams in their daily activities, ensures their training at distance and face-to-face and ensures the interaction between the network as end-users and the IT development team and with the Quality of Data Manager in order to carry out adequate quality control.

Coordination of the Nomenclature National Hubs: The Orphanet coordinating team provides the national Orphanet nomenclature hubs with central support and material ensuring a coherent and mutualised approach and the same level of service quality in each country. This includes training for trainers (Training to empower National Teams to become “trainers”) and training material. A central helpdesk will streamline end-users' demands to the national hub, advanced support being provided by the Orphanet central coordination team when needed. The coordination will provide national hubs with a technical procedure in order to ensure smooth follow-up of the demands. The national hubs network coordination will provide support for organising local activities to maximise mutualisation of efforts.

Quality management system and coordination of quality of data: The quality of the database relies on three pillars: clear and transparent procedures; well-trained teams; overarching quality control. Orphanet has put in place a Quality Management System (QMS) from 2015 on. The Quality of Data Manager coordinates the data quality control actions performed by the whole network to ensure consistency and accuracy of the database.

4) **IT development projects and of the IT infrastructure maintenance**: The coordination team ensures that the IT infrastructure supporting the Orphanet database is maintained and secured, in collaboration with the Inserm Information System department. It coordinates the database and the evolution/development of tools development in order to allow a) Orphanet teams to smoothly perform their tasks, b) maintain a high-quality service for Orphanet’s users and c) ensures evolutions necessary so that services continue to meet the RD community’s needs.

❖ **Core Scientific activities:**

Production of the Rare Diseases nomenclature in English, RD classifications, linearisation of rare disease, alignments of the nomenclature with other medical languages and the production of the ontology, ORDO and HOOM (see chapter 3).

Shared-core scientific activities currently carried out at the OCT level but could be carried out by any ONT with appropriate capacity to do so.

- **Production, publication and update of the Scientific annotations of rare diseases**: genes involved in these diseases and cross-references with other genetic databases, phenotype and disability features, natural history, epidemiological data.
- **Production, publication and update of the Orphanet encyclopaedia dedicated to health professionals.**
- **Production, publication and update of the catalogue of healthcare and research activities with an international dimension and the catalogue of orphan drugs**
- **Informatics developments, innovation and proof of concepts**
- **Post-release Quality Control**

For more information about these activities please refer to chapter three.

2.1.2 Orphanet National Teams composition, missions and roles

Orphanet National Teams (ONT) are located in each participating country of the Orphanet Network. A ONT is composed, at least, of a National Coordinator who is responsible for all the National Orphanet activities. It can also include a project manager, one or several information scientists, translation staff and a Nomenclature National Hub project manager. All team members are under the supervision of the Country Coordinator to whom they report. The information scientist in charge of collecting data concerning expert resources at country level is technically supervised by the Coordinating Team Expert Resources Manager. When applicable, a dedicated person will act as a Nomenclature National Hub project manager, trained by the Coordinating team and under the responsibility of the Orphanet National coordinator.

National teams are responsible for:

- the collection of information on expert centres, medical laboratories, ongoing research and patient organisations in their country and translation of some or all Orphanet Database content in their language if funding available. For the sake of transparency, ONT should also issue at the beginning of each year a table with prioritisation of data resources according to the teams' resources and capacity .
- The establishment of an Orphanet Nomenclature national hub (mandatory for 19 ONTs + 1 observer in 2023 (www.od4rd.eu)). ONT will interact with HCPs' managers and identified target stakeholders in order to promote the nomenclature, assess their needs, organize the capacity building at the national level (by delivering trainings, organizing workshops), and act as the first-level helpdesk (using the OD4RD GitHub as a tool). Local teams will also provide feedback to the coordination level both on the supporting tools and on ORPHAcodes improvement needs (if funding available).

All Orphanet teams work according to [the Orphanet Standard Operating Procedures](#).

Each national team can maintain a web national entry point to Orphanet, providing at minima information on the team composition, sources for data collection and national inclusion criteria (either via the shared tool or via the Institutional webpage see 2.4.1.j. Providing available resources, latest news and updates concerning national activities, in the national language of the country concerned. They can be accessed here: [Orphanet national websites](#). If a team is not in the capacity of administrating a National website, a simple contact form will be made available via this page: https://www.orpha.net/consor/cgi-bin/Directory_Contact.php?lng=FR.

<u>Mission</u>	<u>Responsibility</u>	<u>Contributors</u>
Participation in the governance and strategy of the network	National Coordinator	Team staff
Organisation of the governance and strategy at the national level	National Coordinator	NA
Ensure management of quality control of national data, data production (either core or national) and translation	National Coordinator	Team staff

<u>Mission</u>	<u>Responsibility</u>	<u>Contributors</u>
validity		
Ensure dissemination of team activities and national initiatives	National Coordinator	Team staff
Ensure that the missions of the Orphanet team are met in accordance with the national strategy	National Coordinator/ Project manager if relevant	NA
Provide a catalogue of national expert resources according to Orphanet SOPs	Information Scientists	National Coordinator, project manager
Establish a Orphanet Nomenclature National Hub	National Coordinator	Nomenclature National Hub project manager
Translation of the Orphanet Knowledge base content and/or the Orphanet nomenclature in national language according to Orphanet SOPs.	Translation staff	National Coordinator, project manager

Table 3 Responsibility and contributors to the ONT missions

*including liaison with learned societies, national authorities and patient organisations, and the development of an Orphanet team if applicable.

Roles/tasks of the Orphanet National Team:

There are several possible ways to contribute to Orphanet as a national team:

Mandatory contributions:

- Establish and manage the Orphanet Nomenclature National hub (mandatory for 19 ONTs participating in OD4RD2 in 2023-2025)
- Collection and regular update including QC of information on national expert resources (see section 3.4)
- Organisation of national data validation processes resources (see section 3.4)
- Contribution of country-level information on RD and/or orphan drugs to OrphaNews International
- Contribution to OrphaNetWork newsletter, the internal Orphanet network newsletter: national teams are invited to submit relevant information to OrphaNetWork newsletter and to systematically read every issue and to carry out the action points posted in it
- Carrying out the action points posted in the Quality Control Tasks
- Communication at country level
- Identification of funding opportunities for Orphanet activities in the country
- Promotion of a national policy for RD
- Participation on the Orphanet Management Board (see section 4.1.)
- Establish and manage a national website, using the dedicated tool provided by the coordinating team

or via the Institutional page (refer to 2.4.1.j.) or at minimum a contact form.

Optional contributions (depending on availability of resources):

- Related to National activities:

- Translation and adaptation of the Orphanet nomenclature (see chapter IV)
- Translation of the Orphanet international website (see chapter IV)
- Translation of scientific annotations (see chapter IV)
- Translation of the Orphanet encyclopaedias and/or OrphaNews newsletter (see chapter IV)
- Collection of specific sources of information on RD at national level: review articles or guidelines produced by expert networks or learned societies, as well as articles intended for the general public in a national language could be published in the Orphanet website provided they are compliant with Orphanet quality standards.

- Related to the Core Database activities:

- Production and medical validation of professional encyclopaedia texts
- Acquisition/dissemination of national external material
- Literature review
- Quality control tasks concerning non-national data
- Orphan drugs inventory
- Production of scientific annotations of RD (Genes, Epidemiology, Disabilities, Phenotypes, Natural History)

2.2 Funding and Grant Management

Orphanet is a complex structure, operated by several institutions and financed through grants provided by a variety of funding sources in the form of contracts. Please refer to the activity reports available [here](#) for annual information on funding sources.

2.2.1 Applications for Funding

At the network level:

Applications for Network funding are managed by the OCT as per NA and validated by the MB. The OCT ensures integration in, and partnerships with, consortia and infrastructures relevant to the RD field participating in relevant call for grants, in particular H2020 calls.

Participation and contribution of any ONT is discussed by the MB and according to the proposal submission guidelines.

Any National coordinator can also trigger the participation of the Orphanet Network members in projects they coordinate or contribute to when relevant for Orphanet activities.

At the national level:

All ONT are encouraged to apply for funding at national level.

Funding can be requested from any type of public institution or non-profit private organisations. Sponsoring from for-profit organisations is welcome as long as it has no influence on the content of the website and is non-exclusive.

2.2.2 Grant Management

Administrative and financial coordination of the projects and financial contracts of the network as a whole, including the preparation of proposals, follow-up and reporting are carried out at the OCT level. It ensures the timely and effective communication with the partners in the Network, with Inserm's central administration and with the funders if relevant. It also organises face-to-face Network meetings and trainings.

2.3 Partnerships and technology transfer

The coordination team proposes and implements the technology transfer strategy of the database content and services, comprising both the scientific and financial optimisation of these resources. The partnership development strategy is designed to benefit the whole project, including collaboration with ERNs.

2.3.1 Partnerships strategy

a. International/transnational partnerships

International/transnational partnerships are developed with relevant players in some of the domains Orphanet covers, including ERNs, in order to improve Orphanet's efficiency, improve its visibility, to help Orphanet perform its core added-value duties, and to enable integration of actors in the RD field in Orphanet's activities. Partnerships are also established with end-users who can adapt Orphanet content to their own needs, without duplicating Orphanet's work, thus ensuring that the information is homogeneous amongst the main actors of the domain. Potential partnerships are identified (either pro-actively or directly by the partners) and then a Memorandum of Understanding or Collaboration Agreement is developed in order to define the framework for the partnership by the OCT. MB is informed regularly through the newsletter and during meetings on any new partnership.

b. National non-financial Partnership

Partnerships with other stakeholders at national level is highly encouraged, as long as it contributes to improving the quality and quantity of information relevant for patients, health care providers, researchers, industry and policy makers and the visibility of Orphanet.

