orphanet

2019 Activity Report

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Abbreviation list

BNDMR: French Rare Diseases Data Repository
CEQAS : Cytogenetic European Quality Assessment Service
CHMP : the Committee for Medicinal Products for Human use
CNIL : Commission nationale de l'informatique et des libertés : The French data protection authority
CNSA: French National Solidarity Fund for Autonomy
COMP : the Committee for Orphan Medicinal Products
DG Santé : Directorate General Health and Consumers – European Commission
DIMDI: German Institute of Medical Documentation and Information
ECRIN: European Clinical Research Infrastructure Network
EJHG: European Journal of Human Genetics
EMA: European Medicines Agency
EMBL - EBI: European Bioinformatics Institute
EMQN: European Molecular Genetics Quality Network
EQA: external quality assessment
EUCERD: European Union Committee of Experts on Rare Diseases
FDA: Food and Drugs administration
HGNC : Human Genome Organisation Gene Nomenclature Committee
HPO : Human Phenotype Ontology
ICD: International Classification of Diseases
ICD-10GM: German ICD-10
ICHPT: International Consortium of Human Phenotype Terminologies
IHTSDO: International Health Terminology Standards Development Organisation
INSERM: French National Institute of Health and Medical Research
IRDiRC: The International Rare Diseases Research Consortium
ISO : International Organization for Standardization
IUPHAR: The International Union of Basic and Clinical Pharmacology
MA : marketing authorisation
MedRA: Medical Dictionary for Regulatory Activities
MeSH: Medical Subject Headings
NFU: Netherlands Federation of University Medical Centres
OD: orphan drugs
OJRD: Orphanet Journal of Rare Diseases
OMIM: Online Mendelian Inheritance in Man
ORDO: Orphanet Rare Disease ontology
ORS: Orphanet Report Series
RD: Rare diseases
RD-TAG: The Rare Diseases Topic Advisory Group
RNA: Ribonucleic acid

SNOMED-CT: Systematized Nomenclature of Medicine-Clinical Terms
SOPs: Standard Operating Procedures
UMLS: Unified Medical Language System
UniProtKB : Universal Protein Resource Knowledgebase
URL: uniform resource locator
WHO: World Health Organisation
WP: Workpackage

1. Overview

Orphanet is a unique resource, gathering and producing knowledge on rare diseases so as to contribute to improving the diagnosis, care and treatment of patients with rare diseases. Orphanet aims to provide high-quality information on rare diseases, and ensure equal access to knowledge for all stakeholders. Orphanet also maintains the Orphanet rare disease nomenclature (ORPHA code), essential in improving the visibility of rare diseases in health and research information systems.

Orphanet was established in France by the INSERM (French National Institute for Health and Medical Research) at the instigation of the French Ministry of Health in 1997. This initiative became a European endeavour from 2000, supported by grants from the European Commission: Orphanet has gradually grown to a network of 40 countries in 2019, and 41 in 2020 within Europe and across the globe.

1.1. Orphanet's missions

Over the past 20 years, Orphanet has become the reference source of information on rare diseases. As such, Orphanet is committed to meeting new challenges arising from a rapidly evolving political, scientific, and informatics landscape. In particular, it is crucial to help all audiences access quality information amongst the plethora of information available online, to provide the means to identify rare disease patients, to guide patients and doctors towards relevant services for an efficient patient care pathway, and to contribute to generating knowledge by producing massive, computable, re-usable scientific data.

Orphanet works towards meeting three main goals:

- **Improve the visibility of rare diseases in the fields of healthcare and research by maintaining the Orphanet rare disease nomenclature (ORPHA codes): providing a common language to understand each other across the rare disease field.**

  In a global community, we need to understand each other, although we may not speak the same language. A stable nomenclature, cross-referenced with other international terminologies is therefore essential. In order to improve the visibility of rare diseases in information systems, Orphanet has developed, and maintains, a unique, multi-lingual nomenclature of rare diseases, around which the rest of the data in our relational database is structured. Each disease is assigned a unique ORPHA code: integrating this nomenclature in health and research information systems is essential in ensuring that rare diseases are visible and that different systems can work together. This nomenclature is aligned with other terminologies: OMIM, ICD-10, SNOMED-CT, MedDRA, UMLS, MeSH, GARD. This cross-referencing is a key step towards the interoperability of databases and health information systems.

- **Provide high-quality information on rare diseases and expertise, ensuring equal access to knowledge for all stakeholders: orientating users and actors in the field in the mass of information online.**

  Rare diseases patients are scattered across the globe, as are rare disease experts. Orphanet provides visibility to experts and for patients by providing access to a catalogue of expert services in 35 countries having signed the Network Agreement by disease, such as centres of expertise, laboratories and diagnostic tests, patient organisations, research projects and clinical trials. This data promotes networking, tackles isolation and helps foster appropriate referrals. Orphanet draws on the expertise of professionals from across the world to provide scientific data on rare diseases (gene-disease relationships, epidemiology, phenotypic features, functional consequences of diseases, etc.). In addition, Orphanet produces an encyclopaedia of rare diseases, progressively translated into the 8 languages of the database (English, French, Spanish, Italian, German, Dutch, Portuguese, Polish) with texts also currently available in Greek, Slovak, Finnish, Hebrew and Russian, freely available online. Orphanet integrates and provides access to high quality information produced around the world, such as clinical practice guidelines and information geared to the general public.

- **Contribute to generating knowledge on rare diseases: piecing together the parts of the puzzle to better understand rare diseases.**

  To develop and curate the scientific data in the Orphanet database, Orphanet works with experts from around the globe, from healthcare professionals and researchers, to patient representatives and professionals from the medical-social sector. The wealth of data in Orphanet and the way this data is structured allows additional knowledge to be generated, helping to piece together data that at times can resemble pieces of an irresolvable puzzle. Integration of this data adds value and renders it interpretable. Orphanet provides standards for rare disease identification, notably via the Orphanet nomenclature, an essential key for interoperability. Orphanet provides integrated, re-usable data essential for research on the www.orphadata.org platform and as a structured vocabulary for rare diseases, the Orphanet Ontology of Rare Diseases (ORDO). These resources contribute to improving the interoperability of data on rare diseases across the globe and across the fields of health care and research. They are being integrated in several bioinformatics projects and infrastructures around the world in order to improve diagnosis and treatment. Orphanet is committed to networking with partners across the globe in order to help contribute to generating new knowledge on rare diseases.

The integral role played by Orphanet in the research and care spheres has led to its recognition as an IRDiRC Recognised Resource, integration in the French node of ELIXIR, the European Research Infrastructure Consortium uniting Europe's leading life science organisations, and the designation of Orphadata's freely accessible data sets as an ELIXIR Core Data Resource. Orphanet is also a Human Variome Project Recommended System. Orphanet and the ORPHA nomenclature are also cited as key resources in every European legislative text on rare diseases and as key measures in many national plans/strategies for rare diseases.

1.2. Our services and products

The Orphanet knowledge base is an organised and dynamic collection of information and data on RD and orphan drugs. Added-value data from multiple sources are archived, reviewed, manually annotated and integrated to other data by curators and validated by experts following formalised procedures which are published online in a dedicated section of the website. Furthermore, Orphanet has set up a Quality Management System to ensure the quality of the knowledge base. These unique features make Orphanet an essential tool for different stakeholders, in particular health professionals and researchers, to keep up to date with the constantly evolving knowledge concerning RD.

The data in the database is accessible via a variety of media: the Orphanet website (www.orpha.net), the Orphanet mobile application, the Orphanet data download platform Orphadata (www.orphadata.org), the Orphanet Rare Disease Ontology (ORDO), the HPO-ORDO Ontological Module (HOOM) and the Orphanet Report Series reports.

