

Orphanet Standard Operating Procedures

www.orpha.net

www.orphadata.org



I. Introduction	6
1. Purpose/objectives	6
2. Disclaimer	6
3. Range of application	6
4. References.....	6
5. Filing and updates	7
II. General information on the management of the Orphanet Consortium.....	8
1. Mission.....	8
2. History	8
3. Orphanet Products.....	9
4. Orphanet Management Structure: Governing Boards	10
a) The Management Board	10
b) The International Advisory Board	10
c) Genetic Advisory Board	10
d) National Advisory Board (optional)	11
e) The General assembly of the RD-ACTION Joint action 2015-2018.....	11
5. Role of Orphanet Teams	11
a) The coordinating team	11
b) The Orphanet national teams	12
Roles of a country Coordinator:.....	12
Roles of a Project manager:	12
Roles of the Information scientist:	13
Roles of the Orphanet team:.....	13
c) Orphanet contact point.....	14
d) Application to join the consortium	14
6. Communication between teams	15
a) OrphaNetWork website	15
b) OrphaNetWork newsletter	15
c) Quality Assurance Review	15
d) Translation report	16
7. External Communication Tools	16
a) Press releases	16
b) Web pages on the international website	16
c) National websites.....	16
General content	16
Website administration	17
Editorial policy and quality control.....	18
d) Flyers	18
e) OrphaNews Europe.....	18
8. Agreed principles for running the activities	19
a) Languages.....	19
b) Translation of Orphanet content	19
9. Legal issues and funding.....	19
a) Adherence to legal and ethical requirements	19
b) Tradename/Logo/Design charter	20
c) Intellectual Property Rights (IPR)	20

d) Titles and Membership	20
Titles	20
Membership, partnership and observers.....	21
e) Web addresses	21
f) License to all copyrightable parts of the database	21
g) Resources to be mobilised	22
h) Funding/Sponsoring of the international/national websites	22
i) Visibility package of funding bodies	23
International website	23
National websites	23
j) Non-financial Partnership.....	23
k) Release/Licensing of Orphanet Data	23
III. Information on rare diseases and orphan drugs.....	25
1. Orphanet inventory of diseases	25
a) Definition of an Orphanet disease	25
Rare diseases	25
Non-rare diseases	26
b) Modifications of the Diseases inventory	26
2. Classifications	27
3. Epidemiological data.....	28
4. Natural history	29
5. Annotations and alignments of rare diseases with medical terminologies and databases.....	29
6. Interfacing Orphanet entries with external sources of information	30
7. Orphanet inventory of genes	31
8. Orphanet encyclopaedia.....	31
a) Health professional encyclopaedia	32
Summary information (short definitions/abstracts).....	32
Automatic texts	33
Emergency guidelines	33
b) General public encyclopaedia.....	33
c) Disabilities encyclopaedia	34
9. Quality control	34
10. External sources to be disseminated through the Orphanet website	34
11. Orphan Drugs	35
IV Directory of rare diseases-related expert resources.....	37
1. Data selection	37
2. Data collection	37
3. National validation.....	38
4. Quality control by the coordinating team.....	38
5. Online publication.....	38
6. Data update	38
7. Post-release quality control.....	38
8. Priorities list	39
9. Data extraction and analysis	39
10. Data collection in countries without an appointed team.	40
IV Translation of Orphanet content.....	41
1. Translation of Orphanet content by a national team	41

a) Orphanet International website.....	41
International website layout.....	41
Names of diseases.....	41
Clinical signs and symptoms (phenotypes).....	42
b) Summary information on diseases (abstracts, definitions and short definitions).....	42
c) Emergency guidelines.....	43
d) General public encyclopaedia.....	44
e) Disabilities factsheets.....	45
f) Orphanews.....	46
g) Orphanet Report Series.....	46
h) Note concerning translation of articles disseminated through the Orphanet website.....	46
2. Translation of Orphanet content by a working group in countries where there is no national team.....	46
a) Generalities.....	46
b) Summary information on diseases (Abstracts).....	47
V. Annexes.....	48

I. Introduction

1. Purpose/objectives

The Orphanet “Standard Operating Procedures” (SOPs) provide Orphanet teams with general information related to the Orphanet mission.

It is structured into four different parts:

The first part details the management of the Orphanet network including communication tools, legal and financial issues.

The second part provides documentation of procedures related to data managed only at the coordinating team level: diseases and their classifications and annotations, editorial procedures, and orphan drugs.

The third part emphasizes on the expert directory data collection and update, which are jointly managed by the coordinating team and the national partners.

The fourth part details the 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 & amended yearly.

2. Disclaimer

This publication is part of the project / joint action ‘677024 / RD-ACTION’ which has received funding from the European Union’s Health Program (2014-2020).

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

3. Range of application

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

4. References

Methodology: Linearization of diseases available [here](#).

ICD10 coding rules for Rare diseases: [specific indexation procedure](#).

[International Advisory Board rules of procedures](#).

[Genetic Advisory Board rules of procedures](#).

5. Filing and updates

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

II. General information on the management of the Orphanet Consortium

1. Mission

Orphanet is the **International Rare Diseases and Orphan Drugs base of knowledge**. Its aim is to increase awareness on rare diseases and to improve the diagnosis, care and treatment of patients with rare diseases.

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.

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, the Inserm, the CNAM (French public health insurance fund), the AFM (French association against myopathies) and the FNMF (Federation of non-profit health insurers).

In 2000, the French pilot project became a European one with the support of European Commission grants (DG Public Health and DG Research). Orphanet is now part of a Joint Action of the European Union (RD-Action) after having being a Joint Action (Orphanet Joint Action) from 2011 to 2014.

The database and the website were progressively translated, and are now available in 7 languages: English, French, German, Italian, Portuguese, Spanish and Dutch. Members expanded gradually to 40 countries by 2016*:

- 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, Luxemburg, Malta, Morocco, Norway, Poland, Slovakia, Slovenia, Serbia, Sweden, Turkey (2006)
- Israel, Armenia (2007)
- Canada-Quebec (2011)
- Western Australia (2012)
- Georgia and Tunisia (2014)

- Argentina (2015)

In countries participating in the Joint Action, the coordinator was nominated by the national Ministry of Health, in the other countries either he/she was nominated by the Ministry of Health either he/she was proposed by the institution and validated by the Orphanet management board.

Each country coordinator agrees to advance the objectives of the project and to be responsible for the collection of data on expert resources at a national level according to the present SOPs (standard operating procedures).

*: as of 2015 no team is appointed in Greece.

3. Orphanet Products

Orphanet products include:

- An [inventory of rare diseases](#) classified according to clinical classifications validated by experts. Each disease is indexed with International Classification of Diseases 10 (ICD10), Online Mendelian Inheritance in Man (OMIM), Medical Subject Headings (MeSH), Unified Medical Language System (UMLS), Medical Dictionary for Regulatory Activities (MedDRA); alignments to Systematized Nomenclature of Medicine-Clinical Terms (SNOMED CT) are also produced in the frame of a partnership with The International Health Terminology Standards Development Organisation (IHT SDO). The ‘identity card’ of diseases includes the relevant prevalence class, age of onset class, mode of inheritance and associated genes.
- An [inventory of genes](#) associated with rare diseases cross-referenced with Human Genome Organisation Gene Nomenclature Committee (HGNC), OMIM, Universal Protein Resource Knowledgebase (UniProtKB), geneatlas, Ensembl, Reactome and IUPHAR (International Union of Basic and Clinical pharmacology) . .
- [Epidemiological figures](#) comprising: point prevalence, annual incidence, prevalence at birth and lifetime prevalence (low, high and mean values) per geographical region.
- [A poly-hierarchy evolutive classification system](#)
- [An encyclopaedia of rare diseases](#).
The phenotypes associated to rare diseases and their frequency of occurrence, based on HPO The Orphanet thesaurus of signs and symptoms formerly used to annotate the diseases, cross-referenced with other nomenclatures: HPO (Human Phenotype Ontology), PhenoDB, London Dysmorphology DataBase (LDDDB).
- The [disabilities](#) associated with rare diseases based on a ICF-derived disability thesaurus, the Orphanet Thesaurus of Functioning.
- [An inventory of orphan drugs](#) at all stages of development, from orphan designation to market authorisation
- A [directory of expert resources](#) in the partner countries, providing information on: specialised expert centres and centres of expertise, medical laboratories & diagnostic tests performed, research projects, clinical trials, patient registries, mutation databases, biobanks, networks, technological

- platforms and patient organisations.
- [Three newsletters](#) (in French, in English and in Italian)
- A report series on transversal issues in the field

4. Orphanet Management Structure: Governing Boards

Orphanet is a complex project, 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.