Are highly relevant:

- Partnerships with information producers such as learned societies, governmental agencies, patient organisations;
- Partnerships with research-funding agencies to facilitate the access to data on funded projects;
- Partnerships with the national drug and/or regulatory agency to access data on clinical trials and on Orphan drug accessibility;

- Partnerships with other national websites to establish links, especially medical websites on common diseases. It is suggested that they be offered the list of Orphanet diseases with an expert link to the relevant page, for them to add to their website;
- Partnerships with organisations using health information systems to promote the use of the Orphanet nomenclature.

2.3.2 Valorisation strategy

Datasets protected by a Data Transfer Agreement can be a source of financial revenues when their use is solicited by for-profit organisations. These revenues benefit the development of the Database and other services. A portfolio of services intended to optimise the exploitation of the Database is proposed by the OCT and discussed and validated with the MB.

Orphanet datasets are made available by Orphadata (www.orphadata.org) and Orphanet Rare Diseases Ontology (ORDO), which provide machine-readable formats. These datasets can be used for a variety of purposes, such as coding patients in health information systems or in databases or registers, exploitation of scientific data for research purposes (for example, to generate hypotheses), support for decision-making in health policy or research (by allowing, for example, gap analysis in research, analysis of the state of research funding, etc.).

Please refer to paragraph 2.4 for more info.

2.4 Dissemination and communication

2.4.1 Dissemination of results

The data populating the knowledge base and project results are disseminated through different channels, listed below.

The dissemination strategy is proposed by the OCT/OOC and validated by the MB. New channels can be discussed by the MB/OOC. OCT is the main actor in the dissemination of results but ONT are welcome to participate within their capacity. Production of a dissemination plan in accordance with the grant agreement is carried out if necessary.

a. Orphanet portal/international website

The website is translated into 9 languages and provides access to: a [comprehensive inventory of rare diseases classified according to a polyhierarchical classification system](#), the RD encyclopaedia, an [inventory of high quality articles published by other journals or learned societies](#), an [inventory of orphan drugs and of drugs intended for rare diseases](#), a catalogue of expert services, validated by national experts in the 33 member countries and providing information on: [specialised expert centres and centres of expertise](#), [medical laboratories](#), [research projects](#), [clinical trials](#), [patient registries and variant databases](#), [networks](#), [infrastructures](#) and [patient organisations](#), thematic studies and reports on overarching subjects: the “Orphanet Report Series” (ORS), published as PDF documents, OrphaNews (the newsletter of the rare disease community, written in English, covering both scientific and political news. This newsletter is also published in other languages when funding is available, currently in French and Italian).

Access to information as presented on the orpha.net website is free of charge and intended for consultation purposes only.

b. The Orphadata Science platform

Access to aggregated data or to massive sets of data for research purposes is available via the <http://www.orphadata.com> (www.orphadata.com). The platform provides high-quality datasets related to rare diseases, in a reusable and computable format via a CC BY 4.0 licence.

Orphadata Science provides access, on request, to other elements of the Orphanet database after signature of a DTA (for academia) or signature of a service contract (for fee, in the case of for-profits).

N.B. Any request to the ONT to obtain massive datasets of Orphanet data should be transmitted through the contact form on orphadata.org or via email to data.orphanet@inserm.fr in order to establish the appropriate DTA. ONT should not provide third-parties with massive datasets extracted from Orphanet in any case. ONT are systematically informed of any request from their country to access data specifically pertaining their country requiring the signature of a DTA. A review of all the DTAs/service contracts concluded in the previous period is provided in each OrphaNetwork Newsletter.

Orphadata datasets and the ontologies are updated every six months except the "Nomenclature Pack" which is updated annually (according to the RD-CODE project recommendations www.rd-code.eu which were elaborated following consultation with HCPs and needs assessment) . The date of the last release is indicated and old versions are available on Orphadata Github (https://github.com/Orphanet/Orphadata_aggregated).

c. The Nomenclature Pack: Orphanet nomenclature files for coding

The Orphanet nomenclature is used to code the diagnosis of a rare disease with a unique and time-stable identifier, the ORPHAcodes in order to facilitate data collection, research and analysis. These files provide the computable information necessary to achieve the implementation of ORPHAcodes in Health Information Systems, and ensure easier and accurate coding. Orphanet provides a set of files in XML format, including: the Orphanet nomenclature file, the Orphanet ICD-10 mapping file and a directory containing the Orphanet classifications files. These files are generated and made available in Orphadata once a year (in July), in 9 different languages: Czech, Dutch, English, French, German, Italian, Polish, Portuguese and Spanish. The previous versions and their related change logs remain accessible and downloadable in the dedicated [RD-CODE Github repository](#).

Translation of the nomenclature in other languages can be done within or outside the Orphanet Network on an ad-hoc basis providing signature of Collaboration agreement and DTA. However, only the regular, quality-controlled annual translations are included in the Nomenclature Pack for Coding.

An helpdesk is active since the beginning of the OD4RD/OD4RD2 projects: <https://github.com/OD4RD/Main-Help-Desk> , it is dedicated to answering questions related to the

Orphanet nomenclature content and/or the implementation of ORPHAcodes in Health Information Systems or other systems.

d. The Orphanet Rare Disease Ontology (ORDO)

The Orphanet Rare Disease ontology (ORDO) was jointly developed by Orphanet and the EBI to provide a structured vocabulary for rare diseases capturing relationships between diseases, genes and other relevant features which will form a useful resource for the computational analysis of rare diseases. It derived from the Orphanet database (www.orpha.net). It integrates a nosology (classification of rare diseases), relationships (gene-disease relations, epidemiological data) and connections with other terminologies (MeSH, UMLS, MedDRA), databases (OMIM, UniProtKB, HGNC, ensembl, Reactome, IUPHAR, Geantlas) or classifications (ICD-10 and ICD-11). The ontology will be maintained by Orphanet and further populated with new data. Orphanet classifications can be browsed in the OLS view. The Orphanet Rare Disease Ontology is updated every six months and follows the OBO guidelines on deprecation of terms. It constitutes the official ontology of rare diseases produced and maintained by Orphanet (INSERM, US14).

A document describing ORDO is [available](#) for consultation. These products have been recognised as an [Elixir Core Data Resource](#) and as [Global Core Biodata resource](#). The Orphanet Rare Disease Ontology is updated twice a year in 9 languages and follows the OBO guidelines on deprecation of terms.

Available here:

<https://www.orphadata.com/ontologies/https://www.ebi.ac.uk/ols/ontologies/ordo>
<https://bioportal.bioontology.org/ontologies/ORDO>

Detailed information on ORDO is available here : <https://www.orphadata.com/docs/WhatIsORDO.pdf>

e. HPO - ORDO Ontological Module (HOOM)

Orphanet provides phenotypic annotations of the rare diseases in the Orphanet nomenclature using the Human Phenotype Ontology (HPO). HOOM is a module that qualifies the annotation between a clinical entity and phenotypic abnormalities according to a frequency and by integrating the notion of diagnostic criterion. In ORDO a clinical entity is either a group of rare disorders, a rare disorder or a subtype of disorder. The phenotypes branch of ORDO has been refactored as a logical import of HPO, and the HPO-ORDO phenotype disease-annotations have been provided in a series of triples in OBAN format in which associations, frequency and provenance are modelled. HOOM is provided as an OWL (Ontologies Web Languages) file, using OBAN, the Orphanet Rare Disease Ontology (ORDO), and HPO ontological models. HOOM provides extra possibilities for researchers, pharmaceutical companies and others wishing to co-analyse rare and common disease phenotype associations, or re-use the integrated ontologies in genomic variants repositories or match-making tools.

HOOM is updated twice per year.

HOOM is available here:

<https://www.orphadata.com/ontologies/https://bioportal.bioontology.org/ontologies/HOOM>

Detailed documentation on HOOM is available here:

<https://www.orphadata.com/docs/WhatIsHOOM.pdf>

f. Tools

- [Orphadata APIs](#)

Orphadata API provides several GET to facilitate the exploitation of various rare disease-related datasets. These data are updated twice a year (July and December) and are also available as downloadable files both in XML and JSON formats. Data description is available [here](#). Technical documentation available here: <https://api.orphadata.com/>

- [ORPHAcodes API](#)

In the frame of the RD-CODE project, co-funded by the European Union's Third Health Program, Orphanet developed this API. It intends to support Member States in the implementation of the ORPHA nomenclature to rare diseases-specific codification systems by providing GET to facilitate the exploitation of the Nomenclature Pack files. These data are updated in July every year. Technical documentation available here: <https://api.orphacode.org/>

- [ORPHAcodes Dataviz](#)

This tool allows to visualise and browse Orphanet classifications, it is based on the ORPHAcodes API implementation. <https://dataviz.orphacode.org/>

- [FAIR datapoint](#)

It hosts free orphanet's dataset(s). These data sets are a partial extraction of the Orphanet data base, freely accessible at www.orpha.net (for consultation purposes only). The data sets are available in nine languages: English, French, German, Italian, Portuguese, Spanish, Dutch, Polish and Czech. <https://fairdatapoint.orphadata.com>

- [SPARQL ENDpoint](#)

A sparql endpoint is available, only for testing purposes. <http://www.orpha.net/sparql>
A “blazegraph” sparql endpoint preloaded with ORDO could be downloaded as well from <https://www.orphadata.com/ordo-sparql-endpoint/>

- [ORPHApackets](#)

ORPHApackets releases are produced twice a year (in June and December), synchronized with the ORDO generation, and are freely available in a dedicated GitHub repository. An **ORPHApacket** is a formalized data sharing container embedding “pieces” of knowledge related to known rare disorders derived from the Orphanet knowledge database and ORDO (Orphanet Rare Diseases Ontology). The ORPHApacket format is encoded in JSON or YAML.

- [Mapping service](#)

This tool allows users to search for rare clinical entity and find its references in the associated

terminologies. Orphanet has developed and maintains the Orphanet nomenclature of rare diseases, a multilingual, standardised, controlled medical terminology specific to rare diseases. Each clinical entity is associated with a unique numerical identifier named ORPHAcode, as well as a preferred term, synonyms, classification level, typology, definition and aligned with ICD-10, ICD-11, OMIM, UMLS, MeSH, MedDRA and GARD terminologies when relevant.

g. The Orphanet Report Series (ORS)

ORS are thematic studies and reports on overarching subject, derived from data in the Orphanet database, published as PDF documents in all the database languages. According to the theme they can be published once or twice a year. Methodology for the production of the ORS in question is indicated at the beginning of each document.