- **The Orphanet website provides access to:**
  - A comprehensive inventory of rare diseases classified according to a polyhierarchical classification system. Each disease is mapped with ICD-10, Online Mendelian Inheritance in Man (OMIM), Medical Subject Headings (MeSH), Unified Medical Language System (UMLS), Genetic and Rare Disease Information Center terms (GARD), Medical Dictionary for Regulatory Activities (MedDRA), and associated genes, within its 'identity card' that also includes the relevant prevalence category, age of onset category, and mode of inheritance. Diseases are also annotated with phenotypic features and frequency using HPO, epidemiological data and their functional consequences.
  - An encyclopaedia covering more than 6,800 rare diseases or groups of diseases, with summary texts written by scientific writers and reviewed by world-renowned experts. Summary texts are produced in English and are then translated into French, German, Italian, Portuguese, Spanish, Dutch, and Polish. For certain selected diseases, emergency guidelines and disability factsheets are produced in French and then translated.
  - An inventory of high quality articles published by other journals or learned societies. More than 3800 articles are available via Orphanet, with the permission of the authors and editors, comprising national and international clinical guidelines produced by learned societies that are not published in peer-reviewed journals but available as reports.
  - An inventory of orphan drugs and of drugs intended for rare diseases, at all stages of development, from orphan designation to market authorisation.
  - A catalogue of expert services, validated by national experts in the 35 member countries and providing information on: specialised expert centres and centres of expertise, medical laboratories, research projects, clinical trials, patient registries and mutation databases, networks, technological platforms and patient organisations.
  - Thematic studies and reports on overarching subjects: the "Orphanet Report Series" (ORS), published as PDF documents.
  - OrphaNews. The newsletter of the rare disease community, written in English, covering both scientific and political news. This newsletter is also published in French and Italian.

- **Orphanet data is available via a mobile apps:**
  - **Orpha Guides:** an app in French giving access to information on French national support mechanisms for patients and their families, as well as information concerning the functional consequences rare diseases. The app is available for iOS and Android. This app will be replaced by a new, more comprehensive, Orpha Guides app in 2021.

- **The Orphadata platform** (www.orphadata.org) provides high-quality datasets related to rare diseases and orphan drugs, in a reusable and computable format.
  - Freely available datasets: Orphanet Rare Disease Ontology, Orphanet nomenclature and cross-references with other terminologies, classifications, disorders with associated genes, phenotypes associated with rare disorders, linearisation of rare disorders, epidemiological data;
  - Datasets available via Data Transfer Agreement/Licence: Textual information, catalogues of patient organisations, expert centres, clinical laboratories and diagnostic tests, orphan drugs, research activities.

- **The Orphanet Rare Disease Ontology (ORDO),** a structured vocabulary for rare diseases derived from the Orphanet database, capturing relationships between diseases, genes and other relevant features. ORDO provides integrated, re-usable data for computational analysis.

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

- **The Orphanet Report Series (ORS)** are thematic studies and reports on overarching subject, derived from data in the Orphanet database, published as PDF documents.

1.3. Highlights of 2019

Orphanet international positioning

The Orphanet Network Agreement

At the end of 2018 the Orphanet Network Agreement has now been signed by 36 Institutions from 35 countries (Armenia; Austria; Belgium; Bulgaria; Canada, Croatia; Czech Republic; Hungary; Estonia; Finland; France; Georgia; Germany; Ireland; Israel; Italy; Japan; Latvia; Lithuania; Luxembourg; North Macedonia, Malta; Netherlands; Norway; Poland; Portugal; Romania; Serbia; Slovakia; Slovenia; Spain; Sweden; Switzerland; Turkey and United Kingdom). Orphanet contact points are: Argentina, Australia, Cyprus, Tunisia, Morocco.

Orphanet Network Direct Grant

The Orphanet Network Direct Grant was launched in the framework of the 3rd Health Programme in mid 2018 and will support the Orphanet network until the end of 2020. It includes 35 participants from 22 countries and has the following objectives:

- To provide the RD community with interoperability tools, in particular around an inventory of RD, to allow for semantic interoperability between countries and between domains (health, research);
- To provide high-quality information on RD, in particular through an encyclopedia in several languages;
- To provide a directory of expert services in order to help patients, physicians and stakeholders finding the expertise on a particular disease in Europe and beyond, and to produce data needed to support policy actions;
- To further develop and sustain Orphanet as the reference knowledge base on RD, by establishing and consolidating collaboration within the Orphanet pan-European network and with European Reference Networks (ERNs) for the production, improvement and dissemination of knowledge on rare diseases. It will allow for the creation of a consistent expertise ecosystem for rare diseases in Europe.

Orphanet's sustainability and the EC Steering Group on Promotion and Prevention

To support countries in reaching the international health targets, the European Commission established in 2019 a Steering Group on Health Promotion, Disease Prevention and Management of Non-Communicable Diseases (the Steering Group on Promotion and Prevention, or SGPP). The Steering Group takes positions on priority actions to be implemented in all areas of health promotion and non-communicable disease prevention, including management of rare diseases. DG Santé is trying to make their major achievements in the rare diseases field sustainable after the current Health Programme; as Orphanet is considered as one the major achievements, having being supported for years and its nomenclature being recognised as a best practice in the field, Orphanet's sustainability has been a focus of discussions at SGPP meetings and the Group's input was sought on plans for a sustainable future for the Orphanet Network.

In 2019, within the scope of the activities aimed at reinforcing Orphanet's European position with a view to attaining a sustainable future, a memo explaining Orphanet's EU added-value activities, in particular in relation to ERNs, was sent to different Directorates, resulting in a meeting with ERN related officers, eHealth Network and DG Connect. Orphanet has also, with the help of EURORDIS, asked National Alliances to help advocate for a sustainable future for Orphanet. In 2019, the Orphanet Operational Committee proposed to the Orphanet Management Board to set up a Sustainability Task Force to follow up on sustainability issues and ensure a more prompt and effective reaction to developments at European level.

Following these activities, at the end of 2019 a SGPP Focus Group dedicated to the question of Orphanet's sustainability was established. The Focus Group is chaired by the representative of the French Ministry of Health and Solidarity at the SGPP. The members of the Focus Group have been designated by their respective Member States following a decision of the SGPP. Currently 12 MS are represented, plus Norway: Austria, Belgium, Czech Republic, France, Ireland, Italy, Lithuania, Latvia, Spain and Sweden. The mandate of the focus group to present a final draft document to the Steering Group no later than spring 2020, for the SGPP's approval.

The Orphanet Coordinating team engaged a consultancy firm at the end of 2019 to help Orphanet work on different scenarios for a sustainable future, as well as a business plan for Orphanet.

Collaboration with European Reference Networks (ERNs)

In order to improve rare disease knowledge generation and dissemination, collaboration with the European Reference Networks (ERNs) for rare disease was further developed and formalised in 2019, in order to maximise the pool of expertise within the ERNs. This common endeavour aims to improve rare diseases patients' lives by increasing knowledge and providing equal access to expertise. The Orphanet website can largely disseminate ERNs achievements, above all Clinical Practice Guidelines, and allows every European citizen to identify where ERNs' expertise is located.

The coordination of complementary activities is a key action of the current EC Direct Grant supporting Orphanet, continuing work started under the Joint Action on Rare Diseases, RD-Action. These activities are centred around the improvement and maintenance of the standard Orphanet nomenclature of rare diseases (ORPHAcodes), the scientific annotations in the Orphanet, as well as the production and dissemination of textual information on rare diseases, including abstracts co-produced by Orphanet and ERNs. In addition, Orphanet and ERNs are working to ensure that all stakeholders have access to a directory of healthcare, patient support and research activities related to RD in Member States, in particular the activities of ERNs. Finally, a dedicated ERN section in OrphaNews International, Orphanet's twice-monthly newsletter, provides a showcase for ERN activities.

Orphanet's expertise in standardising clinical information has been associated with the rare diseases and scientific expertise of ERNs to ensure that the nomenclature and classifications reflect current scientific and clinical knowledge. This work provides stakeholders with a common, controlled language as a basis to improve the identification of patients and aid access to diagnosis and care, to better structure and optimise rare disease data, and to improve the interoperability between health

information systems and research data.Several groups of diseases have been revised and finalised so far, including the Orphanet classifications of rare eye diseases (ERN-EYE), primary lymphedema (VASCERN), as well as rare kidney diseases (ERKNet). Collaborations are also underway with other ERNs, including ERN BOND, ERN CRANIO, ERN Skin, MetabERN, EpiCARE, TransplantChild, and eUROGEN.

Collaborations are ongoing to produce information for doctors and patients in a coordinated way together with ERKnet, ITHACA and EpiCare, and others will follow.