Orphanet is managed by several boards, which oversee the project independently of specific projects and grants, in order to ensure the project's coherence, its evolution in relation to technological developments and to the needs of its end-users, as well as its sustainability.

a) The Management Board

The Management Board (MB) is composed of all the country coordinators in charge of data collection at a national level. It is chaired by the project coordinator at the Inserm. Members list is available [here](#).

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 the project. These tasks are achieved through conference calls and by means of an annual meeting, if funding is available.

The members of the MB have access to all information relating to funding and network activities. The members of the MB provide the coordinating team with information on national funding and activities, and the coordinating team reports to the members of the MB about its own scientific activity and financial situation.

b) The International Advisory Board

The International Advisory Board (IAB) is composed of experts proposed by the MB. Their expertise covers the following fields: scientific databases, information technologies, ontology and nomenclature, communication and education, R&D, rare diseases and orphan drugs. This board operates through conference calls and/or meetings if funding is available. Board members are in charge of advising the MB regarding the overall strategy of the project. They are invited to provide comments on the coordinating team's activity report and to answer specific questions at the request of the MB. Rules of procedures and members list available [here](#).

c) Genetic Advisory Board

Members of the Orphanet Advisory Board on Genetics (GAB) are either geneticists members of the MB joining the advisory board on a volunteer basis or geneticists not belonging to the MB. These external

members are invited under proposal of the MB. In that case, external candidates are nominated if the majority of the MB agrees.

Board Members advise Orphanet on topics related to the database of genes and the database of medical laboratories and genetic tests. Rules of procedures and members list available [here](#).

d) National Advisory Board (optional)

Orphanet partners can decide to set up a National Advisory Board, its members being nominated by the appropriate legitimate institutions (learned societies, ministries, etc.), which are defined at country level. National advisory board 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 or abstract translation 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 representatives of both the Committee of Orphan Medicinal Products and the Commission Expert Group on Rare Diseases be solicited to contribute to the Board. This board operates through conference calls.

For the Orphanet teams: the rules of procedures of the national advisory board are available on the [OrphaNetWork site](#)

e) The General assembly of the RD-ACTION Joint action 2015-2018

Orphanet core activities and European national activities receive funding from the European commission since the early 2000. In the frame of the RD-Action Joint action 2015-2018 some of the Orphanet activities are funded by the EC (European commission). In this frame the Orphanet MB refers also to the General assembly of the RD-Action project (please refer to <http://www.rd-action.eu> for additional information).

5. Role of Orphanet Teams

a) The coordinating team

The coordinating team is located in Paris and is responsible for the production of the following website content:

- The inventory of rare diseases (rare diseases) and the collection of data attached to each disease, which includes the name of the disease and synonyms in English, phenotype and disability features, diseases natural history information, epidemiological data, cross referencing, and the poly-hierarchic classification of rare diseases.
- The inventory of genes involved in RD (pathogenic, modifying and susceptibility genes) and associated with RD, genetic tests, mutation databases and/or research projects, and cross-referenced with other databases
- The database regarding medicinal products in development from the orphan designation stage until the market authorisation.

- The coordination of the production, publication and update of the Orphanet encyclopaedia (health professional encyclopaedia and of a general public encyclopaedia) according to Orphanet Quality Standards, including the coordination of the peer-review process and quality control, the identification of articles suitable for publication on the website produced by other journals or learned societies (refer to the second section of this document for more detailed information)
- A thesaurus of functional consequences of rare diseases cross-referenced with other terminologies
- Links to PubMed and other websites concerning rare diseases
- Web pages providing general information about Orphanet, RD and orphan drugs

The coordinating team is also responsible for:

- The coordination of data collection from expert resources in participating countries
- Training and supervision of national teams
- Management of translations
- Quality control of the database
- Technical and IT support
- Database hosting and maintenance
- Security of web-based services and data
- Obtaining funding for core activities
- Orphanet's consortium management
- Provision of management tools

b) The Orphanet national teams

Orphanet national teams are located in each participating country. A national Orphanet team is composed, at least, of a country coordinator who will be responsible for the national Orphanet activities. It can also include one or several information scientists and a project manager.

Roles of a country Coordinator:

These include organisation of the governance of the project at national level, including liaison with learned societies, Health authorities and patient organisations, and the build-up of the Orphanet team if applicable.

The country coordinator is responsible for data quality management about expert resources in the country.

He/she acts as the national contact point for the Health authorities on RD. He/she is a professional well established in the field of RD, with a strong interest for public health and research issues.

The country coordinator participates in the Orphanet MB, edits the national web pages of Orphanet, contributes to the dissemination of national initiatives in the field of RD via Orphanews and the OrphaNetWork internal newsletter, and he/she participates to the annual meeting.

Roles of a Project manager:

Project managers ensure that the roles of the Orphanet team are met and coordinates information scientists'

activities in accordance with the strategy established by the country coordinator. He/she is expected to read the OrphaNetWork internal newsletter and the Orphanet Quality Assurance Review (and the Translation Report if applicable) and to carry out the action points posted in them. He/she is under the supervision of the country coordinator to whom he/she should report to.

Roles of the Information scientist:

These include identification of the sources of information in the country, collection of the information about expert services according to the Orphanet SOPs, validation of the collected data according to the workflow established by the country coordinator and the coordinating team, publication of the data and communication with the coordinating team. He/she is expected to read the OrphaNetWork internal newsletter and the Orphanet Quality Assurance Review (and the Translation Report if applicable) and to carry out the action points posted in them. He/she is under the supervision of the country coordinator to whom he/she should report to. The information scientist at the country level is technically supervised by the Paris-based Expert resources manager.

For the Orphanet national teams: a detailed Orphanet Information scientist Job description is available on the OrphaNetWork site (<https://network.orpha.net/network/cgi-bin/articles.php?lng=en&pg=13>)

Roles of the Orphanet team:

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

Mandatory contributions:

- Collection of information concerning:
 - official sources of expert resources available at the national level (and/or partnerships)
 - expert centres and centres of expertise when applicable
 - laboratories with diagnostic activities
 - patient organisations
 - clinical trials, research projects
 - patient and mutations registries, biobanks
- Regular data update
- Organisation of national data validation processes
- Creation and maintenance of the national Orphanet website
- Contribution to Orphanews Europe (the public newsletter for RD community) regarding country-level information on RD and/or orphan drugs
- Contribution to OrphaNetWork newsletter, the internal Orphanet consortium newsletter: national teams are invited to submit relevant information to OrphaNetWork newsletter to systematically read every issue and to carry out the action points posted in it.
- Reading the Quality Assurance Review and carry the action points posted in it
- Establishment of the Governance for the national team
- 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

Optional contributions (depending on availability of resources):

- Translation of the Orphanet international website
- Translation of the Orphanet RD nomenclature
- Translation of the Orphanet encyclopaedias and/or Orphanews newsletter
- Contribution to the production of the health professional encyclopaedia in English according to the Orphanet procedures
- Production of expert-authored peer-reviewed review articles in the local language
- Production of a general public encyclopaedia (review articles for non-professionals) in the local language according to the methodology established by Orphanet
- 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 the quality standards of Orphanet.

c) 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 on expert resources. The national contact point is in charge of validating the already available national information and of the data submitted by national professionals through the online registration tool.

d) Application to join the consortium

The institution wishing to join the consortium has to express its will to become a partner of Orphanet by sending a letter to the project coordinator, demonstrating its capacity to run the above mentioned activities.

The application ideally should be endorsed by the National Health Authorities of the country, by a letter of support. This is of paramount importance as the data on expert resources posted on the international website have a direct impact on referrals to these resources, however it is not easily applicable for instance in developing countries.