The full list available here:

https://www.orpha.net/consor/cgi-bin/Education_Home.php?lng=EN

h. Scientific publications

Scientific publications related to Orphanet and its content can be produced by any Orphanet team, provided that the article is sent to the Communication manager and the International coordinator in order to make sure that:

- 1) The theme chosen is original and there is no overlap with other work;
- 2) The author list is compliant with the theme of the article and corresponds to all the staff having contributed to the work.

N.B. All publications should be shared with the network and indicated in the corresponding year communication list to make sure that we keep track of all dissemination activities.

i. Oral/poster presentations

These presentations are encouraged and can be given by any member of an Orphanet team. Content should be sent to the OCT for information.

Before submission the abstract should be sent to the Communication Manager and the International Coordinator in order to make sure that:

- 1) The theme chosen is original and there is no overlap with other work;
- 2) The author list is compliant with the theme of the article and corresponds to all the staff having contributed to the work.

N.B. All presentations should be shared with the network and indicated in the corresponding year communication list to make sure that we keep track of all dissemination activities.

j. External National Trainings/Workshops

Once ORPHAcodes implementation process is ongoing in the country, providing training sessions in local language for coders, hospital information managers and statistical services and other stakeholders involved, as well as clinicians in ERN centres and researchers is encouraged (mandatory for OD4RD2 participating teams) provided the ONT has attended the Training for Trainers organised by the Coordinating team.

This activity leverages the ‘train the trainers’ programme developed in EJP-RD for researchers, and its

adaptation to the clinical context during OD4RD and OD4RD2.

Other dissemination activities foreseen are Face-to-face and online events organised to exchange with ERN coordinators and special sessions specifically addressed to Hospital managers

k. National websites

National Teams can maintain a national website provided they have resources to keep it up-to-date. The national website is a national entry point to the Orphanet portal. Only one national entry point is foreseen in any one country, even in federalised countries. If a team cannot maintain a Nation website, at minima a contact form is made available for the users wishing to get in touch with the National Team.

National websites are tools to disseminate results of the ONT and to communicate at national level about activities conducted by the ONT, on events, and on the rare diseases policy in the country. ONT are responsible for the content published on the national website.

ONT can publish report, news, pages specific to their output on the national website.

Procedure on administration and population of national website via the common shared tool is available in the documents listed below (<http://network.orphanet.org/country-sites-tools/>):

l. Tutorials

OCT has made available a series of short tutorials on the use of the website, the nomenclature and Orphanet data related items.

The tutorials are accessible:

- By clicking on the YouTube channel logo on the Orphanet website;
- On YouTube <https://www.youtube.com/channel/UCKMLSL9hlrxz6zKFod5IlnA> .

ONT are also welcome to make tutorials available in their language or subtitle the OCT-produced tutorials (in collaboration with the Communications Manager, who will provide indications on the appropriate format). OCT and the network should be informed upon production.

2.4.2 Internal communication

Orphanet is a multilingual endeavor. It is agreed that the common language used amongst the teams is English.

Communication among participants is facilitated by an internal newsletter edited every 3 months. When necessary in between newsletters, emails and conference calls are organised. In addition, since 2018 internal communication is facilitated by the OOC subgroups through the organisation of focus groups and subgroups meeting (at distance or *de visu*).

For any kind of issue, partner teams are invited to contact the Orphanet coordinating team via the [Internal Issue Tracking Tool](#), which is used to centralise all requests and to dispatch them to the appropriate Orphanet Coordinating Team member.

Channels used for internal communication are listed below, any new channel can be discussed by the MB/OOC.

N.B. Please note that Internal training activities are listed under 2.1.1 as they are intrinsic of scientific coordination of the ONT activities (at the National Hub level and from the population of the database of resources perspective).

a. OrphaNetWork website

The website <https://network.orpha.net/network/> is a site dedicated to national teams and works as a repository for common tools and documents. It is only accessible to Orphanet national teams through a login and password. The OCT administrates it.

b. OrphaNetWork newsletter

Orphanet publishes an internal newsletter (3-4 issues per year), OrphaNetWork News. It aims to inform the partners on the conclusions of the MB monitoring meetings. It also ensures circulation of information, among all partners, relating to each team's activities and outputs in order to facilitate the acquisition of comprehensive knowledge by the network. This newsletter aims to improve the management of the network by communicating on MB, OCT and ONT activities, recommendations, suggestions and achievements, providing information on Orphanet's evolution and tools.

This newsletter is sent within the Orphanet Network to ONT, National Advisory Board members, and IAB members can also subscribe.

National teams are invited to submit relevant information to OrphaNetWork newsletter, to systematically read every issue to make sure no relevant information is missed and to carry out the action points posted in it.

c. Translation Report

Translating teams are contacted regularly every 3 to 4 months via the Ticketing System: RIC tool for new creation and updated of Nomenclature terms and Abstracts/definition translation.

The Translation Report compiles twice per year all the RIC issue regarding translation and it includes all the necessary information for ONTs to carry out translation activities including latest Abstracts and definitions. The report is sent to the teams involved in content translation for the Orphanet international website and/or Orphanet Encyclopaedia translation, (see part V).

d. Open sessions

Since 2021 Open sessions are held regularly, these are open to anyone and not mandatory. They provide an opportunity to exchange and informally discuss on teams' activities, new activities, new services and tools in development as well as ongoing projects and to better understand the different Orphanet activities.

2.4.3 External communication

The coordination team proposes and ensures the communication strategy. The Coordinating Team ensures the dissemination of Orphanet Network's achievements, but also of the most up-to-date scientific and political news on rare diseases through the international newsletter, and coordinates the production of national adaptations of the latter. ONT are invited to actively participate to the external communication as much as they can.

The Channels used for external communication are:

a. National Websites (when applicable)

National websites are tools to communicate at national level on the activities of the ONT, on events, and on the rare diseases policy in the country.

b. Videos Orphanet Know the Rare for better Care and ORPHAcoding

A [video](#) has been released in 2021 explaining Orphanet missions.

A video about ORPHAcoding has been made available in 2021: <http://www.rd-code.eu/why-orphacoding/>. This video is also available in: [Czech](#), [Dutch](#), [German](#), [Finnish](#), [French](#), [Italian](#), [Romanian](#), [Spanish](#)

c. Strategic communication Pack

[This pack](#) contains all the necessary material for an effective Communication Strategy enabling Network and National Coordinators to effectively discuss sustainability issues and funding with the EC and National authorities.

- A short video presenting Orphanet in 1min 30 (see above)
- Target-specific leaflets (EC, Ministries and Hosting Institutions [this two first items could be used as "teasers" to obtain a meeting with authorities"])
- A slide deck (with transcripts) to be used to "pitch" Orphanet, with the aim of convincing the authorities to found the Orphanet National Team and eventually the set-up of the new structure

d. Flyers & Leaflets

The Communication team designs flyers and leaflets about Orphanet services and specific projects. Any ONT can design Flyers and Leaflets, they should be validated with the Communication team at coordinating level.

All are made available on ONW website and/or the Orphanet international website.

e. OrphaNews

- International:

OrphaNews International is the communication tool between Orphanet and the wider scientific community. Registration is possible through the Orphanet website. Scientific and grey literature is surveyed for news on policy concerning rare diseases worldwide. It is available in English, French and Italian (<http://orphanews.org>)

ONT are invited to submit any relevant information to be published to their OrphaNews international correspondent (please refer to the International correspondents' section), such as:

- Announcement of events/meetings/workshops/publications
- National political issues related to RD or OD.

ONT should subscribe to and read the OrphaNews newsletter and are invited to disseminate this newsletter throughout their country to any relevant professionals (ministries, drug agencies, hospitals, experts, etc.) and informing them that subscription is possible online.

- National edition:

The tool used to produce OrphaNews (Contao) is available to Orphanet National Teams if national funding allowing the translation/editing of the newsletter is secured. National editions are currently produced in France and Italy. Third parties should be invited to publish their information in OrphaNews. The country coordinator can act as editor for his/her country.

f. Booths

Orphanet booths can be held in any relevant conference by any team.

OCT should be informed prior to the event and its result shared with the Network through the internal newsletter.

2.4.4 Visibility package for funding bodies

a. International website

The front page of the website displays the logos of every agency providing funding for the European project or officially supporting the core activity.

Some sections of the website may have different logos when grants are restricted to specific activities.

On the footer of all pages on the international website, 3 mandatory logos are displayed: Inserm, French Ministry of Health and European Commission.

In the footer of the international website there is a separate section to the right to display the designations/labels awarded to Orphanet/Orphadata such as IRDiRC Recognized Resource, HVP Recommended System, ELIXIR Core Data Resource, etc. On the Orphadata Science pages we also display the Global Core Biodata Resource logo and Global Core Biodata Resource.

b. National websites (when applicable)

a) On the footer of national websites developed using the internal Orphanet Network tool, 2 mandatory logos are displayed: Inserm, and European Commission.

There is space to add the Institutional logo as well as ONT financial partners' logos on the national website. Partnership in-kind can also justify the addition of logos of contributing institutions.

Finally, according to the participation of OCT/ONT in projects/grants, additional funder(s) logo(s) should be indicated in all communication material as indicated by the relevant Grant Agreement.

b) On the footer of national websites developed within the Institutional page one logo is mandatorily displayed: the Orphanet logo. In addition to this according to the Grant OCT/ONT is participating in, additional funder(s) logo(s) should be indicated in all communication material as indicated by the relevant Grant Agreement.

N.B. For both type of National websites: The national additional logos/sponsors policy is defined by the ONT however logos/sponsors policy should be provided/advertised on the national website for transparency reasons.