At the national level, the project RD-Code has been co-funded by the EC in order to support Member States in improving gathering information on rare diseases by implementation of ORPHAcodes Within the project, a direct link with ERNs is established as it is foreseen that ERNs will use ORPHAcodes in their clinical patient management system (CPMS). The ORPHAcode helpdesk is available and it is dedicated to answering questions related to the Orphanet nomenclature and the implementation of ORPHAcodes in Health Information Systems. This is of particular importance in HCPs hosting ERNs.

OrphaNetWork Committee (OOC)

This committee, internal to the Orphanet network, is in charge of defining a strategy to ensure that the Orphanet 'culture' is well defined and assimilated amongst all consortium members. It is also mandated with the elaboration of an effective two-way communication strategy. The Committee has, to date, focused on activities aimed at the national positioning of Orphanet with a view to the sustainability of the network.

Publication: New estimate of worldwide population affected by a rare disease at any point in time

An article published in the European Journal of Human Genetics in September 2019, and co-authored by Orphanet, Orphanet Ireland and EURORDIS, presents an analysis of the prevalence data in the Orphanet database and estimates that the number of people living with rare diseases between 263–446 million people in the world. The publicly available epidemiological data in the Orphanet database was used to carry out this analysis and the figures are derived from data from 67.6% of the prevalent rare diseases; the diseases analysed are rare according to the European definition and exclude rare cancers, infectious diseases, and poisonings.

The analysis of this dataset provides an estimation of the population prevalence of rare diseases of 3.5–5.9% of the population affected globally at any point in time. The paper highlights the policy implications of these estimates. Indeed, it strengthens the rare disease community's current discourse, that rare diseases affect millions of people and are thus a global health priority. Future registry research and the implementation of rare disease codification, notably through the introduction of ORPHA codes, in healthcare systems will further refine the estimates.

Second high level event of the NGO committee for rare diseases

On the 21 February 2019 at the United Nations (UN) Headquarters in New York, the Second High-Level Event of the NGO Committee for Rare Diseases was held. The event was organised by Rare Diseases International, EURORDIS and Ågrenska, and was held under the sponsorship of the Permanent Mission of Estonia to the United Nations, co-hosted under the auspices of 13 other permanent missions (Belgium, Brasil, Cyprus, France, Japan, Kuwait, Luxemburg, Malta, Romania, Serbia, Spain, Sweden, Thailand, and the United Arab Emirates), with speakers from the World Health Organisation. The

objective of this meeting of the Committee was to launch a call for the the integration of rare diseases into the upcoming landmark UN political declaration on universal health coverage (UHC), adopted at the first-ever UN High-Level Meeting on UHC during the UN General Assembly in September 2019, and a UN resolution on rare diseases. Ana Rath, Director of Orphanet, shared the upcoming results of the publication based on Orphanet data and co-authored by Orphanet and EURORDIS concerning the prevalence of rare diseases in the world with the audience in a presentation entitled: Ana Rath presented the Orphanet nomenclature to the audience : "Giving existence to people living with a rare disease in health systems".

RD-CODE: supporting the implementation of ORPHAcodes in health information systems

RD-CODE (www.rd-code.eu/), co-funded by the Third health Programme, started on January 2019 and will end in June 2021. The objective of this project is to support Member States in improving gathering information on rare diseases by implementation of ORPHA codes. The implementation process will be guided by the "Standard procedure and guide for the coding with Orphacodes" and the "Specification and implementation manual of the Master file" both developed in the framework of the previous Joint Action on Rare Diseases RD-ACTION (2015-2018).

The aim of the RD-CODE project is to promote the use of the Orphanet nomenclature for implementation into routine coding systems. This enables a standardised and consistent level of information to be shared at European level. Starting with countries that have no systematic implementation of ORPHA codification yet, but that are already actively committed to doing so, this project will demonstrate real-world implementation to guide other countries in the future.

The reference documents "Standard procedure and guide for the coding with ORPHA codes" and the "Specification and implementation manual of the Master file" both developed in the framework of the previous Joint Action on Rare Diseases RD-ACTION (2015-2018) are being updated according to the field's needs and are freely available on the project website. Furthermore, recommendations on how to code undiagnosed RD patients in Health Information Systems will be delivered by the project, to make all patients affected with a rare disease visible.

Within the project, a direct link with ERNs is established as it is foreseen that ERNs will use ORPHAcodes in their clinical patient management system (CPMS). The ORPHAcode helpdesk is available and it is dedicated to answering questions related to the Orphanet nomenclature and the implementation of ORPHAcodes in Health Information Systems. This is of particular importance in HCPs hosting ERNs.

Orphadata becomes an ELIXIR Core Data Resource

Orphadata was formally designated as an ELIXIR Core Data Resource at the start of 2019. The ELIXIR Core Data Resources are a set of European data resources of fundamental importance to the wider life-science community and the long-term preservation of biological data. These resources include services such as data platforms and knowledge bases that are authoritative in their field of expertise. Orphadata was added to this list after a detailed study conducted by an independent panel of reviewers following Orphanet's decision to adopt a more open licence, compatible with Open Science principles (Creative Commons BY-4.0). The knowledge bases singled out as Core Resources, to which Orphanet now belongs, work as "conceptual authorities" with a clear role in the standardisation of evolving concepts.

Orphanet will play this role for rare diseases within the scientific community. The Core Data Resources are also at the core of ELIXIR's long-term sustainability strategy as a European infrastructure for information and life sciences data. ELIXIR aims to ensure that these resources are available long-term and that the life-cycles of these resources are managed such that they support the scientific needs of the life-sciences, including biological research.

European Joint Co-f und Programme on Rare Diseases

The European Joint Programme on Rare Diseases (EJP RD; http://www.ejprarediseases.org/) brings over 130 institutions from 35 countries: to create a comprehensive, sustainable ecosystem allowing a virtuous circle between research, care and medical innovation to improve the impact, reuse and funding of RD research.

The EJP RD actions are organised within four major Pillars assisted by the central coordination and transversal activities.

Orphanet as a network is a partner, and co-leads the Pillar 2 of the EJP. Orphanet will develop its collection of research data and resources, and provide training on the Orphanet nomenclature and ORDO, foreseen for 2020.

SOLVE-RD: Horizon 2020 project to solve unsolved rare diseases

Led by the University of Tübingen, the Solve-RD consortium (www.solve-rd.eu), allocated €15 million by the European Commission Horizon 2020 programme, has worked from 2018 to improve the diagnosis of rare diseases, hand in hand with the new European Reference Networks (ERN) on rare diseases. The Orphanet coordinating team at leads the work package in charge of collecting standardised genetic and phenotypic information concerning unsolved rare diseases cases from ERN cohorts and the European Genome Archive, and developing an ontology of unsolved cases that will work alongside the Orphanet Rare Disease Ontology (ORDO) and the HPO-ORDO Ontological Module (HOOM) in order to make new diagnostic hypotheses. In 2018 the project kicked-off, and the Orphanet team has spent the first two years of the project developing the Rare Disease Case Ontology and co-designing similarity algorithms in order to contribute to the ambitious goals of the project.

Rare 2030 foresight study launched to prepare a future European RD policy

Rare2030 is a new two-year EU Pilot Project launched at the start of 2019, commissioned by the European Parliament, that will guide a reflection on rare disease policy in Europe through the next ten years and beyond. Since the adoption of the Council Recommendation on European Action in the field of Rare Diseases in 2009, the European Union has fostered tremendous progress to improve the lives of people living with rare diseases. Rare 2030 will guide a reflection on rare disease policy in Europe through the next ten years and beyond.The project, coordinated by EURORDIS, in which Orphanet-

INSERM US14 is a partner, was launched in January 2019 in Brussels. It will gather the input of a large group of patients, practitioners and key opinion leaders to propose policy recommendations that lead us to a better future for people living with a rare disease in Europe. In order to reach these recommendations, an extensive literature review was conducted in 2019 to build a knowledge base, using sources including OrphaNews and the Orphanet database, in order to identify trends and drivers of change that affect the future of rare diseases and inform policy options. Orphanet was one of the lead partners in this work. This knowledge base has informed structured stakeholder dialogue to identify trends and drivers of change of most relevance for policy recommendations. A number of plausible alternative future scenarii concerning the state of health and care for people living with a rare disease in 2030 and beyond were constructed in 2020 on the basis of most relevant trends and drivers. Key stakeholders are debating these scenarii and their implications to gather consensus around them. In the last stage of the project (end of 2020), patients, the public and experts at EU and national levels will propose policy options that can pave the way towards preferred future scenarios. Final policy recommendations will be presented at the European Parliament at the start of 2021.