The application is reviewed for eligibility by the MB. The response cycle will last no more than two months.

For the Orphanet national teams: the detailed procedure of “How to join the Orphanet consortium” is available on the OrphaNetWork site (<https://network.orpha.net/network/cgi-bin/articles.php?lng=en&pg=13>)

6. Communication between teams

For any kind of issue, partner teams are invited to contact the Orphanet coordinating team through the address below, who centralises all requests and dispatches them to the appropriate Orphanet coordinating team member (IS-coordination.orphanet@inserm.fr)

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.

This website contains:

- EC Contracts, financial documents and reports
- Orphanet Directories
- Technical procedures
- Leaflets, posters
- PowerPoint presentations on the project
- Reports from work groups and meetings
- A back issue archive of the OrphaNetWork newsletter (see below)
- A back issue archive of the Quality Assurance Review (see below)
- A back issue archive of the Translation Report (see below)

b) OrphaNetWork newsletter

Orphanet publishes an internal bi-monthly newsletter, OrphaNetWork news.

This newsletter is sent within the Orphanet network to country coordinators, project managers and information scientists. National Advisory Board members, scientific board members and IAB members can also subscribe.

This newsletter aims to improve the management of the consortium by communicating on national team activities, recommendations, suggestions and achievements, providing information on the project's evolution and tools.

National teams are invited to submit relevant information to OrphaNetWork newsletter, to systematically read every issue and to carry out the action points posted in it.

c) Quality Assurance Review

A general dissemination document, called the "Orphanet Quality Assurance Review" is sent to all information scientists every three months to help them collecting and updating information for Orphanet. This document includes new and updated procedures, and specific projects to be implemented.

National teams are invited to systematically read every issue and to carry out the action points posted in it. National teams are also contacted through the internal tool Collector for the purposes of Quality assurance (QA).

d) Translation report

This report is sent every three months to the teams involved in the Orphanet international website content translation and/or in the Orphanet Encyclopaedia translation (see part IV). It includes all the necessary information for carrying out monthly translation activities by the national teams.

7. External Communication Tools

a) Press releases

Press releases are sent out as often as necessary to inform the press about the launch of new services. They are sent to national teams for translation and for release to the specialised media of the country. National teams are invited to keep an up-to-date list of journalists to whom they can send these press releases.

b) Web pages on the international website

The international website houses information in the “Events” or “Other Documents” section of the website’s home page. National teams are invited to submit information for publication in these sections concerning relevant international events.

c) National websites

National teams are invited to establish and manage a national website, using a dedicated tool provided by the coordinating team.

National websites are tools to communicate at national level on activities of the national Orphanet team, on events, and on the rare diseases policy in the country. The national website is a national entry point to the Orphanet portal in the 7 available languages (Dutch, English, French, German, Italian, Spanish, and Portuguese). Only one national entry point is foreseen in any one country, even in federalised countries.

Any request related to national websites should be sent to admincs.orphanet@inserm.fr.

General content

Each national website is made on the same structure and composed of two different groups of pages:

Mandatory pages:

- a homepage which explains that the country website is a national entry point to the Orphanet portal and with free content box for relevant country news (see below)

- general information pages, provided by the coordinating team and translated in the national language(s): “About Orphanet”, “About rare diseases”, “About orphan drugs”, “Quality charter” and “Legal notice”
- national mandatory pages present the national Orphanet team, its governance, its sponsors and partnerships

Free content pages:

- the national extra-pages are a set of pages to present:
 - information related to Orphanet national team activity
 - country-specific information on RD and orphan drugs policies. For this section it is recommended to publish information from and/or a link to the national edition of the report on the State of the Art of Rare Diseases Activities published by RD-ACTION joint Action
 - links to some specific parts of the international Orphanet website
- on the homepage:
 - news from the country about RD and Orphan Drugs (OD) policies
 - information related to Orphanet national team activity
- national events: link some national events of interest in the field of RD and OD
- documents: link some national or international documents of interest in the field of RD and OD policies (i.e. national plan/strategy for rare diseases, national edition of the State of the Art of RD Activities report).

For logos policy on national website, please consult paragraph 9.8.

Website administration

Every partner has to designate two persons in charge of the website:

- An editor-in-chief responsible for the content and quality of the provided information (the country coordinator).
- An administrator in charge of creating and maintaining the country site (the country coordinator, the information scientist or a trustworthy colleague).

The administrator tasks are:

- Translation of the general information pages (“About Orphanet”, “About Orphan Drugs”, “About Rare Diseases”, “Quality charters”, “Legal notice”);
- Translation of the website texts in the translation management tool;
- Creation of content for the local mandatory pages (Homepage, Team/Contact, Governance, Sponsors/Partners);
- Creation of extra content for the country’s local menu (max: 6 pages);
- To enliven the site through news, events, and documents (the international news common to all countries will be automatically published).

For the Orphanet national teams: the procedure concerning “How to start an Orphanet national website” is available on the Orphanetwork site (<https://network.orpha.net/network/cgi-bin/articles.php?lng=en&pg=80>)

Editorial policy and quality control

In order to ensure high quality standards and better accuracy of these websites, the following points should be respected:

- 1- The national pages are not intended to reproduce or translate any content from the international Orphanet base of knowledge *i.e.* disease summaries or related texts, lists of patient organisations, laboratories, research projects, etc...
- 2- Any information specific to a RD or group of diseases should be put on the international Orphanet website only, and therefore transmitted to the coordinating team.
- 3- The Orphanet coordinating team is legally responsible for any content published on the national websites. Therefore, any unauthorized content will be removed from the national website without delay when identified.

The coordinating team carries out a regular quality control on the published national websites. The website administrator and editor-in-chief of a national website should comply with any request of modification or suppression of content from the coordinating team.

d) Flyers

The coordinating team has designed flyers about Orphanet services.

For the Orphanet teams: These flyers are available in electronic format on the OrphaNetWork website and can be distributed to professionals in health care institutions and research centres and congress to increase awareness of the website and the services specifically offered to the rare diseases community. They are updated when necessary to explain new services. It is recommended that they be translated if necessary.

e) OrphaNews Europe

OrphaNews Europe is the fortnightly newsletter in English. With over 16,000 readers, OrphaNews Europe is the communication tool between RD-ACTION and the wider scientific community. Registration is possible through the Orphanet website.

National teams should subscribe to and read the Orphanews newsletter.

National teams are invited to disseminate this newsletter throughout their country to any relevant professionals (from ministries, drug agencies, hospitals, experts, etc.) and informing them that subscription is possible online.

National teams 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

Third parties should be invited to publish their information in OrphaNews. The country coordinator can act as editor for his/her country.

8. Agreed principles for running the activities

a) Languages

Orphanet is a multilingual project. The common language used amongst the teams is English.

The Orphanet coordinating team is in charge of maintaining the database in French and in English. Some national Orphanet teams are in charge of providing translations in their own language (currently German by Germany, Spanish by Spain, Italian by Italy, Portuguese by Portugal, Dutch by Belgium).

Additional languages can be added if resources are available for translation and quality control (see below).

b) Translation of Orphanet content

Translation of the different contents in the Orphanet website is possible, depending on available funding.

National teams can decide to translate all, or only part of the website content. This content can be divided into several different translation packages, either mandatory or optional, as described in [part IV](#) of this document.

9. Legal issues and funding

a) Adherence to legal and ethical requirements

Orphanet is committed to maintaining unrestricted access to the website, keeping it free of charge for any personal use.

Collection of data and communication of information is carried out in accordance with all legal provisions in force in the participating countries including any professional codes of ethics, any law concerning data protection, intellectual property rights and any other applicable law or regulation.

The information communicated and the services developed on Orphanet comply with the codes and recommendations issued by the *ad hoc* committees recognised at national or international level, especially concerning the respect of patients' rights, the respect of the confidentiality of information, the ownership of medical information, the practice of on-line medicine, and the security of networks.

Up till now, 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 Autorité de la Santé \(2008\)](#)

All information is updated when scientific news allows it, and at least once a year for data relating to expert resources.

b) Tradename/Logo/Design charter

Orphanet is a tradename which has been registered in Europe, USA, Canada, Japan, Australia and Israel and is owned by the Inserm.