2.5 Adherence to legal and ethical requirements

To date, the codes and charters to which Orphanet adheres include the following:

- [The HONcode](#)
- [The eHealth Code of Ethics \(http://ihealthcoalition.org/ethics/ehcode.html\)](http://ihealthcoalition.org/ethics/ehcode.html)
- [The "Guidelines for Medical and Health Information Sites on the Internet" from the American Medical Association](#)
- [Recommendations from the French National Board of Physicians \(Conseil National de l'Ordre des Médecins\)](#)
- [The Methodological guidelines for the elaboration of a written document for Medical and Health information from the Haute](#)
- [General Data Protection and Regulation](#)

2.6 Tradename/Logo/Design charter

2.6.1 Use of Orphanet logos within Orphanet operations

Orphanet is a tradename which has been registered in Europe and internationally and is co-owned by the Inserm and the French Ministry of Health.

The logo and the design chart must be respected for all communication documents.

The Orphanet logo must appear on all documents used to run the activity.

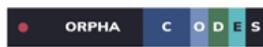
The ORPHAcodes logo can be used in all the dissemination material concerning the Nomenclature and the ORPHAcodes.



Orphanet is a tradename which has been registered in Europe and internationally and is co-owned by the INSERM and the French Ministry of Health.



Orphadata is a tradename which has been registered in Europe and internationally and is owned by the INSERM.



ORPHAcodes is not a trademarked name, nor is the logo registered ; Orphanet/INSERM owns the ORPHAcodes logo.



Know the rare... is not a trademarked name, nor is the logo registered ; Orphanet/INSERM owns the logo.

Fig 4 Orphanet Logos

Orphanet Network Members are allowed to use the Orphanet, Orphadata and ORPHAcodes logos on communication documents and documents used to run Orphanet activities only ; indeed the Orphanet logo must appear on all documents used to run the activity.

When using the logos, Network Members must adhere to the following guidelines :

- The Logo(s) must be used in its original form and may not be altered, distorted, or modified in any way.
- The Logo(s) must not be used in any manner that may mislead or confuse consumers or imply any association with or endorsement by Orphanet or INSERM beyond the permitted use.

Some of Orphanet's partners (for example, in the context of a European project) may use Orphanet's logos in communications materials, in the same way as Orphanet Network Members.

If you have any doubts concerning use of the logos, please contact media.orphanet@inserm.fr

2.6.2 Use of Orphanet logo outside of Orphanet operations / Third party use of the Orphanet logo

Prior approval from the Orphanet Coordinating Team must be sought for any use of the Orphanet/Orphadata logo outside of Orphanet operations and/or by third parties.

1. Requests to use the Orphanet/Orphadata logo are transmitted to the Communications Officer (media.orphanet@inserm.fr).
2. Users must submit a request detailing the intended use, including any designs or contexts in which the Logo will appear (e.g. communications document draft, mockup of website page and URL)
3. All uses of the Logo must be pre-approved in writing (email) by the Orphanet Coordination Team before publication. If granted, the user of the logo may only use the logo in the context for which the request was made. The user may not use the logo for in other contexts and must not :
 - Use the Logo in a way that is offensive, misleading, or illegal.
 - Use the Logo on any products or materials that promote competing services or products.
 - Use the Logo in any context that diminishes the reputation of Orphanet/INSERM
 - The User acknowledges that INSERM/French Ministry of Health is the sole owner of the Orphanet (and INSERM is the sole owner of the Orphadata logo) logo and all associated rights. No ownership rights are transferred to the User through the use of the Logo.
4. Logo use requests (approvals and denials) are logged and archived by the Coordinating Team.
5. INSERM reserves the right to revoke their approval at any time, for any reason, without prior notice. Upon termination, the User must immediately cease all use of the Logo.
6. The user agrees to indemnify, defend, and hold harmless INSERM from any claims, damages, losses, or expenses arising from the User's use of the Logo.

2.6.3 Using our logo when linking to Orphanet from other websites

We are often asked to approve the use of the Orphanet logo on other websites when linking to an Orphanet page/resource. Approval requests may be submitted for our consideration, but we instead advise to quote Orphanet as indicated in 2.8

2.6.4 Use of the logo for promotion

1. Using our logo to publicise that a resource is registered with Orphanet
Use of our logo is on your website/communications materials to publicise your resource's registration in the Orphanet knowledge base **is not permitted**.
2. Use of our logo to promote an event
 - **Only events where Orphanet** (either Coordinating Team or National Team) **is organiser or co-organiser** may use the Orphanet logo(s) in their communications materials. Requests may be made for consideration on an ad hoc basis.

2.7 Titles and Membership

2.7.1 Titles

The title "Director of Orphanet" applies only to the Orphanet Network Coordinator.

The title: “Orphanet Coordinator for [country name]” is used by National Coordinators.

The title: "Orphanet contact point" applies to the person who has accepted to be a Orphanet spokesperson in the country where there is no active team (not having signed the NA).

2.7.2 Membership, partnership and observers

“Orphanet Member” applies to the institution hosting an Orphanet team and having signed the Network Agreement with the Inserm.

“Orphanet Observer” applies to the institution which applies to join the Orphanet Network.

“Orphanet Partner” applies to the group/institution(s) with whom a scientific partnership is ongoing defined by a collaboration agreement or/and a Memorandum of Understanding (MoU).

2.8 How to quote

When quoting Orphanet, please use the following format:

- Orphanet: an online rare disease and orphan drug data base. Copyright, INSERM 1999. Available on <https://www.orpha.net>. Accessed (date accessed).
- The appropriate form when quoting an Orphanet text is: Author(s). “Name of disease”. Orphanet Encyclopaedia, Month, year, URL address.
- The appropriate form when quoting an Orphanet Emergency Guideline is : Author(s). [Name of disease]. Orphanet Emergency Guideline, Month, year, URL address.
- The appropriate form when quoting an Orphanet General Public text is : Author(s). [Name of disease]. Orphanet General Public Encyclopaedia, Month, year, URL address.
- The appropriate form when quoting an Orphanet Disability Factsheet is : Author(s). [Name of disease] Orphanet Disability Factsheet, Month, year, URL address.

When quoting Orphadata, please use the following format:

Orphadata: Access data from Orphanet. © INSERM 1999.

Available on <http://www.orphadata.com>. Data version [e.g.XML data version].

IV. Orphanet knowledge base content, its services and products

1. General information

The Orphanet Knowledgebase is an organised and dynamic collection of information and data about RD and Orphan Drugs. Data from multiple sources (fig.1) are archived, reviewed, manually annotated and integrated to other data by curators and validated by experts and quality controlled. This methodology follows formalised procedures (figure 2) which are published online by type of data in a dedicated section of the website [here](#). All technical procedures are also made available for the ONT in the internal website (<http://network.orphanet.org/procedures-2/>).

Orphanet is committed to providing quality data to its users, and as such a pre and/or post release quality control is performed at Orphanet in order to insure the quality of all the data registered. This quality control is performed according to a predetermined program, updated every year.

In order to improve our operations and allow our users to assess the way in which we work, Orphanet is working towards ISO 9001 certification for its activities. In this framework, Orphanet is publishing procedures ([here](#)) explaining the way in which we work, our workflow and exclusion/inclusion criteria for each type of data.

Experts (including collaborating ERNs) contribute to the quality, consistency and comprehensiveness of the data the list of experts having contributed is published annually [here](#)).