Improving quality, transparency and traceability

- **In addition to the general SOPs** available online since 2013, the following procedures were available online in 2019:

General procedures

- Orphanet Standard Operating Procedures
- International Advisory Board rules of procedure
- Orphanet Advisory Board on Genetics Rules of procedures

Procedures concerning the nomenclature

- Orphanet nomenclature and classification of rare diseases
- ICD-10 coding rules for rare diseases
- Naming rules for the rare disease nomenclature in English
  This document has been translated into Polish (2017) and Spanish (2018) and German (2019) and Japanese (2019)
- Nomenclature production in national language
- Linearization rules for Orphanet classifications

Procedures concerning the collection of information related to rare diseases

1) Scientific information

- Creation and Update of Disease Summary Texts for the Ophanet Encyclopaedia for Professionals
- Orphanet inventory of genes related to rare diseases
- Epidemiological data collection in Orphanet

2) Expert ressources

- Glossary and representation of terms related to diagnostic tests
- Data collection and registration of expert centres in Orphanet

- Data collection and registration of patient organisations in Orphanet
- Data collection and registration of diagnostic tests in Orphanet
- Data collection and registration of research projects in Orphanet

- Orphanet published **a dedicated Orphanet Report Series crediting the experts having contributed to the update of scientific data in Orphanet** in 2019.

- **Application of the General data protection regulation (GDPR) to Orphanet data: t**he GDPR has entered into force on 25 of May across Europe. Having as a legal basis the INSERM's public interest missions, Orphanet collects personal information of professionals declaring their activities and /or contribute to Orphanet content as experts. A mailing was sent to all the professionals in the database announcing the developments next to come in Orphanet in order to comply with the regulation, as well as allowing them to retire their names and personal data from the database if they wish. Orphanet technical SOPs have been updated to take the regulation into account, and a training session was organised for all Orphanet network members including the extra-European ones, for the GDPR applies to them because the data is stored in France.

Orphanet database updates

- **Scientific information:** the Encyclopaedia of RD, the Inventory and classification of RD, the inventory of genes and the inventory of Orphan drugs have all been expanded and updated.
- **The catalogue of expert services:** expert centres, medical laboratories, clinical trials, research projects, networks, registries, infrastructures, mutation databases, biobanks and patient organisations have been expanded and updated.

Orphanet documents update

- **The Orphanet Report Series have been updated:** List of Rare Diseases, Prevalence of Rare Diseases, Lists of Orphan Drugs, Registries, List of Research Infrastructures useful to Rare Diseases in Europe, Orphanet Activity Reports, List of experts contributing to the database, and User surveys, as well as the Report *'Vivre avec une maladie rare en France' (Living with a rare disease in France).* The list of rare diseases was produced for the first time in Polish and Czech. **The Orphanet Activity report 2018 was translated into French. A leaflet presenting Orphanet's activities and latest developments has also been produced in English.**
- **The Orphanet annual user survey was updated in 2018 in order to improve the way in which we collect user feedback. A first, general survey was launched at the start of 2019, with a series of minisurveys sent to those interested to gather detailed feedback on specific products. This campaign was carried out again at the start of 2020.**

Orphadata

- **The Orphadata catalogue was updated.**

Users satisfaction

- **Users are satisfied with the services provided by Orphanet:** in the 2019 satisfaction survey, 97 % of respondents stated that they were very satisfied or satisfied with Orphanet, an increase of 4% compared to the previous year.
- **10.4 million PDF documents downloaded in 2019.**
- **Over 19 million visitors last year from 236 countries.**

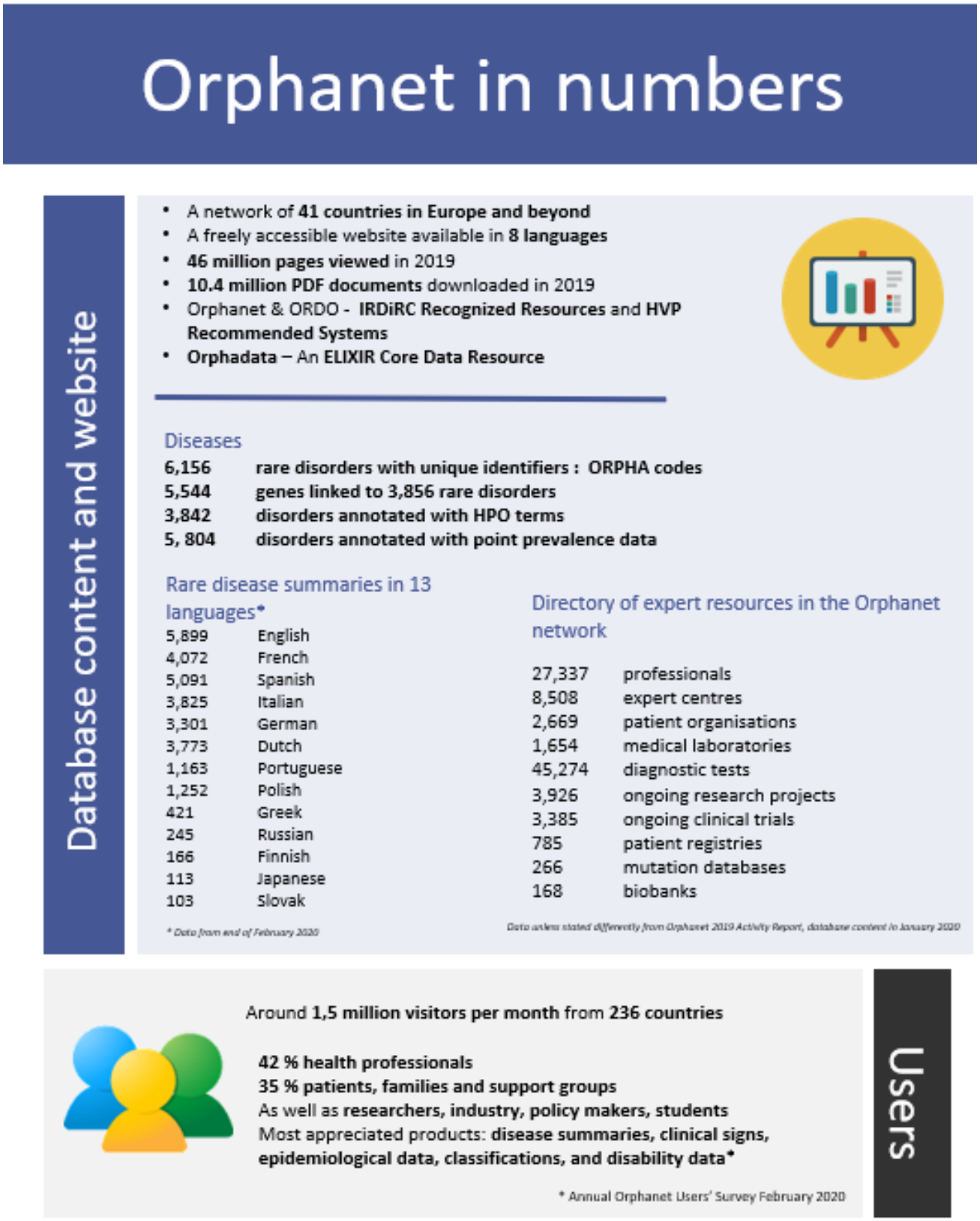


Figure 1 Orphanet in numbers (January 2020)

2. Orphanet network

2.1. The Orphanetwork Direct Grant

Orphanet has become a backbone for the rare disease community, with the substantial amount of data developed being not only essential as leverage both for scientific projects as well as policies related to rare diseases in Europe, but also for increasing the awareness and the dissemination of knowledge on RD. Orphanet is mentioned in the European Union's principal documents on RD (e.g. the Commission Communication "Rare diseases: Europe's challenges" of 11 November 2008 and the Recommendation of the Council on an Action in the field of rare diseases of 8 June 2009) as the source of current information on RD in the EU as well as a strategic element of any national plan/strategy on RD, which each Member State was encouraged to develop by the end of 2013. It is also mentioned as a key tool for information on RD in the directive on the application of patients' rights in cross-border healthcare (2011).