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.

c) Intellectual Property Rights (IPR)

Inserm holds the IPR on the database structure and content, the website design, the logo and the tradename.

National teams own the data collected for the directory of expert resources at their country level. In the case of the coordinating team being unable to keep the website accessible and up-to-date, the national teams are then free to withdraw their data and to re-use it as they wish. National teams may freely use the data they have collected for publications. They are however not allowed to provide this data to third parties for any type of use without the express consent of the Inserm.

The rights and duties are defined in the Data Transfer Agreement (DTA) form which has to be signed by each national collaborating institution.

d) Titles and Membership

Titles

The title “Director of Orphanet” applies only to the project coordinator.

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

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 (no DTA signed).

Membership, partnership and observers

Orphanet member applies to the institution hosting an Orphanet team and having signed the DTA with the Inserm.

Orphanet contact point applies to the institution in those countries where no dedicated funding is allocated to Orphanet activities, therefore there is no active data collection on expert resources.

Orphanet observer applies to the institution which applies to join the Orphanet consortium.

Orphanet partner applies to the group/institution(s) with whom a scientific partnership is ongoing defined by a contract or/and a Memorandum of Understanding (MoU).

Orphanet collaborator applies to an institution/group with whom a scientific collaboration is ongoing not defined by specific contract/MoU.

e) Web addresses

The official address of the website is www.orpha.net. The front page is the English one.

Other URLs (uniform resource locator) have been purchased, including Orphanet.eu, Orphanet.org and Orphanet.net. Users are redirected to www.orpha.net.

The addresses [www.orphanet.\[countrycode\]](http://www.orphanet.[countrycode]) should give access to the Orphanet international home page in the respective national language (ex: www.orphanet.de gives access to the international front page in German). If not applicable, this address should redirect to the national website when it exists.

The addresses [www.orphanet-COUNTRY.\[countrycode\]](http://www.orphanet-COUNTRY.[countrycode]) should be used for the national websites. In the case of several national languages this address should be [www.orphanet-COUNTRY.\[countrycode\]/\[language\]](http://www.orphanet-COUNTRY.[countrycode]/[language])

f) License to all copyrightable parts of the database

We apply the [Creative Commons Attribution-NoDerivs](https://creativecommons.org/licenses/by-nd/4.0/) License to all copyrightable parts of our database. This means that a person is free to copy, distribute, display and make commercial use of the database in all legislations, provided that they give Orphanet credit. However, if it is intended to distribute a modified version of the database, permission first must be asked.

Freely accessible parts of the database for re-use are the list of diseases cross-referenced with external resources, linked to genes and clinical signs, and classified, as well as the thesaurus of clinical signs. Parts of the database needing an explicit permission for re-use are: expert resources directory and database of

orphan drugs.

g) Resources to be mobilised

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

The workload to document the expert resources and edit the national web pages is roughly 1 full time equivalent for 30 million inhabitants, of someone trained or experienced in documentation in the field of health/biology (master level or PhD).

The national coordinator should be able to dedicate at least 15 days per year to Orphanet, depending on the level of development of the expert resources in the country and the scope of the envisaged activities of the team.

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

The institutions could also contribute to the funding of core activities provided by the coordinating team. The contribution will be discussed by the MB when reviewing the application. The contribution could be proportional to the expected workload generated by the inclusion of the new partner and will reflect the share of the new country within the consortium, as a combination of the size of the country in terms of population, and of its budget dedicated to health and research.

h) Funding/Sponsoring of the international/national websites

All Orphanet national teams are encouraged to apply for funding at national level.

Funding can be requested from any type of public institutions 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.

For Orphanet teams: Contract and Memorandum of Understanding templates are available on the OrphaNetWork website.

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

On the footer of national websites, the 3 mandatory logos are displayed: Inserm, French Ministry of Health and European Commission. A free space allows the addition of national financial partners' logos. Partners' logos are added on the national website if their contributions reach a minimum amount to be defined by each country. Partnership in kind can also justify posting logos of contributing institutions. The decision is left to the national team but logos/sponsors policy should be provided/advertised on the national website for transparency reasons.

i) Visibility package of funding bodies

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

National websites

The logos are displayed on the footer of the national website; logos/sponsors policy is defined by the national teams.

j) Non-financial Partnership

Partnership with other stakeholders 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 agency to access data on clinical trials
- 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

k) Release/Licensing of Orphanet Data

Access to information as presented on the orpha.net website is free of charge and intended for consultation purposes only. Access to aggregated data or to massive sets of data for bioinformatics purposes is available on [Orphadata portal](#) where the following data can be downloaded (this list can evolve over the time):

- [Disorders, cross referenced with other nomenclatures](#)
- [Orphanet classifications](#)
- [Phenotypes associated with rare disorders](#)
- [Disorders with their associated genes](#)
- [Linearisation of disorders](#)

- [Orphanet Rare Disease Ontology](#)
- [Sparql ENDPOINT](#)

The [Creative Commons Attribution-NoDerivs](#) Licence applies to this data.

Only non-nominative data are accessible in accordance with personal data protection laws. The dataset is updated once a month. The date of the last release is indicated

Orphadata provides access, on request, to other elements of the Orphanet database after signature of a Data Transfer Agreement (DTA). You can consult details of the data sets in the [academic catalogue](#) and the [industry catalogue](#).

Public institutions and private non-profit institutions are not charged. For-profit organisations are charged with a margin to provide additional funding for the core activity: this agreement takes the form of a service contract, signed between the client, INSERM-TRANSFERT, and Orphanet.

Any request to the national team to obtain massive datasets of Orphanet data should be transmitted through orphadata.org in order to establish the appropriate DTA. National teams should not provide third-parties with massive datasets extracted from Orphanet in any case. The national teams are systematically informed of any request from their country to access data requiring the signature of a DTA.

How to quote

When quoting Orphanet, please use the following format:

Orphanet: an online rare disease and orphan drug data base. © INSERM 1997.
Available on <http://www.orpha.net>. Accessed [date accessed].

When quoting Orphadata, please use the following format:

Orphadata: Free access data from Orphanet. © INSERM 1997.
Available on <http://www.orphadata.org>. Data version [e.g.XML data version].

III. Information on rare diseases and orphan drugs

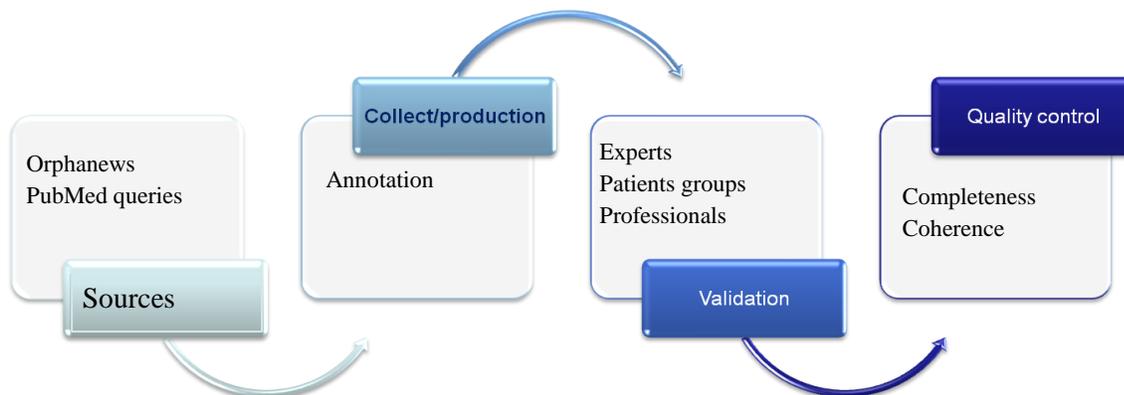


Figure 1: Orphanet overall methodology for data production

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).

When information is not available on one of this media, it is indicated.

1. Orphanet inventory of diseases

a) Definition of an Orphanet disease

Rare diseases

Entries in the Orphanet diseases database correspond to rare diseases (defined in Europe as having a prevalence below 1/2,000), or rare forms of common diseases considered as unique entities because of their specific presentation needing particular clinical expertise.