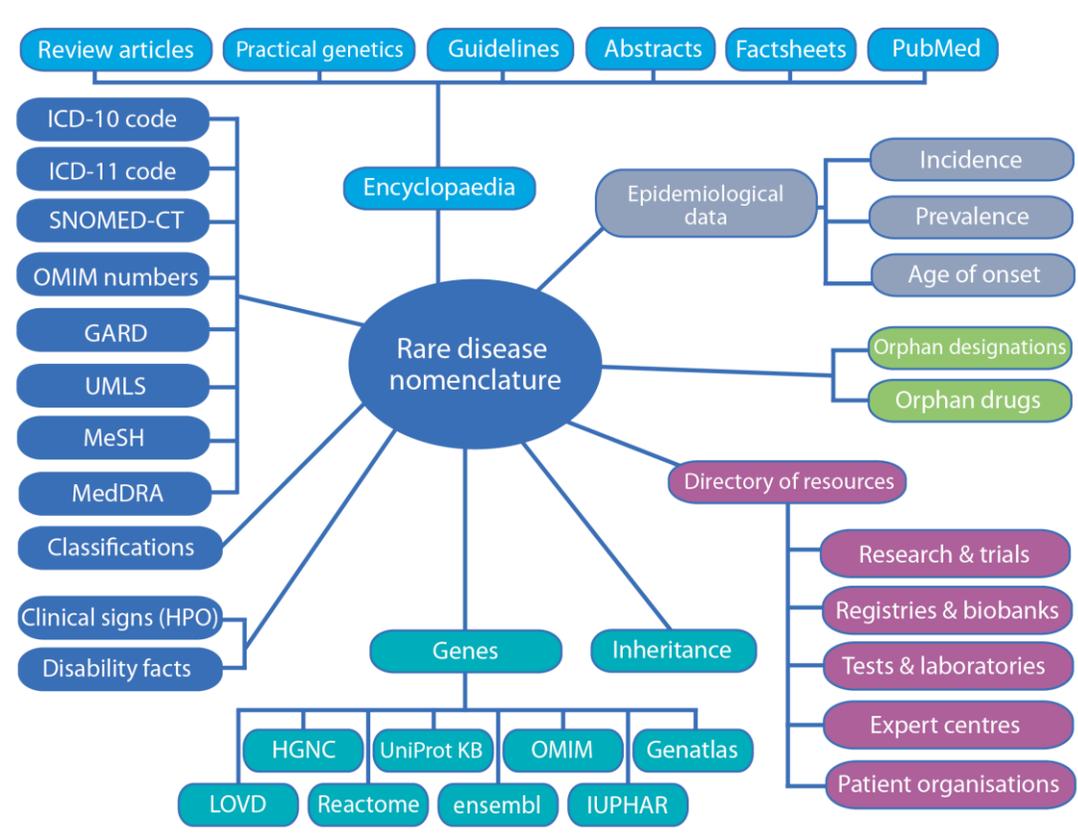


Figure 4 Orphanet Knowledge base content at a glance

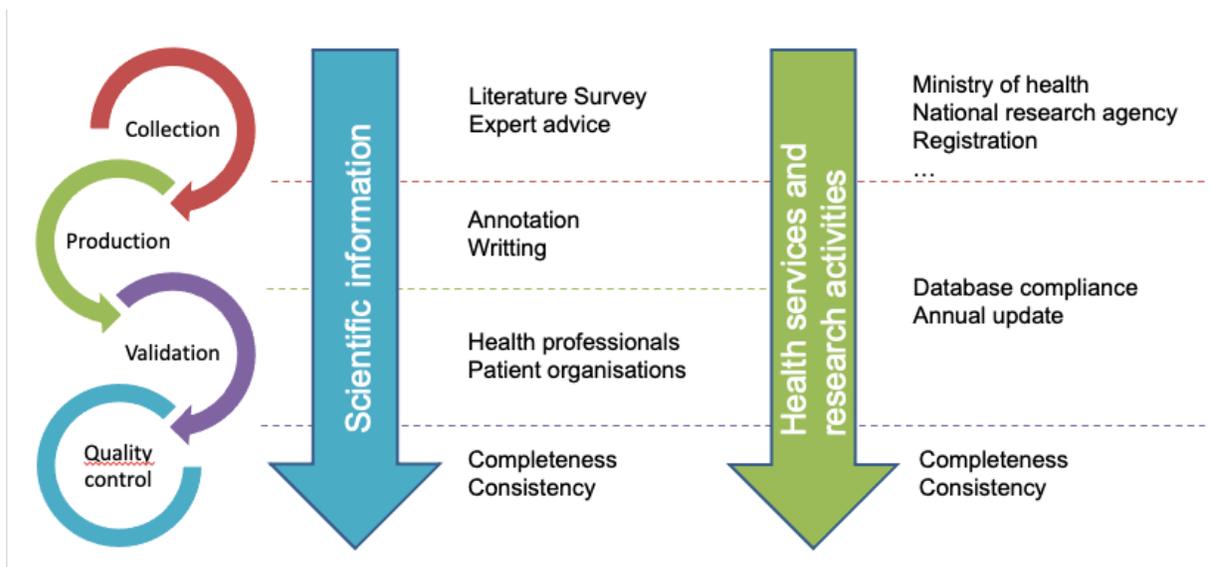


Figure 5 Orphanet overall methodology for data production

2. Accessibility

[Orphanet](#) knowledge base data are accessible via a variety of platforms: the Orphanet website (www.orpha.net), the Orphanet data download platform “Orphadata” (www.orphadata.com), the [Orphanet Rare Disease Ontology \(ORDO\) and HOOM](#), and the [Orphanet Report Series reports](#) as well as via a variety of services /tools : <https://www.orphadata.com/tools/>. For more information please refer to the Dissemination paragraph (Section II paragraph 2).

3. Information and data on rare diseases and orphan drugs

3.1 Disease database

Orphanet maintains and updates the rare disease nomenclature, alignments with other terminologies and genetic databases according to the evolution of scientific knowledge.

The Orphanet nomenclature is at the centre of a rich network of relations inside the Orphanet database and its ontological expression (ORDO, for Orphanet rare diseases ontology, HOOM for HPO-ORDO ontological module), comprised of genes interrelated with other resources (HGNC, OMIM, UniProt, ensembl, Reactome, IUPHAR, Genatlas, LOVD), epidemiological data (prevalence and incidence per geographical area), natural history (age of onset, age of death), disability data (activity limitation and participation restriction), medical terminologies (MeSH, MedDRA, SNOMED CT, ICD-10, ICD-11, UMLS) and resources (OMIM, GARD and HPO).

The scientific literature is constantly surveyed in order to update the inventory of RD, the epidemiological and natural history information, the phenotypic and functional information. Literature survey results are disseminated to Orphanet teams in charge of the scientific content of the database including the nomenclature. The methodology also includes considering the input from the RD community in a systematic way and through direct contacts with expert groups, and in particular, ERNs.

Information on rare diseases is accessible through the “[Rare diseases](#)” tab on the Orphanet website, through the [Orphadata website](#) and through the [Orphanet Rare diseases Ontology](#) (ORDO) and HOOM. N.B. Synchronisation of these services with the Database may vary: this information is provided within each service.

3.1.1 Orphanet nomenclature of RD, Orphanet classification of RD and alignments to other medical terminologies

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 generic international medical 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 **classifications** 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.

A procedural document [here](#) describes the production, validation and update process of the Orphanet nomenclature and classification of rare diseases.

A procedural document describing how the RDs in the Orphanet Classifications are linearised is available online:

[Linearisation rules for Orphanet classifications](#)

Additional procedural documents describing how the Orphanet Nomenclature of RD is produced are available online:

[Naming rules for the rare disease nomenclature in English](#)

Rare disorders are aligned with several medical terminologies, including ICD-10, ICD-11, OMIM phenotypes, UMLS, MeSH, MedDRA and SNOMED-CT, the latter in the frame of a collaboration with SNOMED International.

- Mapping with ICD-10 and ICD-11 codes is an on-going process intended to identify every rare disorder as precisely as possible in the WHO ICD. It is manually curated. Mappings with UMLS, MeSH, MedDRA and SNOMED-CT are semi-automatic: candidate mappings are automatically generated and submitted to manual curation.
- Rare disorders are manually mapped to one or more OMIM Phenotype numbers (For OMIM Gene numbers, see below).

All these mappings are qualified (exact; narrow-to-broad; broad-to-narrow; see table 1) and information on the validation status is noted. Further annotations are carried out for ICD-10 terms: specific code, inclusion or index term, code attributed by Orphanet, with the validation status (table 1).

Furthermore, specific PubMed queries, resulting from mapping Orphanet terms with MeSH descriptors, led to the construction of a list of indexed publications in scientific journals.

The frequency of the updates depends on the targeted terminology:

- monthly updates are carried out for ICD10, ICD-11 and OMIM Phenotype numbers;
- annual updates are carried out for UMLS, MeSH and MedDRA (after UMLS-AB release);

Mappings with ICD-10, ICD-11, OMIM phenotype, UMLS, MeSH, and MedDRA are available on the [Orphanet](#) website, [Orphadata](#) and [ORDO](#). [Qualification of the mappings are only available on Orphadata and ORDO. A human-readable mapping file is also produced annually \(in October\) as a result of h collaboration with SNOMED International and published in Orphadata.](#)

Proximity relationship	Definition
Exact	E (Exact mapping: the two concepts are equivalent)
NTBT	NTBT (ORPHACode is narrower than the targeted code used to represent it)
BTNT	BTNT (ORPHACode is broader than the targeted code used to represent it)
ND	ND (not yet decided/unable to decide: the alignment cannot be qualified by any of the existing labels)
Specificity relationship	
Specific code	Specific code (ICD-10/ICD-11: ORPHACode has its own code in the targeted terminology)
Index term	Index term (ICD-10: Orphanet entity listed in the ICD-10 Index. ICD-11: Orphanet entity listed in the ICD-11 Foundation)
Attributed code	Attributed code (ICD-10/ICD-11: The targeted code is assigned by Orphanet)
Inclusion term	Inclusion term (ICD-10: Orphanet entity included under an ICD-10 category and has not its own code)

Table 6 Mapping qualifiers used to align rare diseases registered in Orphanet with several medical terminologies. Mappings are understood from Orphanet to the target terminology.

A Procedural document describing how the ICD10 indexation is produced is available online [ICD-10 coding rules for rare diseases](#)

3.1.2 Scientific annotations

a) Epidemiological data

Epidemiological data are produced proactively through literature review, as well as by survey of prevalence and incidence figures produced by registries. Data comprise: point prevalence, incidence, birth prevalence, lifetime prevalence, and number of cases/families per geographical area. Figures are submitted for expert validation and used to update the epidemiology section of summary information on RD (Orphanet encyclopaedia).

Prevalence range (deducted from point prevalence figures in Europe or worldwide if there is no data available in Europe), are displayed on the website.

All the epidemiological figures as well as numbers of cases and families reported in the literature are available on the [Orphadata](#) website and [ORDO](#).

Point prevalence, prevalence at birth, annual incidence figures (worldwide estimations, or European estimations if a worldwide estimation is not available) and cases and families reported in the literature are published in two [Orphanet Report Series](#) (in all the Orphanet languages) that are updated annually.

Methodology is specified in the following documents:

[Epidemiological data collection in Orphanet](#)

b) Natural history

Disease inheritance patterns, age of onset and age of death categories are indicated for each disease. This means better information on rare diseases can be provided and used for data analysis, i.e. differentiating pediatric diseases from adult ones. Data are derived from the literature and from the Orphanet encyclopedia.

Age of onset and inheritance information are available on the [Orphanet](#) website, [Orphadata](#) and [ORDO](#).

c) Genetic annotations

Genes related to rare disorders (pathogenic, modifying and susceptibility genes) are continuously entered in the database according to scientific information available from peer-reviewed publications. Candidate genes and biomarkers are also added when they are tested in clinical practice. Genes are associated with one or more rare disorders, and if relevant with one or more genetic tests, variant databases or patient registries and/or research projects in the database. Cross-references with external databases such as HGNC, OMIM (Gene), GenAtlas, UniProtKB, Ensembl, Reactome, IUPHAR-DB and LOVD are carried out semi-automatically each month to allow interoperability between the Orphanet nomenclature and gene-related resources. The role of genes in the aetiology of RD is also provided (causative, major susceptibility factor, modifier, major role in the phenotype, etc) and validated according to published validation criteria and to expert validation, in particular through the Genetic Advisory Board, but also during the update of the Orphanet encyclopaedia.