The European Commission decided in 2018 to allocate a Direct Grant within the 3rd Health programme to Orphanet: the Orphanetwork Direct Grant will run from 1st June 2018 to 31 December 2020. The objectives of the project are:

- To provide the RD community with interoperability tools, in particular around an inventory of RD, to allow for semantic interoperability between countries and between domains (health, research);
- To provide high-quality information on RD, in particular through an encyclopedia in several languages;
- To provide a directory of expert services in order to help patients, physicians and stakeholders finding the expertise on a particular disease in Europe and beyond, and to produce data needed to support policy actions;
- To further develop and sustain Orphanet as the reference knowledge base on RD, by establishing and consolidating collaboration within the Orphanet pan-European network and with European Reference Networks (ERNs) for the production, improvement and dissemination of knowledge on rare diseases. It will allow for the creation of a consistent expertise ecosystem for rare diseases in Europe.

The main expected outcome of this project was to consolidate Orphanet as the European database for rare diseases, achieving a position of the international reference for information and data on rare diseases in a steady RD ecosystem as the result of the close cooperation between Orphanet and European Reference Networks.

2.2. Orphanet's Governance

To ensure optimal governance and efficient management of the workflow, Orphanet's governance is organised by three different boards:

- The **Management Board**, composed of country coordinators, is in charge of identifying funding opportunities, approving the global strategy of the project and thus guide the

project in its endeavour to provide an optimum service for the end-users, and considering the inclusion of new teams as well as ensuring the continuity of the project.

- The **Orphanet Operating Committee** is an internal consultative Board was installed in 2018 and is in charge of proposing a strategy allowing the consolidation of theOrphanet 'culture' amongst all consortium members, and to determine how to move towards a more effective bilateral communication within the network. This will help Orphanet as a network, achieve the three strategic axes agreed on by the Management Board in order to confirm Orphanet as the reference European database (consolidate Orphanet's position, make Orphanet sustainable, improve quality, transparency and traceability of data production).

External boards:

- The **International Advisory Board**, composed of international experts, is in charge of advising the Management Board regarding the overall strategy of the project.
- The **Genetic Advisory Board**, composed of geneticists is in charge of advising Orphanet on topics related to the gene database and the database of genetic tests and laboratories.

These boards discuss the evolution of the project in scope and depth; ensuring its coherence and its evolution, in relation to technological developments and to the needs of its end-users, as well as its sustainability.

In 2018, Orphanet member countries signed a new Network Agreement. The initial signatories were 33 Institutions from 32 countries: Armenia; Austria; Belgium; Bulgaria; Canada; Croatia; Czech Republic; Estonia; Finland; France; Germany; Georgia; Hungary; Ireland; Israel; Italy; Latvia; Lithuania; Netherlands; Norway; Poland; Romania; Serbia; Slovenia; Slovakia; Spain; Sweden; Switzerland; United Kingdom; Georgia; Malta and Japan.). In 2019 3 additional countries joined the Network: Luxembourg, North Macedonia, Turkey. Five countries complete the network as contact points: Cyprus, Morocco, Tunisia, Argentina, Australia.

The Agreement officialised the existence of the network 'per se' and independently of the European Commission grant agreements, creating, with the recognition of Orphanet's *de facto monopoly* by the European Commission, a clear position for the network.

2.3. Expansion of the network

Since its creation, the quality of data provided by Orphanet has built its reputation and as a result Orphanet has grown as a European consortium, gradually expanding to a Network of 35 countries (in 2019) and 5 contact points. In 2011, Orphanet went further west to include Canada. The network expanded towards Australasia, with Western Australia joining in 2012. In 2014, Georgia and Tunisia joined the consortium followed by Argentina (the first South American country), in 2015. Japan officially joined Orphanet in 2017, with Luxembourg, North Macedonia and Turkey joining in 2019. Russia joined in 2020, and collaboration is underway to explore the possibility of creating an Orphanet – China team.

Please refer to the organisational chart at the end of this document for more information about the participating Institutions and team members.

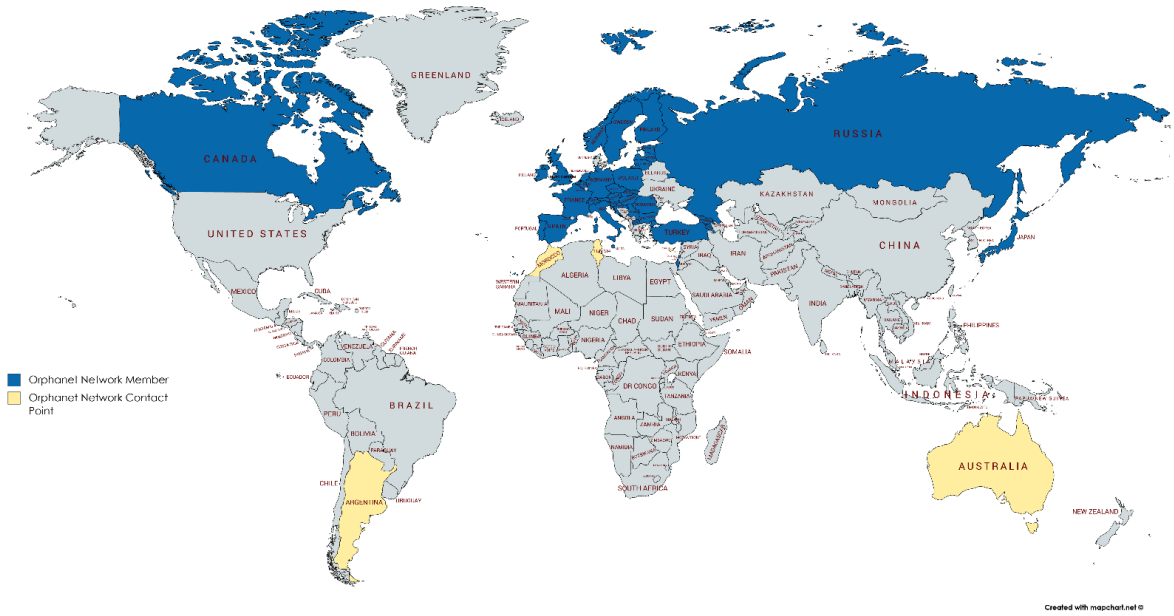


Figure 2 Orphanet Network Members (December 2019)

2.4. Orphanet members and scope of their activity

2.4.1. COORDINATING TEAM

INSERM (the French National Institute of Health and Medical Research), having run Orphanet since 1997, coordinates the Orphanet network. The INSERM team is based at Service Unit 14.

The coordinating team is responsible for the coordination of network activities, the hardware and software aspects of the project, the database of rare diseases (including nomenclature in English, classifications, ontology, gene-disease relationships, scientific annotations), the Quality Management System and the Quality of Data (including the quality control and the coordination of the catalogue of expert resources in the participating countries), the production of the encyclopaedia, technology transfer/business development, partnerships, and the global communication strategy, as well as the training of all members of the network..

The coordinating team is also in charge of updating the database in regards to medicinal products in development, from their designation stage to their marketing authorisation.

A transition in the distribution of activities is underway so as to allow Orphanet network members to take on responsibilities in the core database activities (it started with the production of the encyclopaedia, by having medical writers in several countries and now encyclopaedia medical validators are located in different teams within the network) in addition to the collection and translation activities described in 2.4.2.

2.4.2. MEMBERS

The establishment of a catalogue of resources can only be achieved by the consolidation of data collected at the country level. The identification of expert services requires a very good knowledge of the national research and health care institutions and their organisation. All national coordinators are located in high-profile institutions, which provide a suitable work environment for the information scientists, in terms of documentation, secretarial facilities and access to the network.

Members are responsible for collecting, validating and submitting data on expert centres, patient organisations, medical laboratories, research projects, clinical trials, registries, infrastructures, and networks.