Entries in the Orphanet database of rare disorders encompass a spectrum of phenomes from a category of disorders to subtypes of disorders. This spectrum comprises:

- Groups of disorders either family of clinically-related disorders, *e.g.* Ceroid lipofuscinoses, or a category intended to organise other entries in a classification, *e.g.* neurodegenerative diseases.

- Disorders (encompassing diseases, syndromes, anomalies, particular clinical situations).
- Subtypes (sub-forms of a disorder that could be clinical, i.e. according to the severity of the disorder, or etiological, i.e. genetic subtypes or pathological, i.e. histological).

This typology is available only on [Orphadata](#) and [ORDO](#). On the website, it is displayed as textual information in the encyclopaedia for professionals.

Rare disorders in the Orphanet database are thus clinically homogeneous entities, whatever the number of genes or other etiological factors leading to them. In general, information (texts, annotations, indexation) is given at the disorder level in this organisation of phenomes. However, the information can be associated to groups of disorders or subtypes, if relevant.

A rare disorder in the Orphanet database corresponds to an entity described in at least two independent individuals, confirming that the clinical signs are not associated by fortuity. Hence, new syndrome proposals on the basis of one single case are not accepted as new entries, unless there is a specific resource (*e.g.* a genetic test) to be registered, or due to the need to represent exhaustively a group of disorders (*e.g.* Congenital disorders of glycosylation).

Entries are represented by a preferred term and as many synonyms as necessary. A unique identifier, the ORPHA number, is randomly attributed by the database to each entry. This number is never re-used, so it is stable on time.

Rare diseases list in alphabetical order is published as an Orphanet report series (ORS) entitled “[List of rare diseases and synonyms in alphabetical order](#)”.

Non-rare diseases

Orphanet registers genetic tests exhaustively including tests offered for non-rare diseases in at least a country of the consortium. Similarly, some orphan designation can be indicated for non-rare diseases. Orphanet does not provide information on those non-rare diseases, except for the information on constitutional molecular genetic tests and orphan designations.

b) Modifications of the Diseases inventory

The Orphanet inventory of diseases is updated on a monthly basis. It is based on:

- Monitoring of the scientific literature to identify:
 - New described disorders
 - New identified genes for rare disorders
 - New published classifications
 - New information modifying the definition of an already listed disorder
- Requests or suggestions coming from the national information scientists in order to add resources to the database (medical laboratories, research projects...) and/or expert advice (i.e. from experts editing texts)

for Orphanet, or revising the Orphanet classification).

- Decisions on any modification of the Orphanet diseases list are agreed upon at a monthly meeting held by a medical and scientific committee within Orphanet, constituted by medical doctors and scientists. The nomenclature officer prepares the material for each meeting, (*i.e.* literature search, published classifications and experts feedback when necessary). All material is submitted to this committee. Decisions are made case by case. They include:
 - Creation of a new entity (newly described entities/lacking entities)
 - Modification of an entity already in the database (*e.g.* nomenclature, hierarchical relationships with its subtypes and/or the group of disorders it belongs to)
 - Historical entity (*e.g.* an entity described many years ago for which there are no further publication)
 - Obsolescence of erroneous entries (*e.g.* duplicated entities)
 - Deprecation of entries when an entity no longer exists *per se* but has been recognized as being another entry. In this case, a “move to” relationship is established between both entries in order to redirect users on the targeted entry.

For each new entry, decisions are made on:

The type of phenome in question (group, disease, syndrome, subtype, etc.).

The main classification it belongs to (linearization; see below).

Secondary classifications it belongs to.

Nomenclature (the main name of the disease in English and in French, all its synonyms and acronyms, key words if needed).

When available, indications are given on the appropriate OMIM numbers, genes and epidemiological data.

A meeting report is published after each meeting. All national teams implement the decisions made with regard to national activities in order to reach the completeness and coherence of the database.

The minutes of the meeting are also sent to the national teams within the Quality Assurance Review while a summary table and a ready-to-translate table are sent to the national teams with the Translation report in order to inform them and to have the names of the new entries translated.

For Orphanet teams: these reports are also available on OrphaNetWork (<https://network.orpha.net/network/cgi-bin/articles.php?lng=en&pg=97>). Teams are entirely responsible for the translation of new entries.

2. Classifications

As stated above, phenomes are organised in classifications according to different criteria, resulting in several types of classifications:

- The clinical classifications of rare disorders are based on clinical criteria. Disorders are classified by body system (e.g. respiratory, digestive) in order to correspond to medical domains that are mostly organised in such way. Additional criteria (pathological, etiological, etc.) are used in details of the classification when relevant in clinical practice. Orphanet classifications of rare disorders are displayed on the website. In these classifications, every Orphanet disease is classified under one or more categories. For example: Cystinosis is classified under “metabolic disorders” and under “rare renal diseases”. Indeed, Orphanet classifications are multi-hierarchical, polyparental classifications.
- Other scientific classifications follow other (mechanistic, pathological, etiological) criteria. They come from the literature or are elaborated by Orphanet following expert advices. They can be used to represent expert resources on the website (i.e. Classification of ciliopathies can be used to represent research projects on this group of disorders).

In order to sort out rare diseases by medical specialty and to avoid multiple counting due to polyhierachy, it is necessary to have also a monohierarchical view (a linearization) in which a disease belongs to one medical specialty only. The rules for this linearisation are formalized in a dedicated document available [here](#).

The information regarding linearisation is only available on the [Orphadata](#) website.

Classifications are regularly revised totally or partially (by group of disorders) according to:

- New published classifications
- Expert advice (i.e. a group of disorders is revised when an expert reviews an in-house disease abstract, or an entire classification is revised for instance when the World Health Organisation’s (WHO) ICD is revised with the help of worldwide experts)
- Local revisions (monthly updates of the database and quality control to detect inconsistencies lead to local modifications of the hierarchies)

Revision proposals are submitted to the monthly meeting held by the medical and scientific committee within Orphanet (see above) for approval and subsequently implemented.

3. Epidemiological data

Data on point prevalence, annual incidence, prevalence at birth, lifetime prevalence, number of cases and families reported in the literature are collected. Every data is combined to a geographical area (country, continent or worldwide) or a population and sources are documented. Data collection is manually curated and a validation status is available.

Sources for epidemiological data collection are:

- Scientific literature
- Registries/projects (RARECAREnet, EUROCAT, etc.)
- National/international Health institutes and agencies (Institut National de Veille Sanitaire, French

Institute of Health Surveillance; American Center of Disease Control and Prevention, American National Cancer Institute, EMA, WHO etc.)

- Medical texts, grey literature and reports from expert networks
- Orphanet collaborating experts

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 cases and families reported in the literature are available on the [Orphadata](#) website and [ORDO](#).

Absolute point prevalence, prevalence at birth, annual incidence figures and cases and families reported in the literature are published in two [Orphanet Report Series](#) (in all the languages) updated every six months.

All this information feed into the epidemiology section of the abstracts displayed in the website.

4. Natural history

Data on age of onset, inheritance and age of death are also collected. Age of onset and inheritance information is available on the [Orphanet](#) website, [Orphadata](#) and [ORDO](#). The age of death that is considered a sensitive data and is not available on the [Orphanet](#) website but only on [Orphadata](#) and [ORDO](#).

5. Annotations and alignments of rare diseases with medical terminologies and databases.

Rare diseases are annotated with phenotypes (clinical features), the frequency (very frequent, frequent or occasional) of each clinical sign is indicated for every indexed disease. The threshold for the terms referring to the frequency of clinical signs is as follows:

- occasional: <30%
- frequent: 30% < clinical signs < 80%
- very frequent: > 80%

Rare diseases are currently being annotated with phenotype terms from Human Phenotype Ontology (HPO), the frequency of occurrence of these phenotypic features for each disease, and further precisions for diagnostic criteria and pathognomonic signs are registered.

Rare diseases are aligned with several medical terminologies, including ICD10, UMLS, MeSH, MedDRA and SNOMED-CT, the latter in the frame of a collaboration with the International Health Terminology Standards Development Organisation (IHTSDO).