Information on genes involved in rare disorders is accessible through the “[gene](#)” tab on the Orphanet website, through the [Orphadata website](#) and through the [Orphanet Rare Diseases Ontology](#) (ORDO).

A procedural document describing how the Orphanet inventory of genes is updated and maintained the inclusion criteria in use is available online [here](#).

-d) Phenotypic annotations/ Clinical Signs and Symptoms

Annotations with disease phenotypes are performed using Human Phenotype Ontology (HPO) of phenotypic terms. For each phenotypic term associated with a rare disease, the frequency of its occurrence (very frequent, frequent and occasional) is annotated. When consensus diagnostic criteria are published in peer-reviewed publications, the information is also associated to the annotated phenotypic features. Phenotypic feature that is sufficient by itself to establish definitively and beyond any doubt the diagnosis of a disorder is also further qualified as a pathognomonic sign.

It constitutes a unique resource allowing for a better diagnosis of rare diseases in the care setting, as well as for a better interoperability between health records, patient registries and variants databases,

thus fostering research.

Frequencies	Definition
<i>Obligate</i>	<i>The phenotypic abnormality is always present and the diagnosis could not be achieved in its absence</i>
<i>Very frequent</i>	<i>The phenotypic abnormality is present in 80 to 99% of the patient population</i>
<i>Frequent</i>	<i>The phenotypic abnormality is present in 30 to 79% of the patient population</i>
<i>Occasional</i>	<i>The phenotypic abnormality is present in 5 to 29% of the patient population</i>
<i>Very rare</i>	<i>The phenotypic abnormality is present in 1 to 4% of the patient population</i>
<i>Excluded</i>	<i>The phenotypic abnormality is always absent AND is an exclusion criterion for diagnosing the disorder</i>
<i>Diagnostic criterion</i>	<i>A diagnostic criterion is a phenotypic feature used consensually to assess the diagnosis of a disorder. Multiple sets of diagnostic criteria are necessary to achieve the diagnosis. Orphanet indicates only diagnostic criteria that are consensually accepted by the experts of the medical domain AND published in medical literature. Depending of the medical consensus, they could be further qualified as minor, major, etc. This level of precision is yet not included in the Orphanet dataset.</i>
<i>Pathognomonic sign</i>	<i>A pathognomonic sign is a feature sufficient by itself to establish definitively and beyond any doubt the diagnosis of the disease concerned (i.e. heliotrope erythema for dermatomyositis).</i>

Table 7 *Frequencies definitions*

The information provided is estimated for the entire population of patients in routine care. Some phenotypic abnormalities reported may occur individually with a variable temporality or severity, while others, not listed, may still be encountered.

Phenotypic annotations are not yet available for all rare diseases; the annotation process is ongoing.

The data is available on Orphanet via the [Clinical Signs and Symptoms tab](#), in the [Orphadata website](#) and in [HOOM](#).

e) Functional Consequences of RD

Orphanet provides information on activity limitation/participation restriction (functional consequences) described in rare disorders, using [the Orphanet Functioning Thesaurus](#), derived and adapted from the International Classification of Functioning, Disability and Health – Children and Youth (ICF-CY, WHO 2007).

It constitutes a unique source of information allowing professionals to evaluate patients’ future needs as regards compensation for disabilities related to rare diseases. This data is also of use for social sciences and health economics research.

The information provided is the result of general points of view collected from medical experts, disability professionals and patient support groups/representatives when available, issued from their expertise and experience, along with a scientific literature review. It describes the difficulties of the patient population affected by a specific disease, receiving optimal standard care and management (specific and/or symptomatic management, prevention and prophylaxis, devices and aids, care and support). This general information may not apply to specific cases. Some difficulties that are not listed here can be reported, or

can occur with a different temporality or degree of severity. It is of the utmost importance to check if the provided information is relevant or not to a specific case.

Functional consequences are organised by their frequency in the patient population.

Each functional consequence is recorded by:

- its frequency in the patients' population:
 - very frequent: more than 80%
 - frequent: between 30% and 80%
 - occasional: fewer than 30%
- its temporality:
 - permanent limitation/restriction: the functional consequence is present throughout the life of the patient. It can be congenital, secondary to loss of a skill or a participation. It can be a direct or indirect consequence of the disease or of its treatment.
 - transient limitation/restriction: the functional consequence occurs during acute episodes, periodic crises or relapses. It resolves or reduces spontaneously or by the action of a treatment or care.
 - delayed acquisition: a skill or a participation is performed later than by a healthy person.
- the degree of its severity:
 - low: activity or participation can be carried out with little difficulty by the patient alone.
 - moderate: activity or participation can be carried out with some technical and/or human assistance
 - severe: activity or participation cannot be carried out without substantial technical and/or human assistance.
 - complete: activity or participation cannot be carried out, even with technical and/or human assistance.
 - Unspecified: limitation/restriction is difficult to quantify or highly variable between patients (ranging from 'Low' to 'Complete')
- The loss of ability when relevant, defined by the progressive and definitive loss of a skill or participation over the course of the disease.

A functional limitation is mentioned as « undefined » when the current knowledge does not enable Orphanet to provide information about the extent of the consequences on daily life.

The unaffected activities and participation are not listed.

Some environmental factors requiring particular attention to moderate the patient's disability(ies) are also listed.

This information is restricted to the consequences of the disease and its management on the patient's functioning and daily life. Clinical aspects (including fatigue, pain, impact of the disease on the patient's psychological state) are described through other documents (i.e. Disability factsheets).

Information on functional consequences of rare disorders is accessible through the "[disability](#)" tab on the Orphanet website and through the [Orphadata website](#).

3.2 Inventory of Orphan Designations and Drugs

The inventory of orphan designations and drugs includes all those substances that have been granted an orphan designation for a disease considered as rare in Europe, whether they were further developed to become drugs with marketing authorisation (MA) or not. The Orphanet database also includes drugs without an orphan designation as long as they have been granted a MA issued by the European Medicine Agency -EMA (centralized procedure) and have a specific indication for use in a rare disease. Some drugs (substance and/or trade name) are included in the database because they are tested in a clinical trial performed on a rare disease, even if they do not have a regulatory status.

Drugs with a regulatory status in Europe are collected from reports issued by two committees of the EMA: the COMP (Committee for Orphan Medicinal Products) and the CHMP (Committee for Medicinal Products for Human use). Furthermore, orphan designations and drugs with a regulatory status in the USA (FDA) are collected. Data on OD is updated when there are changes to the regulatory status (active/withdrawal), variations of the therapeutic indication or a modification of sponsor/MA holder.

Information corresponding to regulatory status in a particular geographical area and for a particular disease or group of diseases can be managed at national levels for the countries outside the scope of the EMA, after agreement with the coordinating team. However, for European countries, this information remains under the responsibility of the coordinating team.

For European countries, collection of additional information at national levels, such as accessibility or reimbursement status in each country, is highly encouraged. This information is displayed in the countries' website (ex: list of drugs available for patients in a specific country) or it could also be sent to the coordinating team to allow publication in an aggregated manner (for example new ORS). Of note, this information could also be gathered during the annual update of the document "State-of-the-art" to which Orphanet National coordinators contribute.

Information on Orphan Drugs (OD) is accessible through the "["Inventory of Orphan Drugs" tab](#) on the Orphanet website and through the [Orphadata website](#).

Data is also released via an Orphanet Report Series that is updated every trimester: [Lists of medicinal products for rare diseases in Europe](#).

A detailed procedure is available online: [Data collection and registration of medicinal products intended for rare diseases in Orphanet](#)

3.3 Orphanet Encyclopaedia

Orphanet provides an Encyclopaedia for health professionals and one intended for patients (general public encyclopaedia) in order to deliver information on as many aspects concerning each rare disease as possible. Different levels of editorial resources are defined and different types of texts can be associated to each disease.

Information in each Orphanet encyclopaedia is accessible from the disease page of the Orphanet website, through the "["Encyclopaedia for patients" tab](#) or the "["Encyclopaedia for professionals" tab](#) on the

Orphanet website and through the [Orphadata website](#).

When information is not available in one of these media, it is indicated.

3.3.1 Orphanet Encyclopaedia of Rare Diseases

Textual information for each rare disease completes the Orphanet nomenclature and produces the Orphanet encyclopedia of RD.

In particular:

All the rare disorders in the database are described with at least a definition and according to the following criteria:

- Disorders involving a very limited number of published cases (prevalence less than 1/1,000,000) can be described by using only a short definition (see below). The link to PubMed provided by Orphanet gives access to the few publications and therefore completes the available information.
- Disorders involving a larger number of cases, or having a significant number of publications, are described in abstracts comprising the group of diseases it belongs to and the specific clinical particularities. Production of abstracts is guided by prioritisation criteria based on the prevalence of the diseases, and the availability of drugs, amongst other criteria.

A procedural document describing how the summary information is updated and maintained is available online [here](#).

Automatic texts

For some entries (group of diseases, categories, deprecated and obsolete entries, particular clinical situations for which there is an orphan designation) no short definitions nor abstracts are written (some exceptions exist), but automatically generated texts provide information on the nature of the entry.

Emergency guidelines

Emergency guidelines are concise guidelines intended to improve management, in an emergency situation, of patients with a known rare disease. They are structured in two parts: one for the pre-hospital care environment and one for the hospital emergency department environment.

- Emergency guidelines on a given disease are written by an expert from a reference centre in France, and in collaboration with patient organisations for the non-medical aspects.
- They are submitted for peer-review to a committee of emergency physicians designated by the French Emergency Medicine learned society
- The final version is validated by the authors before its publication on the Orphanet website
- An Orphanet medical project manager, who controls for homogeneity and completeness of the articles, coordinates the entire editorial process.

Disabilities factsheets

Diseases having associated activity limitations and participation restrictions are described in "Disability

factsheets". These contain information intended to give a better understanding and assessment of the needs of people with disabilities associated with a rare disease and to promote guidance and appropriate support in the French national health care system, as well as in the French social support system. They are intended for professionals in the field of disability as well as for patients and their families.