Translation of the Orphanet content in the national language is also managed by the national teams, provided that they have a sufficient budget. At the end of 2018 Belgium, France, Germany, Italy, Poland, Spain and Portugal are undertaking the translation of the entire database and website's content into their national language. The Orphanet nomenclature is currently translated into the 8 languages of the website, and also in Czech. The translation of the nomenclature and abstracts in Japanese is ongoing. In 2018 the website was progressively translated into Polish and a Polish version of Orphanet was launched

Management of the national website/entry point to the Orphanet portal is also carried out by every national team in their national language as well as national and international communication and dissemination activities on National team and Network achievements.

Since the beginning of RD-ACTION National teams can also participate in core database activities if resources are available. The Orphanet Ireland team have contributed to the IT developments undertaken in 2018, as well as the production of the encyclopedia, as has Orphanet Sweden. Orphanet Slovakia and Orphanet Lithuania have also contributed to the medical validation of the encyclopedia.

2.4.3. ORPHANET CONTACT POINTS

All national contact points are located in high-profile institutions. However, in these countries no dedicated funding is allocated to Orphanet activities, therefore there is no active data collection on expert services. The contact points conduct communication and disseminating activities, notably to raise awareness of rare diseases, and Orphanet, in their country.

3. Orphanet: Products and services

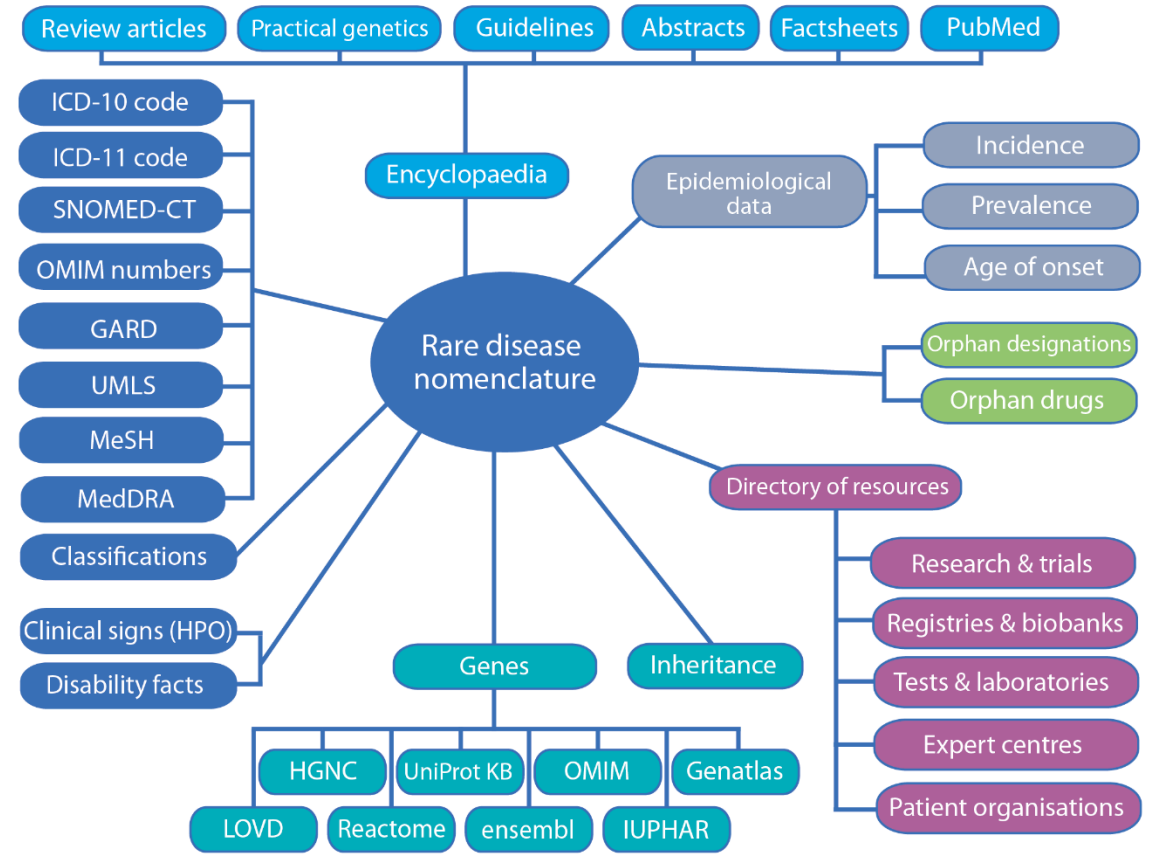


Figure 3 The Orphanet database

The Orphanet Knowledgebase is an organised and dynamic collection of information and data about RD and Orphan Drugs. Value added data from multiple sources are archived, reviewed, manually annotated and integrated to other data by curators and validated by experts following formalised procedures which are published online. A list of expert reviewers having contributed to the scientific content is presented each year as a dedicated Orphanet Report.

Disorders in the Orphanet disease database correspond to rare diseases (defined in Europe as having a prevalence of not more than 1/2,000 persons in the European population), and rare forms of common diseases.

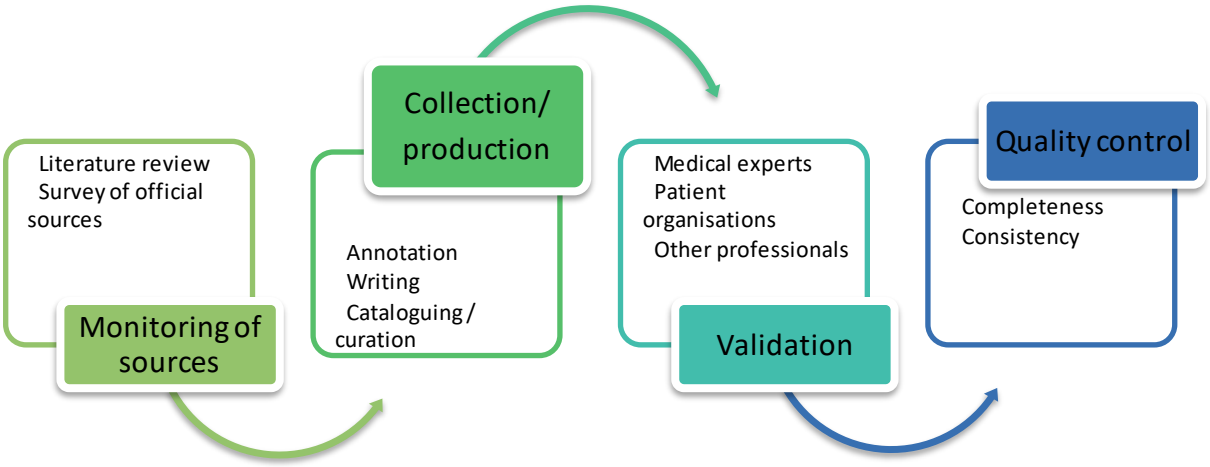


Figure 4 Orphanet data production methodology

The update of the scientific content of the database is performed using a four step methodology (Figure 4) which consists of a survey of sources, allowing for the collection and production of data by identifying new syndromes, genes or treatments, for the update of classifications of diseases, for the production of various texts (encyclopaedia, guidelines, etc.) and for the update of the update of the catalogue of expert resources in participating countries. All texts and data (annotations on epidemiological data, phenotypes, functional consequences of the disease, genes, etc.) are externally validated (either by internationally recognised experts, learned societies and/or patient organisations, according to the type of text or data). A final step of quality control is carried out to ensure the coherence and completeness of the database.

All the teams that make up the Orphanet network are responsible for the collection, validation and submission of data on expert services in their country. In order to publish data which is relevant and accurate (complete, valid and consistent with other data from the database), validation and quality control is carried out by the coordinating team, and regular updates are performed with other country teams via an intranet.

Also, additional services and new collaborations, notably recently with the European Reference Networks for rare diseases, are developed regularly to resolve the issue of information dispersion and to address specific needs of the different stakeholders.