- Indexation with ICD10 codes is an on-going process intended to classify every rare disease 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.
- Diseases are also manually mapped to one or more OMIM numbers.

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 done for ICD10 terms: specific code, inclusion or index term, code attributed by Orphanet, with the validation status (table 1, for ICD10, see the [specific indexation procedure](#)).

Furthermore, specific PubMed queries, resulting from mapping Orphanet terms with MeSH descriptors, proposed 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 and OMIM
- Annual updates are carried out for UMLS, MeSH and MedDRA (after each UMLS release)

All this information is available on the [Orphanet](#) website, [Orphadata](#) and [ORDO](#) except SNOMED-CT

E	exact mapping (the terms and the concepts are equivalent)
NTBT	narrower term maps to a broader term
BTNT	broader term maps to a narrower term
W	incorrect mapping (two different concepts)
NTBT/E	narrower term maps to a broader term because of an exact mapping with a synonym in the target terminology
BTNT/E	broader term maps to a narrower term because of an exact mapping with a synonym in the target terminology
W/E	incorrect mapping (two different concepts) but syntactically exact mapping to a synonym or a preferred term in the target terminology
ND	not yet decided/unable to decide
The following are attributed to ICD10 codes only :	
Specific code	The term has its own code in the ICD10
Inclusion term	The term is included under a ICD10 category and has not its own code
Index term	The term is included in ICD10 index and refers to one more general code
Attributed code	The term does not exist in ICD10 and a code was attributed by Orphanet

Table 1: Mapping qualifiers used to align rare diseases registered in Orphanet with several medical terminologies. Mappings are understood from Orphanet to the target terminology.

6. Interfacing Orphanet entries with external sources of information

Relevant external websites containing added-value information on rare diseases are linked after editorial

selection. External websites are annotated according to their public (general public, professionals), their conditions of access (free, paid), their origin (university, patient organisations, public health agencies, etc.), the kind of information they diffuse (e.g. general information on the disease, databases outside Europe and not otherwise documented in Orphanet).

7. Orphanet inventory of genes

Genes involved in rare diseases (pathogenic, modifying and susceptibility genes) are entered in the database. Candidate genes are also added when they are tested in clinical practice. Genes are associated with at least one disease, and if relevant to one or more genetic tests, mutation databases or patient registries and/or research projects in the database.

Sources for creation/update of a gene entry are:

- Cross-reference with external databases (such as HGNC, OMIM, Genatlas and UniProtKB, Ensembl, Reactome and IUPHAR).
- Expert advices from update of the Orphanet encyclopaedia from professionals.
- Scientific literature
- Expert websites
- Requests from Orphanet national information scientists
- Spontaneous communications from the researcher discovering the gene.

Gene nomenclature includes main name and symbol of the gene (from HGNC), its synonyms and previous names and symbols according to HGNC. Automatic mappings with OMIM, UniProtKB, Genatlas Ensembl, Reactome and IUPHAR-DB are available. Chromosomal location is indicated as well as the nature of the genetic entity (gene with protein product, locus, non-coding RNA).

The relationship between a gene and a disease is qualified according to the role the gene plays in the pathogenesis of a disease. Genes are annotated as causative, modifiers (both from germline or somatic mutations), major susceptibility factors or playing a role in the phenotype (for chromosomal anomalies). When the causative mutations are of germline origin, the functional consequences of the mutations could be documented as a loss or a gain of protein function.

Information on the nature of the gene is also available on the [Orphadata](#) website and [ORDO](#) .

8. Orphanet encyclopaedia

Three kinds of Orphanet encyclopaedia exist: one for health professionals, one intended for patients (general public encyclopaedia) and one related to disabilities. In order to deliver information on as many aspects on each rare disease as possible. Different levels of editorial resources are defined and different types of texts can be associated to each disease.

a) Health professional encyclopaedia

This encyclopaedia comprises the different types of in-house produced texts listed below,

Summary information (short definitions/abstracts)

All the diseases in the database should be described with summary information (i.e abstracts, definitions or short definitions) according to the following criteria:

- Diseases involving a very limited number of cases published (prevalence less than 1/1,000,00,000) can be described in a short definition (see below). The link to PubMed provided by Orphanet complete the information giving access to the few publications on them.
- Diseases involving a larger number of cases, or having a significant number of publications, should be described in abstracts or at least by a short definition comprising the group of diseases it belongs to and its specific clinical particularities.

Orphanet abstracts are unique, originally written in English by a member of the editorial team and reviewed by at least one invited expert. Textual information on a disease can be presented in the form of an abstract, definition or short definition.

The abstracts and definitions are structured in up to 10 sections, according to the following outline:

Definition of the disease – Epidemiology – Clinical description – Aetiology – Diagnostic methods – Differential diagnosis - Genetic counselling (if relevant) – Antenatal diagnosis (if relevant) – Management – Prognosis.

- Abstracts and definitions are submitted to a selected expert (invited according to his/her publications on the subject and or recommended by learned society or by a member of one of the Orphanet national scientific advisory boards (NAB) and/or belonging to an officially designated reference centre). Additional information on the diseases (i.e. classification, nomenclature, epidemiological data, clinical signs, genes, etc.) is requested from the expert if not already documented in the database, or validation of the existing data is requested.
- Short definitions are written by a member of the editorial team and validated in-house by medical staff.

Textual information is updated in a regular basis, or every time that an important scientific discovery needs to be included.

Abstracts and definitions produced/updated during a two-months period are compiled and quality controlled in a three steps fashion:

- Editorial quality control, performed by the manager of the Orphanet editorial team, in order to check the homogeneity in the level of quality of their content.
- Global quality control performed by the quality manager in order to check the coherence between the summary information, the data registered in the Orphanet database and the use of the official nomenclatures.

- English editing performed by an English native speaker medical writer
New and updated texts are sent to the Orphanet national teams for translation (see part IV).

Automatic texts

For some entries (for group of diseases, deprecated entries, subtypes of disorders, particular clinical situations for which there is an orphan designation and conditions for which there is a pharmacogenetic test) no short definitions nor abstracts are written, but automatically generated texts provide information on the nature of the entry.

Emergency guidelines

Emergency guidelines are concise charts 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 and one for the hospital emergency department.

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

b) General public encyclopaedia

The general public encyclopaedia is 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 *Haute Autorité de Santé* (HAS) has been established in order to guarantee the quality of the texts.

To complete this encyclopaedia, general public-intended texts produced by others (i.e. patient organisations, expert centres) in any language, can be published in Orphanet (please refer to paragraph 1.4).

- Priority subjects are defined by the Orphanet Editorial committee according to the prevalence of the disease, the need for information (i.e. following expert advice), the existence of partnerships with other organisations, etc.
- Articles are produced by the coordinating editorial team including physicians and scientific writers from Orphanet.
- They are then submitted to experts on the disease, to practitioners in the field of disabilities, and to patient support groups for evaluation.

- The text is published on-line in Orphanet after final validation by all those involved. The names of every expert or support group having participated in the editorial process are mentioned in the text.
- Translations of this encyclopaedia are feasible if funding is identified (see part IV).

c) **Disabilities encyclopaedia**

Diseases having disability can be described in disability factsheets which 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 national health care system as well as in the care and social support system. They are intended for the professionals in the field of disability as well as to the patients and their families.

Disability factsheets are produced by the Orphanet editorial team and reviewed by a medical staff. 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 measure and consequences in everyday life (taken from the corresponding text from the Orphanet general public encyclopaedia).

9. Quality control

Post-release quality control is performed on a monthly basis to ensure the coherence between the most up-to-date summary information published in the Orphanet encyclopaedia and rare disease nomenclature, epidemiological data, indexation and genes.

10. External sources to be disseminated through the Orphanet website

The editorial team is in charge of identifying articles suitable for publication on the website produced by other journals or learned societies. External material can be 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 to assess the quality and reporting of practice guidelines). Permission from the copyright holder is requested so as to give access to the full text through the Orphanet website.

National teams can submit the material to recommend by sending it to the coordinating team together with: reasons for recommending it after evaluation for compliance with Orphanet Quality Standard, then permission to publish the article free to access in Orphanet will be asked by the coordinating team.