Disability factsheets were produced by the Orphanet editorial team in collaboration with the French Network for RD (Filières de Santé Maladies Rares) that prioritised the diseases to cover and reviewed by medical staff. They were further reviewed by RD experts; patient organisations and professionals from the med-social sector. Each text contains a description of the disease (adapted from the corresponding text from the Orphanet Encyclopaedia for professionals) and a focus on disability-related measures and consequences in everyday life (taken from the corresponding text from the Orphanet patient encyclopaedia). Funding is no longer available therefore text production ceased in 2020. To complete this encyclopaedia, however, factsheets texts produced by others (i.e. patient organisations, expert centres) in any language, are published in the Orphanet website (please refer to paragraph 1.4). Also, the methodology is provided on demand to networks or organisations that want to produce this content and disseminate it through the Orphanet website.

3.3.2 Articles for General Public

The Articles for general public are informative texts produced by Orphanet staff and peer-reviewed by disease experts and dedicated patient organisations. It was initially a French project intended to give complete, honest, up-to-date information to patients and their relatives on the disease(s) they are concerned by, using easy-to-understand language. A methodology following the recommendations of the French Department of Health (*Haute Autorité de Santé* (HAS)) was used in order to guarantee the quality of the texts. Funding is no longer available therefore text production ceased in 2017. To complete this encyclopaedia, however, general, public-intended texts produced by others (i.e. patient organisations, expert centres) in any language, are published in the Orphanet website (please refer to paragraph 1.4). Also, the methodology is provided on demand to networks or organisations that want to produce this content and disseminate it through the Orphanet website.

3.3.3 External articles to be disseminated through the Orphanet website

The editorial team is in charge of identifying articles, published in peer-reviewed journals or learned societies, suitable for publication on the website. External material is disseminated through the Orphanet website if it responds to Orphanet's established quality criteria or, for clinical practice guidelines, AGREE II instrument criteria (the international tool used to assess the quality and reporting of practice guidelines). Permission from the copyright holder is obtained, giving access to the full text through the Orphanet website.

National teams can submit material to include by sending it, together with the reasons for recommendation (after evaluation for compliance with Orphanet Quality Standards), to the coordinating team. Then, permission to publish the article (free to access via Orphanet) will be requested by the coordinating team. A detailed procedure is available here:

[Collection and dissemination of disease information for health professionals and the general public](#)

(For Orphanet teams: technical procedure and evaluation sheets available [here](#)),

3.4 Catalogue of rare diseases-related expert resources

Orphanet provides a catalogue of:

- Expert centres and officially designated centres of expertise (if applicable in the country)
- Medical laboratories and diagnostic tests
- Patient organisations
- Patient registries
- Variant databases
- Biobanks
- Research projects
- Clinical trials
- Infrastructures for research
- Networks of expertise

When applicable, networks of expert resources are also collected: international alliances/federations, expert networks (including ERNs), multinational registries, biobanks and research infrastructures. Data collection is carried out according to Orphanet SOPs and pre and post-release quality controlled. Information scientists performing multinational expert resources collection liaise with relevant Orphanet national teams to make sure that the national counterparts of multinational activities are entered in the database and linked to the multinational resources correctly.

Information on the expert resources is accessible through the [Orphanet website](#), through the [Orphadata website](#).

3.4.1 Data selection

A pre-requisite before data selection, is to define the national sources of information that should match the inclusion criteria defined for each type of data. These sources of information should be advertised on the national website. National teams are advised to establish partnerships with official sources. Professionals can also declare their activities through an online form (in development after suspension of the Online collector tool).

Supranational information (such as EU-funded multinational research projects or multinational clinical trials) is managed by the coordinating team. National and regional information is collected at national level.

3.4.2 Data qualification

Depending on the expert resource, annotations are provided in order to describe each resource in an informative way. Therefore, types of expert centres (medical management or genetic counselling; paediatric or adult), categories of research projects and clinical trials, phases of

clinical trials and specialty, technique and purpose of diagnostic tests are annotated.

3.4.3 Pre-release national validation

Expert centres and research projects not from official sources should be validated by a National validator.

This validation can be provided by the national coordinator, the SAB and/or health authorities.

The national validation process should be communicated to the coordinating team and clearly advertised on the national website.

3.4.4 Pre-release quality control by the coordinating team

The coordinating team is responsible for overall completeness and coherence of the information published on the Orphanet website. Thus, a weekly review of new or updated data on expert resources is held by the coordinating team. Corrective actions to avoid missing information and/or mistakes can then be suggested by the coordinating team to each country team. Special attention is given to the mapping between the Orphanet nomenclature of rare diseases and the registered expert resources.

3.4.5 Data registration

Each country can either directly enter the collected data in the Orphanet database using the in-house edition tool (when sufficient funding for a dedicated professional is available at national level), or send it to the Orphanet coordinating team for registration.

Once it has been registered, data is stored in the Orphanet database.

If needed, data can be registered as “offline”. This way, information not meant to be for public access (i.e. not published on the Orphanet website), such diagnostics tests, can still be collected and stored into the database for further analysis.

3.4.6 Data publication

Once information meets Orphanet quality standards, it is published online. It is accessible through the Orphanet website, and Orphadata.

3.4.7 Post-release quality control

The post-release quality control includes the following activities:

Quality control projects: Projects organised by the coordinating team on a regular basis to check the completeness and consistency of the data. These projects are published in the Quality Assurance Review and must then be treated by the national teams within the deadline.

Post release national review: At least once a year, the coordinating team can make available to the national teams a directory of the expert resources registered for their country. National teams are invited to review the data to ensure data is still relevant, up-to-date, accurate and comprehensive. The post-release validation process has to be defined by each team, communicated to the coordinating team and advertised in the national website. National teams can, at any time, make specific extractions from the

database to perform this post-release quality control.

3.4.8 Priorities list

The utmost priority is given to resources obtained from officially-designated sources when applicable not least ERNs, and, in the case of the research related expert resources (research projects, patient registries, biobanks, clinical trials, mutation databases, and infrastructures for research) if they are funded by a member agency of the [IRDiRC consortium](#) (International Rare Diseases Research Consortium).

3.4.9 Data extraction and analysis

Data extraction for a given country can be performed by national teams through a secured URL protected by login and password. **Only national data are accessible to the teams.** Flat files are downloadable from this application.

Data statistics on an International scale, are available [here](#). National teams can access this secure URL using their login and password.

For external users, please refer to [Orphadata](#).

3.4.10 Data collection in countries without an appointed team.

Patient organisations in countries where there is not a national team can be registered in the database if:

- They are an alliance and/or part of [Eurordis](#) or [Rare Disease International](#)
- AND they have legal status or they are registered in an official journal.

Research related resources (research projects, clinical trials, patient registries, biobanks and variant databases) are also collected and registered in Orphanet database if they are funded by a member of the IRDiRC consortium (International Rare Diseases Research Consortium, list of members available [here](#)) located in a country for which there is no Orphanet national team.

However, a disclaimer on the corresponding webpage is shown informing the users that this information could be not up-to-date as no team in the country is available for updating the information

Procedural documents describing how the Directory of rare diseases-related expert resources is updated and maintained are available online:

- [Glossary and representation of terms related to diagnostic tests](#)
- [Data collection and registration of medicinal products intended for rare diseases in Orphanet](#)
- [Data collection and registration of expert centres in Orphanet](#)
- [Data collection and registration of patient organisations in Orphanet](#)
- [Data collection and registration of diagnostic tests in Orphanet](#)
- [Data collection and registration of research projects in Orphanet](#)
- [Data collection and registration of Clinical trials in Orphanet](#)
- [Data collection and registration of patient registries in Orphanet](#)
- [Data collection and registration of biobanks in Orphanet](#)

V. Translation of Orphanet content

1. Translation of Orphanet content by a national team

Translation of the content within the Orphanet database is possible, depending on available funding. Translation of the Orphanet database and related documents into a given language can be performed by any Orphanet National Team (ONT) or person designated/appointed by the National coordinator.

The ONT is entirely responsible for the translation and its validation: non-medical translated content must be validated by the national team while medical translated content must be validated by the National coordinator, or a physician designated by him/her.

National teams can decide to translate all, or only part, of the database content. An internal document evaluation the translation workload is available [here](#).

This content can be divided into several different optional translation packages, as follows:

1.1 Orphanet Nomenclature production in national language

Production (translation and adaptation) of the Orphanet Rare Disease Nomenclature in languages other than English can be performed by the relevant Orphanet National Team (ONT) following signature of Attachment 2 of the NA with the Orphanet Coordinating Team (OCT), or the person(s) designated/appointed by the National Coordinator. Alternatively, a third party, with the agreement of the ONT, can be designated to take on this responsibility, as determined in a specific DTA. Once the production started, the ONT, or the third party, engages to maintain and update the production in national language in parallel with the production of the nomenclature in English carried out by the OCT. ONT are entirely responsible for the quality of the Orphanet Rare Disease Nomenclature in their language. Medical validation of the nomenclature in national language is mandatory.

Implementation in the database and dissemination of Orphanet RD Nomenclature in national language is carried out by the OCT (Orphanet website and Orphadata).

A procedural document describing how the nomenclature in national language (other than English) is updated and maintained is available online [here](#).

A procedural document describing how the Nomenclature production in national language is carried out is available online:

[Nomenclature production in national language](#)

1.2 Orphanet International Website

1.2.1 International website layout

Translation of the Orphanet International Website in languages other than English can be performed by the relevant Orphanet National Team (ONT) after having signed a Data Transfer Agreement (DTA) with the Orphanet Coordinating Team (OCT), or those designated/appointed by the National Coordinator.

Once the production started, the ONT engages to maintain and update the production in national language in parallel as the English production is carried out by the OCT. ONT are entirely responsible for the publication and quality of the Orphanet International Website in their language.