3.1. Orphanet content: Inventory of rare diseases

Orphanet provides a comprehensive inventory of rare diseases classified according to a polyhierarchical classification system. As new scientific knowledge issues arise, the Orphanet RD inventory and classification system is maintained with regular additions/updates of diseases based on peer-reviewed publications and expert advice (including ERNs). This extensive and evolutionary system consists of classifications organised according to the medical and/or surgical speciality that manages specific aspects of each rare disease within a healthcare system. The diseases have been classified within each speciality according to clinical criteria or aetiological criteria, when diagnostically or therapeutically relevant. The Orphanet classification provides the scope and level of granularity (Figure 5) needed by health professionals with different specialties, including categories (e.g. rare neurological disease), clinical groups (e.g. rare ataxias), disorders (e.g. Machado-Joseph disease) and subtypes (e.g. Machado-Joseph disease type 1).

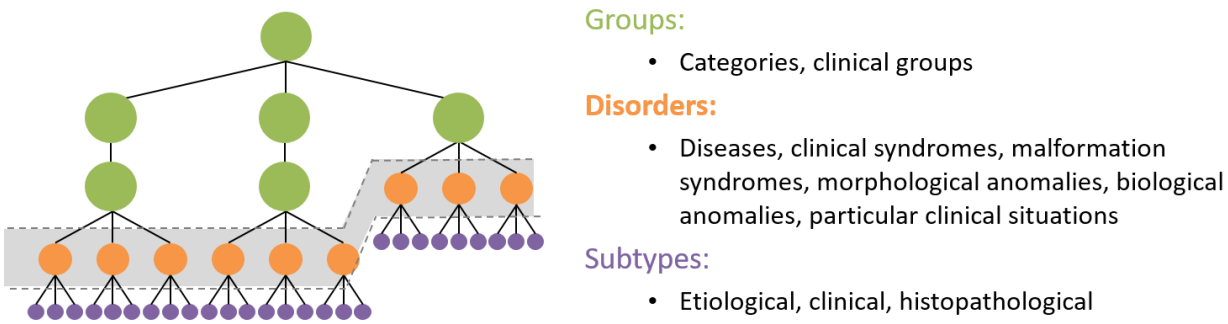


Figure 5 Schema of the Orphanet nomenclature and classifications

Since 2014, each entity in the nomenclature is assigned precisely one of these categories, allowing more accurate information on their typology and exact count. In addition, for diseases now recognised as part of another disease, Orphanet redirects users towards the disease that is now accepted according to recent literature. The disease database contains 9,299 clinical entities[1] and their synonyms (including 6,156 disorders[2]). The nomenclature and classifications can be viewed directly on the www.orpha.net website and/or extracted from Orphadata in XML and JSON formats. An annual version of the nomenclature is released for routine codification in health information systems, as part of a Nomenclature Pack for implementation, developed in the frame of the RD-CODE project. In this pack Orphanet provides a set of files in XML format, including the Orphanet nomenclature file, the Orphanet ICD-10 mapping file, a directory containing the Orphanet classifications, and a PDF describing in details all files enclosed in the Orphanet nomenclature pack for coding.

[1] Diseases, malformation syndromes, morphological anomalies, biological anomalies, clinical syndromes, particular clinical situation in a disease or syndrome, group of phenomes, etiological subtypes, clinical subtypes, histopathological subtypes, data from January 2020.

[2] Diseases, malformation syndromes, morphological anomalies, biological anomalies, clinical syndromes, particular clinical situation in a disease or syndrome, data from January 2020.

The Orphanet nomenclature is aligned to other terminologies so as to provide a backbone for semantic interoperability between different systems. Rare diseases are aligned with ICD-10 codes (see Table 1). This process follows a set of rules, depending on whether rare diseases are mentioned or not in the tabular list or in the index of ICD-10. Rules for attribution of an ICD-10 code for diseases that are not listed in the ICD are established. More details on the process can be found in Orphanet's ICD-10 coding rules for RD procedure. The ICD-10 alignment is manually curated. Alignments with ICD-11 codes will be released in the near future.

Codes	Aligned ORPHA numbers
ICD-10	6,847

Table 1 Number of disorders, groups of disorders or subtypes aligned to ICD-10 codes (January 2020)

Diseases are mapped to one or more OMIM numbers (see Table 2). Exact mappings between the Orpha nomenclature and other terminologies (UMLS, GARD, MeSH and MedDRA) are available online (see Table 2). Mappings to SNOMED-CT are produced in collaboration with IHTSDO and will be available in 2020 from SNOMED International and via Orphadata. Mappings are carried out in a semi-automatic way and are manually curated. Updates follow UMLS releases once a year.

All mappings from the Orphanet nomenclature to the target terminology are qualified (exact; narrow-to-broad; broad-to-narrow) and information on the validation status is available. Further annotations are carried out for ICD-10 terms: specific code, inclusion or index term, code attributed by Orphanet, with indication of the validation status.

Terminologies/resources	Mapped disorders, groups of disorders & subtypes
UMLS*	4,745
MeSH*	1,731
SNOMED CT*	5,702
MedDRA	1,148
OMIM**	4,609
GARD	3,756

*Table 2 Number of mapped diseases (groups of disorders, disorders and sub-types) per terminology (January 2020) *Exact mappings only **All mappings*

The Orphanet nomenclature is annotated with phenotypic traits information. From 2015, Orphanet disorders are annotated with the Human Phenotype Ontology, a standard and controlled terminology covering phenotypic abnormalities in human diseases, recognised as the reference in the domain, and a designated IRDIRC Recognized Resource. Each phenotypic term is associated with the frequency of occurrence (obligate, very frequent, frequent, occasional, very rare, excluded), and whether the annotated HPO term is a major diagnostic criterion or a pathognomonic sign of the rare disease. As a

result of this work, 3,842[3] diseases are annotated with HPO terms. Further annotations to HPO are being carried out. Based on these annotations, partnerships are being developed to provide an optimised assistance-to-diagnosis tool.

Orphanet provides **epidemiological and natural history information** on each rare disease. Disease inheritance and age of onset categories are provided (Table 3). Point prevalence, annual incidence, prevalence at birth and lifetime prevalence data are now documented in addition to the prevalence intervals available on the website (for Europe, USA and worldwide) (Table 4). Minimum, maximum and mean figures for each item are documented according to geographic zones, when information is available in Orphadata. The number of cases or families reported in the literature is also indicated for very rare diseases. Data sources and validation status are supplied for all data. This new epidemiological data is available for more than 5,800 diseases (groups of diseases, disorders and sub-types) and constitutes a unique and global source of information which we hope is useful to all users concerned, namely policymakers, the research community and the orphan drug industry involved in orphan drug development. The data are made available for download on www.orphadata.org.

Natural history data	Number of groups of disorders, disorders and sub-types
Average age of onset	6,198
Mode of inheritance	5,303

Table 3 Number of disease (groups of diseases, disorders and sub-types) per natural history data (January 2020)

Epidemiological data	Number of groups of disorders, disorders and sub-types
Point prevalence	5,804
Prevalence at birth	517
Lifetime prevalence	46
Annual incidence	582

Table 4 Number of diseases (groups of disorders, disorders and sub-types) per epidemiological data (January 2020)

Orphanet also provides **information on activity limitation/participation restriction (functional consequences)** described in rare diseases, using the Orphanet Functioning Thesaurus, derived and adapted from the International Classification of Functioning, Disability and Health – Children and Youth (ICF-CY, WHO 2007). The provided information is assessed from the whole patients' population

[3] As of January 2020.

affected by the disease, receiving standard care and management (specific and/or symptomatic management, prevention and prophylaxis, devices and aids, care and support). Functional consequences are organised by their frequency in the patient population. Each functional consequence is recorded with: frequency in the patients' population, temporality, degree of severity, loss of ability when relevant, defined as the progressive and definitive loss of a skill or participation over the course of the disease. There are 493 clinical entities with functional consequences annotated[4].

3.1.1. ADDITIONAL FUNCTIONALITIES IN 2019

A process to evolve the Orphanet nomenclature model started in 2019 in order to best respond to users' needs, in particular as regards coding situations.