(For Orphanet teams: technical procedure and evaluation sheets available [here](#)), contact person (publisher, learned society etc) of the institution holding the copyright.

If/when permission is granted the article will be displayed at the bottom of the appropriate disease page together with other texts linked to the disease. Information about its language and date of production will also be given.

These texts can be added whatever their language.

Eight distinct external resources are accessible from the Orphanet website:

- **Review articles** published in peer-reviewed journals are identified through survey of the literature, this includes Review articles published in the Orphanet Journal of rare Diseases (OJRD). **Practical genetic articles:** Articles of clinical genetics produced by the European Journal of Human Genetics (EJHG), which is an Orphanet partner.
- **Clinical genetics review:** These are peer-reviewed disease **descriptions focused on genetic** aspects with an implication in the diagnosis, management, and genetic counseling of patients and families with specific inherited conditions. This category comprises mostly GeneReview articles.
- **Best practice guidelines:** These guidelines are recommendations for the management of patients, issued by official organisations. There are two kinds of best practice guidelines: anesthesia guidelines and clinical practice guidelines. They are both produced by learned societies and published either in scientific journals or in learned societies or health agencies websites. A methodology of assessment has been developed to review the clinical practice guidelines based on the AGREE II instrument and thus allowing link of only the most accurate ones to the corresponding disease. Anesthesia guidelines are assessed by Orphananesthesia, a project of the German Society of Anesthesiology and Intensive Care Medicine
- **Guidance for genetic testing:** This collection comprises summary recommendations intended to disseminate best practice in genetics testing. They include Gene Cards (published in the EJHG).
- **Information on diagnostic criteria** is presented in concise documents intended to avoid serial misdiagnosis and facilitate early therapeutic management. This information is extracted from peer-reviewed journals and validated by international experts, with reference to the original paper given at the top of the page.
- **Emergency guidelines** produced by national learned societies.
- **General public** articles produced by official organisations.

11. Orphan Drugs

The list of orphan 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 EMA (centralised procedure) with a specific indication for 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, but they do not have a regulatory status.

Drugs with a regulatory status in Europe are collected from reports issued by the 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 OD with a regulatory status in the USA are currently being collected, but the list should not be considered as exhaustive at present.

Data on OD is updated when there are changes in 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 level for the countries outside the scope of EMA after agreement with the coordinating team. However, for European countries, this information remains under the responsibility of the coordinating team.

OD are published on the Orphanet website can be download on orphadata.org and data is also released within an ORS that is updated every trimester: [Lists of medicinal products for rare diseases in Europe](#),

For European countries, collection of additional information is highly encouraged at national level such as accessibility or reimbursement status in each country. This information should be displayed on the country sites (ex: list of drugs available for patients in a specific country). 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 EUCERD/CEGRD document "State-of-the-art".

IV Directory of rare diseases-related expert resources

Orphanet provides a directory of:

- Expert centers and centres of expertise (if applicable)
- Medical laboratories and diagnostic tests
- Patient organisations
- Clinical trials
- Patient registries/databases
- Mutation databases
- Biobanks
- Research projects
- infrastructures for research

Networks of expert resources are also collected with the exception of diagnostic tests.

1. Data selection

A pre-requisite before data collection is to define the national sources of information that should match the selection criteria defined for each type of data. These sources of information should be advertised on the national website.

2. Data collection

Data collection is done through partnerships with official sources. It can also be self-declared by professionals involved in the expert resource through the [online registration tool](#).

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

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, professionals wishing to provide information not for public access (i.e. not published on the Orphanet website), such as research projects or diagnostics tests, can still be collected and stored into the database for further analysis.

3. National validation

Each country should define, per type of data, their validation process before publication, if necessary. This validation step is meant to ensure that data is relevant for the rare diseases community and the Orphanet users.

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.

4. 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 to each country team. Special attention is given to the mapping between the Orphanet nomenclature of rare diseases (genes and/or drugs) and the registered expert resources.

5. Online publication

Once information meets Orphanet quality standards, it is published online. Minor changes are possible in a continuous basis.

6. Data update

Update of the directory of resources is performed once a year. Every professional registered in the database is contacted and encouraged to access the online registration tool and update his/her activities. Depending on the country, the update is managed either by the country team or at the coordination level. The tool is available for professionals to update whenever they want all or part of their information in Orphanet.

7. Post-release quality control

At the coordinating level: the coordinating team organises regular quality control on published data to ensure its quality over time and between countries. This quality control aims to provide data homogeneity and completeness. National teams can be, in that frame, asked to collect missing information and/or correct mistakes.

At National level: Published data on expert resources should be quality controlled in each country in order to be sure that:

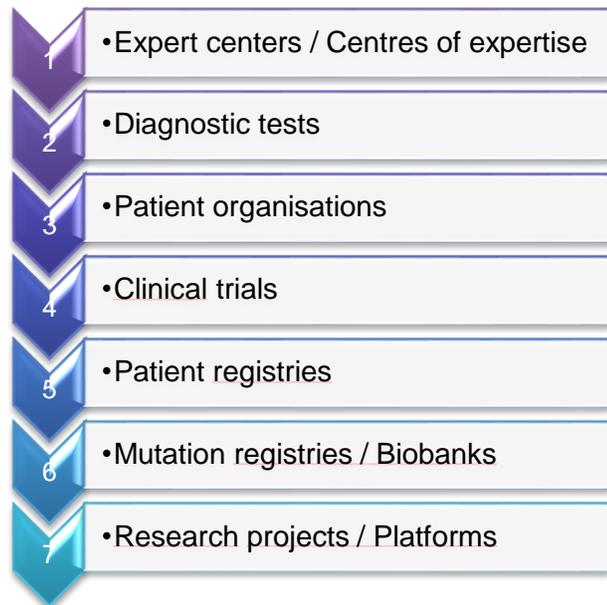
- all the relevant expert resources are there (**completeness** for a country at a given time)
- no superfluous resource is present, which means, all the expert resources collected comply with the

- inclusion criteria according to the Orphanet standards (**relevance**)
- information given is exact (at the best of the validator's knowledge) (**accuracy**)

This post-release quality control (PRQC) should be organized at the National level and advertised in the national website.

8. Priorities list

Among Orphanet resources, the following priority is suggested for data collection and registration. However, priority should be given to certain resources if they are already available for publication in a given country, provided they comply with the Orphanet quality criteria:



The utmost priority is given to resources related to European-funded networks and officially-designated ones when applicable.

For each type of resource, a specific list of priorities as well as specific procedures to each type of data is detailed in the annexes.

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 secured URL using their login and password.

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

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](#)
- AND they have legal status or they are registered in an official journal.

Research related resources (research projects, clinical trials, patient registries, biobanks and mutation databases) are also collected and registered in Orphanet database if they are founded by a member agency of the IRDiRC consortium (International Rare Diseases Research Consortium, list of members available [here](#)) located in a country for which there isn't an Orphanet national team.

Patient registries, biobanks, mutation databases and platforms can also be registered if they fulfill inclusion criteria (procedure for exhaustive list of inclusion criteria soon available online).

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

IV Translation of Orphanet content

1. Translation of Orphanet content by a national team

Translation of the different contents in the Orphanet website is possible, depending on available funding.

Translation in a given language of the Orphanet database and related documents can be performed by any Orphanet national team or persons designated/appointed by the country coordinator.

The national team 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 country coordinator or a physician designated by him/her.

National teams can decide to translate all, or only part of the international website content.

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

a) Orphanet International website

International website layout

It includes:

- layout, menus and static pages,
- general explanatory pages (in common with national websites),
- help pages and warnings.

The coordinating team provides the national team with all the content to be translated.

Once translated, this content is validated by the national team before online publication.

Regular updates of this content are sent to the national teams.

Names of diseases

Translation of diseases names includes:

- preferred term,
- synonyms,
- key-words.

The coordinating team provides the national team with tables containing disease names to be translated (preferred terms, synonyms and key-words). For every new language, an initial file containing the entire and most up-to-date list of terms is provided.

As the nomenclature is updated every month, a file containing the new and modified diseases is sent regularly to all the partners, in the Translation report.