1.2.2 Scientific annotations of the Inventory of RD

Translation of the scientific annotations in languages other than English can be performed by the relevant Orphanet National Team (ONT) after having signed a Data Transfer Agreement (DTA) with the Orphanet Coordinating Team (OCT), or the people designated/appointed by the National Coordinator. Once the production started, the ONT engages to maintain and update the production in national language in parallel with the production in English carried out by the OCT. ONT are entirely responsible for the publication and quality of the translation in their language.

1.3 Summary information on diseases (abstracts, definitions)

Abstracts and definitions can be translated into any other language, whether the rest of the database has been translated or not. The translation must be validated by medical staff (either the National Coordinator or by a physician designated by him/her).

If the website is translated, summary information will be displayed in the disease page format, as it is in the English pages of the website. If it is not, translated summary information is posted in PDF format using a pre-defined format at the bottom of the relevant disease page in all languages, together with other texts linked to the disease. Information about its language and date of production is also given.

1.4 Emergency guidelines

Emergency guidelines can be translated into any other language, whether the rest of the database has been translated or not. Translations are posted in the Detailed Information section at the bottom of the disease page, together with other texts linked to the disease. Information about its language and date of production is also given.

There are two different possibilities according to the validation process foreseen:

a) **Exact translation:** If the translation is validated by the National Coordinator, or by a physician designated by him/her, the text should be translated verbatim, without adding or withdrawing any facts, except for the specific sections providing information on local services (*i.e.* emergency departments, relevant contact persons/services, information websites).

Translation is endorsed by the Orphanet National team and it is specified so in the document. The name of the professional having validated the translation is acknowledged in the document.

b) **Adaptation:** If the translations are validated by national emergency medicine/intensive care learned societies, the text can be amended according to the remarks of the national experts. In this case, a disclaimer informing that the National Orphanet Team has adapted the guidelines with the collaboration of experts of the learned societies is added. A reference to the original French recommendations (with a link to these) is also present.

In the case that the translating team wishes to make suggestions to update or to improve the guidelines' contents, requests should be sent to translation.orphanet@inserm.fr in order to initiate a standard update cycle (as well as to ensure that all Orphanet users benefit from this input).

Local updates are allowed only when collaboration with national emergency medicine learned societies is established and acknowledged in the final document.

1.5 Disabilities factsheets

Orphanet produced the Disabilities factsheets in French and they are displayed at the bottom of each specific disease page in the “Detailed information” section. They can be translated into any other language, whether the rest of the database has been translated or not.

Translations are posted at the bottom of the disease page, in the “Detailed information” section, together with other texts linked to the disease. Information about its language and date of production is also given.

Upon request, the OCT provides the partner with the texts.

There are two different possibilities depending on the validation process foreseen:

a) **Exact translation:** Texts are translated verbatim, without adding new facts, except for the specific sections providing information on local services and policy (e.g. social aid, prenatal diagnosis, etc...). If this adaptation is not possible, the section on local services and policy can be omitted from the translation. A disclaimer is inserted specifying that some of the information mentioned (e.g. drug treatments, prenatal diagnosis, etc) may not be relevant and/or applicable in other countries. Translation should be validated by the country coordinator, or by a physician, and ideally by an inexperienced reader for the non-medical content (however, this is not mandatory), both designated by him/her. The persons having validated the text are acknowledged in the national document.

b) **Adaptation:** Texts can be amended according to the remarks of the national experts. In this case a disclaimer informing that the local Orphanet team, with the collaboration of the experts of the learned societies, has adapted the article is included. A reference to the original French article (with a link to it) is also added.

In the case that the translating team wishes to make suggestions to update or improve the text content, requests should be sent to translation.orphanet@inserm.fr in order to initiate a standard update cycle (as well as to ensure that all Orphanet users benefit from this input). Local updates are not allowed in any country.

1.7 Activity Report and leaflets

The ONT can translate, into their language, the Annual Activity Report that is produced by the OCT every year.

The ONT can also translate the leaflets produced annually by the OCT.

1.8 OrphaNews

OrphaNews, the Orphanet electronic newsletter, is produced by the OCT in English and can be translated into any other language, whether the rest of the database has been translated or not. It is published every two weeks.

The ONT can decide whether to translate all the articles present in each newsletter or only part of it.

Additional articles of national interest can be added. Additionally, it can decide the frequency at which the national language newsletter is published. The country coordinator shall appoint an editor for the newsletter, as well as nominate an editorial board.

Access to a dedicated interface is granted so the translation can be directly integrated into the database, published online and sent to the subscribers by the national team newsletter editor.

The editorial board of the national newsletter is in charge of the validation of the translation.

1.9 Translation of Orphanet content by a working group in countries where there is no national team

Translation of the Orphanet encyclopedia and /or the nomenclature into a given language where there is no National team can be performed if these are carried out by a working group lead by a translation coordinator and provided that translations are expert-validated. The translation coordinator is entirely responsible for the translation and its validation: non-medical translated content must be validated by the translation coordinator while medical translated content must be validated by a physician(s). Before starting the translation activities, a DTA must be signed by the partner and the OCT.

1.9.1 Summary information on diseases (Abstracts)

Summary information can be translated into any other language; however, the translation must be validated by a physician.

The translated summary information is posted in PDF format at the bottom of the disease page, together with other texts linked to the disease. Information about its language, date of production and weight of the PDF file is also given (if and when the website is translated, summary information will be displayed in the disease page, as it is in the English pages of the website).

Upon starting the collaboration, Orphanet provides the translation coordinator with a first batch of the most updated abstracts. The number of abstracts to be translated in this first batch is decided by the translation manager. Translation should be verbatim, without adding new facts, and correct from a medical point of view. Attention should be paid to respect the nomenclature of genes and proteins, as well as the specific medical terms. Translation should be validated by a physician (i.e. a member of the NAB). The persons having translated and validated a text, as well as the companies providing financial support, will be acknowledged in the PDF document.

In case the translating coordinator wishes to make suggestions to update or improve the summary information's content, requests should be sent to translation.orphanet@inserm.fr in order to initiate a standard update cycle (as well as to ensure that all Orphanet users benefit from this input). Local updates are not allowed in any language.

1.9.2 Orphanet Nomenclature

Orphanet Nomenclature can be translated into any other language; however, the translation must be validated by a physician and/or a board of physicians, according to the Orphanet translation procedures.

The translated nomenclature is made available through the Orphadata portal via the alignments datasets (<https://www.orphadata.com/alignments/>) under CC-BY 4.0 Licence . Information about its language, date of production is also given.

Upon starting the collaboration, Orphanet provides the translation coordinator with excel file containing the whole nomenclature content. The translating team sends Excel file with Translated Data that has been medically validated to the Orphanet Coordinating Team in the standard Excel. Differential files containing modified/newly created terms for translation will be sent every June thereafter by the Orphanet Coordinating Team to the translating team. The translating team should provide following these updates, an Excel file containing the updated, full nomenclature translation (i.e. NOT just the differential).

In case the translating coordinator wishes to make suggestions to update or improve the nomenclature content, requests should be sent to translation.orphanet@inserm.fr in order to initiate a standard update cycle (as well as to ensure that all Orphanet users benefit from this input).

VI. Annexes

Annex 1: List of abbreviations

AFM: French Association against Myopathies
CHMP: the Committee for Medicinal Products for Human use
CNAM: French Public Health Insurance Fund
CNSA: French National Solidarity Fund for Autonomy
COMP: the Committee for Orphan Medicinal Products
DG Santé: Directorate General Health and Consumers
DTA: Data Transfer Agreement
EC: European commission
EJHG: The European Journal of Human Genetics
EMA: The European Medicines Agency
EUCERD: The European Union Committee of Experts on Rare Diseases
FNMF: Federation of non-profit health insurers
GAB: Orphanet Advisory Board on Genetics
GARD: GARD is a database that provides the public with access to current, reliable, and easy to understand information about rare or genetic diseases in English or Spanish.
HAS: Haute Autorité de Santé
HGNC : Human Genome Organisation Gene Nomenclature Committee
HPO : Human Phenotype Ontology
IAB : International Advisory Board
ICD: International Classification of Diseases
IC
ICHPT: International Consortium of Human Phenotype Terminologies
IHTSDO: International Health Terminology Standards Development Organisation
Inserm: The French National Institute of Health and Medical Research
IPR: Intellectual Property Rights
IRDiRC: The International Rare Diseases Research Consortium
IUPHAR: The International Union of Basic and Clinical Pharmacology
LDDB: London Dysmorphology Database
MA : Marketing Authorisation
MB: Management Board
MedRA: Medical Dictionary for Regulatory Activities
MeSH: Medical Subject Headings
MoU: Memorandum of Understanding
OD: Orphan Drugs
OJRD: Orphanet Journal of Rare Diseases
OMIM: Online Mendelian Inheritance in Man
ORDO: Orphanet Rare Disease Ontology
ORS: Orphanet Report Series

QA: Quality Assurance
RD: Rare Diseases
NAB : National Advisory Board
SNOMED-CT: Systematized Nomenclature of Medicine-Clinical Terms
UMLS: Unified Medical Language System
UniProtKB: Universal Protein Resource Knowledgebase
URL: Uniform Resource Locator
WHO: World Health Organisation
SOPs : Standard Operating Procedures

Annexe 2: Orphanet National Teams activity Indicators and thresholds

INDICATORS	Threshold for green (calculation based on M(-2)M(-14))
Management Board attendance = Participation in the Governance and Network life	60% of the Instances in the year
Article in the internal newsletter/poster AM = Participation Network life	1/year
Expert Ressources update = Quality image	5% of all national Data/year
Quality Contorl Task = Quality image	50%/year
Trainings = Teams capacity, Quality image, Network life	50% of the instances of the year
Translation Nomenclature = Quality image	1/year
Translation abstracts = Quality image	15
Translation website = Quality image	90%

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

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https://www.orpha.net/pdfs/orphacom/special/eproc_SOPs.pdf