Updating the nomenclature of diseases in a given language is mandatory as soon as the initial list of terms has been translated.

Translation should not be a literal one, but adapted to the national medical practice if needed. Synonyms can be added/ suppressed in order to perfectly fit national use. All the commonly used acronyms should be included, in order to facilitate searching via the search engine of the website.

It is mandatory for translations to be validated by the country coordinator, or by a physician designated by him/her. Validation is necessary to assure correctness, medical usefulness, and coherence across the nomenclature. Correctness of these translation is under the responsibility of the translating teams.

After validation, the complete files are sent to the translation manager for incorporation in the database.

Clinical signs and symptoms (phenotypes)

Orphanet uses HPO Terminology to annotate rare diseases with their phenotypic features. HPO terms used in Orphanet should be translated in national languages. New HPO terms incorporated to Orphanet are transmitted to national teams for translation in the Translation report.

The coordinating team provides tables containing labels to be translated.

Translation should be validated by the country coordinator or by a physician designated by him/her. It should assure the relevance and clinical usefulness of the terms according to the national uses.

Validated translation is sent to the coordinating team for incorporation to the database.

b) Summary information on diseases (abstracts, definitions and short definitions)

It can be translated in any other language, whether the rest of the website is translated or not. The translation must be validated by the country coordinator or by a physician designated by him/her.

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

National teams wishing to start translating all or some of the summary information into a new language

should inform the coordinating team to initiate the collaboration.

As a starting point, the coordinating team provides the national team with a first batch of the most up-to-date summary information in English, and monthly updates of approximately 50 summary information per month. The number of summary information to be translated as a first batch is to be decided by the national team, afterwards the monthly updates are mandatory.

Translation should be exact, without adding new facts, and correct from a medical point of view. Attention should be paid to respect the nomenclature of genes and proteins, and to specific medical terms. Translation should be validated by the country coordinator or by a physician designated by him/her (*i.e.* a member of the national NAB). The persons having validated a text will be acknowledged on the national website.

In case the translating team wishes to make suggestions to update or to improve the abstract's content, requests should be sent to the person responsible for the Orphanet Encyclopaedia in order to initiate a standard update cycle (and to make sure all the Orphanet users benefit from this input). Local updates are not allowed in any country.

c) Emergency guidelines

These guidelines can be translated in other languages. Translations will be 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 will also be given.

The coordinating team provides the partner with the texts on request.

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

- a) **Exact translation:** If the translations are validated by the country coordinator or by a physician designated by him/her, texts should be translated exactly, 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). Please note that by validation we mean the validation of the accuracy of the translation, and not the validation of the content. A disclaimer should be inserted specifying that some of the procedures mentioned, particularly drug treatments, may not be valid in the country. Disclaimer at the end of the original version, specifying the persons who have drafted the guidelines, should be translated as well. Translation will be endorsed by the Orphanet local team and specified so in the document. The name of the professional having validated a translation, will be acknowledged in the document.
- b) **Adaptation:** If the translations are validated by national emergency medicine/intensive care learned societies: the texts can be amended according to the remarks of the national experts. In this case when final validation is granted by the experts of the learned societies and amendments have been added, the disclaimer at the end of the original (French) version specifying the

persons who have drafted the guidelines should be replaced by one informing that the local Orphanet team has adapted the guidelines with the collaboration of the experts of the learned societies. A reference to the original French recommendations (with a link to them) should be added.

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

Local updates are allowed only when collaboration with national emergency medicine learned societies is established.

d) General public encyclopaedia

Orphanet produces a general public encyclopedia in French, which is displayed at the bottom of each specific disease page in the detailed information section.

These texts can be translated in other languages. Translations will be 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 will also be given.

The coordinating team provides the partner with the texts on request.

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

- a) **Exact translation:** Texts should be translated exactly, without adding new facts, except for the specific sections providing information on local services and policy (e.g. social aid, prenatal diagnosis...). If this adaptation is not possible, the section on local services and policy can be omitted from the translation. A disclaimer should be inserted specifying that some of the information mentioned (e.g. drug treatments, prenatal diagnosis...) 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. Please note that by validation we mean the validation of the accuracy of the translation, and not the validation of the content. The persons having validated a text will be acknowledged in the national document.
- b) **Adaptation:** The texts can be amended according to the remarks of the national experts from the emergency learned societies. In this case when final validation is granted by the experts and amendments have been added, the disclaimer at the end of the original (French) version specifying the persons who have drafted the article should be replaced by one informing that the local Orphanet team has adapted the article with the collaboration of the experts of the learned societies. A reference to the original French article (with a link to them) should be added.

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

e) Disabilities factsheets

Orphanet produces disabilities factsheets in French, which are displayed at the bottom of each specific disease page in the detailed information section.

These texts can be translated in other languages. Translations will be 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 will also be given.

The coordinating team provides the partner with the texts on request.

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

- a) **Exact translation:** Texts should be translated exactly, without adding new facts, except for the specific sections providing information on local services and policy (e.g. social aid, prenatal diagnosis...). If this adaptation is not possible, the section on local services and policy can be omitted from the translation. A disclaimer should be inserted specifying that some of the information mentioned (e.g. drug treatments, prenatal diagnosis...) 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 a inexperienced reader for the non-medical content (however this is not mandatory), both designated by him/her. Please note that by validation we mean the validation of the accuracy of the translation, and not the validation of the content. The persons having validated a text will be acknowledged in the national document.
- b) **Adaptation:** the texts can be amended according to the remarks of the national experts. In this last case when final validation is granted by the experts of the learned societies and amendments have been added, the disclaimer at the end of the original (French) version specifying the persons who have drafted the factsheets should be replaced by one informing that the local Orphanet team has adapted the article with the collaboration of the experts of the learned societies. A reference to the original French article (with a link to them) should be added.

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

f) Orphanews

Orphanews, the electronic newsletter of RD-ACTION, is produced in English and can be translated in any other language. It is published every two weeks.

The national team can decide whether to translate all the articles present in each newsletter or only part of it, it can also decide the frequency at which the newsletter in the national language is published. The country coordinator shall appoint an editor of the newsletter and nominate an editorial board.

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

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

g) Orphanet Report Series

Orphanet report series can be produced in several languages, provided the content exists in this language. Some ORS are produced by extracting data from the database, thus pre-existing translations (*i.e.* diseases names) are mandatory when diseases names are required. Other ORS address policy themes and are produced in the frame of specific projects or partnerships.

h) Note concerning translation of articles disseminated through the Orphanet website

Articles disseminated through the Orphanet website but not produced by us, or that have been published in other journals cooperating with Orphanet could theoretically be translated provided specific permission is obtained from the copyright holder; the translation process should not be initiated before the appropriate permissions are obtained.

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

a) Generalities

Translation in a given language of the Orphanet encyclopedia can be performed by a working group lead by a translation coordinator and translations have to be 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.

The translation coordinator agrees to work according these Standard operating procedures signing the appropriate document; therefore, he/she is entirely responsible for the translation and its validation.

b) Summary information on diseases (Abstracts)

It can be translated in any other language. The translation must be validated by a physician.

The translated summary information will be 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 will also be 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 of the collaboration Orphanet provides the translation coordinator with a first batch of the most updated abstracts. The number of abstracts to be translated as a first batch is to be decided by the translation coordinator; afterwards the monthly updates of approx. 50 abstracts per month are mandatory.

Translation should be exact, without adding new facts, and correct from a medical point of view. Attention should be paid to respect the nomenclature of genes and proteins, and to specific medical terms. Translation should be validated by a physician (i.e. a member of the national SAB). The persons having translated and validated a text will be acknowledged on the pdf document. The companies providing financial support will also be acknowledged on the pdf document.

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

V. Annexes

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: Directorat 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
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
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
LDDDB: 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

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

Editor of this procedural document: International coordinator, Sylvie Maiella -

This procedural document has been approved by Orphanet Management Board - Quality control: Charlotte Gueydan

The correct form when quoting this document is: “Orphanet Standard Operating procedures, Orphanet, June 2016, V2.1”

http://www.orpha.net/orphacom/special/SOPS_V2.1.pdf