3.2. Orphanet content: Orphanet inventory of genes

Genes involved in rare diseases are entered in the database and updated regularly according to new scientific publications. Genes are associated with one or more diseases, with one or more genetic test, and mutation databases and/or research projects. The data registered includes: annotation with the main name and symbol of the gene (from HGNC) and its synonyms, as well as its HGNC, UniProtKB, Genatlas and OMIM references (in order to cross-reference these websites), in addition to Ensembl (an EMBL-EBI database that maintains automatic annotations for selected eukaryotic genomes), Reactome (an EMBL-EBI open-source, open access, manually curated and peer-reviewed pathway database) and IUPHAR/BPS Guide to Pharmacology databases. The relationship between a gene and a disease is manually qualified according to the role that the gene plays in the pathogenesis of a disease: causative (both from germline or somatic mutations), modifiers (germline), major susceptibility factors, or playing a role in the phenotype (for chromosomal anomalies). For the disease-causing germline mutations, the information, whether pertaining to a gain or loss of function for the protein, is also provided when available. Information on the typology of the gene (i.e. gene with protein product, non-coding RNA, disorder-associated locus), its chromosomal location and all former symbols and synonyms is also provided. Candidate genes are also included but only when they are tested for in a clinical setting. These annotations represent a unique, added-value service for diagnostic and therapeutic research.

3.3. Orphanet content: Orphanet encyclopaedia

Three distinct encyclopaedias are provided on the Orphanet website: one for health professionals, one for the general public, and one related to disabilities.

3.3.1. HEALTH PROFESSIONALS ENCYCLOPAEDIA

- **Summary information**

Textual information on a disease can be presented in the form of a definition, an abstract, or as an automatically generated text (6,841 entities in the database had one of these forms of textual information) at the end of 2019.

[4] As of January 2020.

Orphanet texts (apart from the automatically generated) are unique and written in English by a member of the editorial team and validated by a medical validator. A definition is produced for every rare disorder by a medical writer and submitted for medical validation. Abstracts are reviewed by an invited world-renowned expert. Abstracts are structured in up to 10 sections: Disease definition – Epidemiology – Clinical description – Aetiology – Diagnostic methods – Differential diagnosis – Antenatal diagnosis (if relevant) – Genetic counselling (if relevant) – Management and treatment – Prognosis. Summary information for 5,836 rare diseases was available online at the end of 2019[5].

They are progressively translated into the seven other languages of the website (French, Italian, Spanish, German, Polish, Portuguese and Dutch). In addition, 166 abstracts are translated in Finnish, 422 in Greek, 879 in Polish, 255 in Russian, and 95 in Slovak: they are available as PDFs ("Summary information") via the bottom of the corresponding disease page. For an additional 1,005 clinical entities in the disease inventory, textual information is provided through automatically generated texts (for diseases labelled as a 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 in the inventory).

- **Orphanet Emergency Guidelines**

These guidelines are intended for pre-hospital emergency healthcare professionals (a dedicated section is included for their use) and for hospital emergency departments. These practical guidelines are produced in collaboration with French reference centres and patient organisations, and are peer-reviewed by emergency health care physicians from learned societies (*SFMU* in France): as of the start of 2020, 103 emergency guidelines in French are available online. They are being translated into the following six languages: English, German, Italian, Portuguese, Spanish and Polish. 42 emergency guidelines are available in English (including those contributed by BIMDG, 46 in Italian, 24 in German, 45 in Spanish, 17 in Portuguese, and 16 in Polish. Emergency guidelines were downloaded more than 593 854 times in 2019.

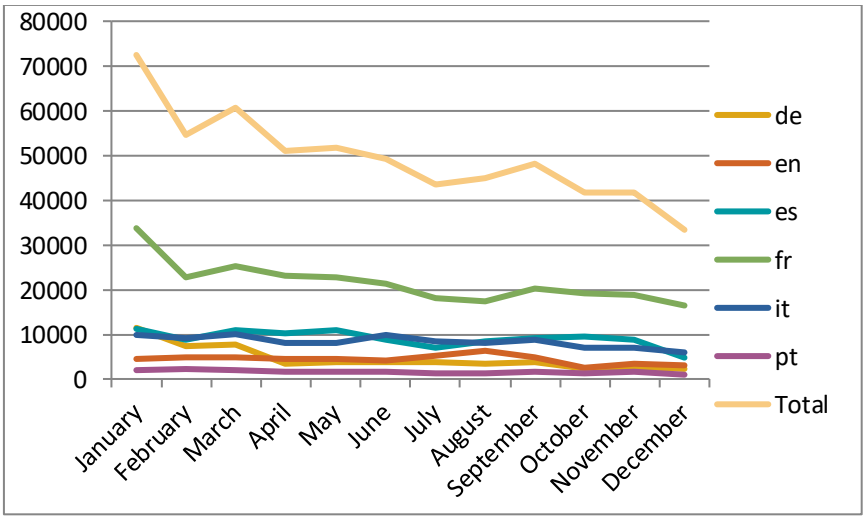


Figure 6 Downloads of Orphanet Emergency Guidelines

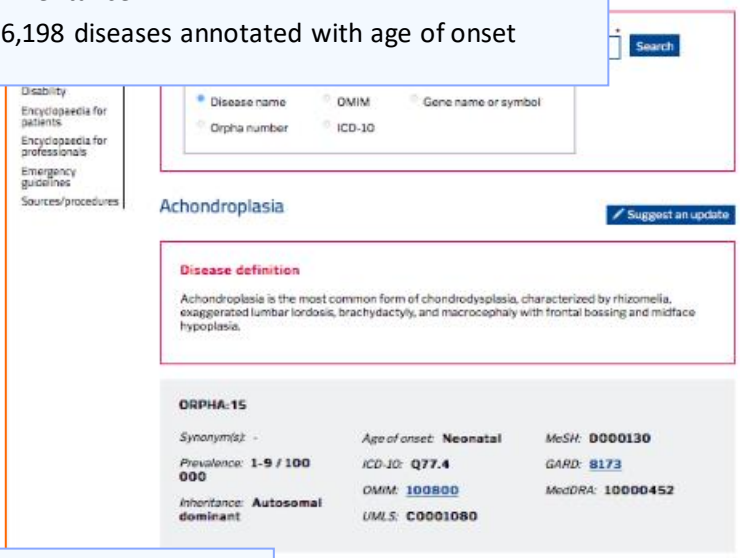
[5] Data extraction 16/12/2019

Epidemiology:
5,804 diseases annotated with point prevalence data

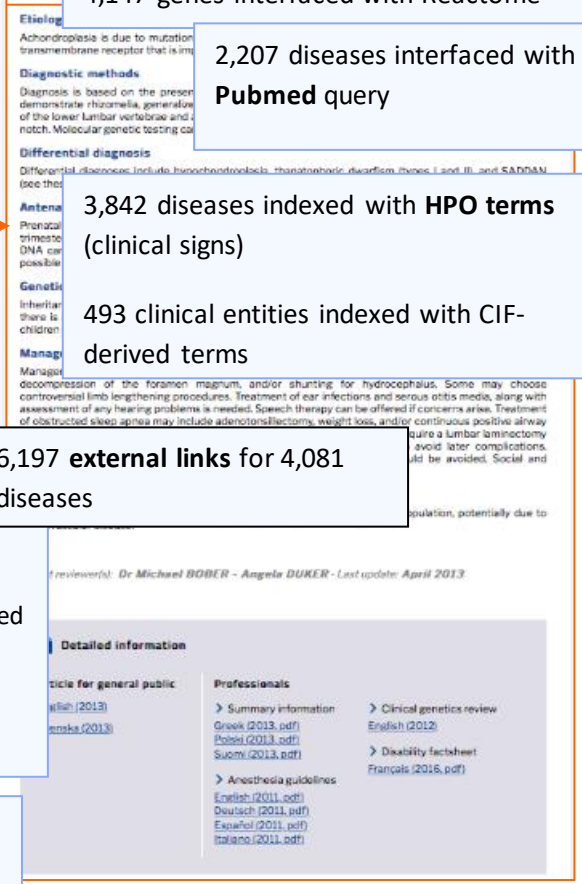
Natural history:
5,303 diseases annotated with mode of inheritance
6,198 diseases annotated with age of onset

Mappings:
6,847 diseases mapped to ICD-10
4,609 diseases mapped to OMIM
4,745 diseases mapped to UMLS
1,148 diseases mapped to MedDRA
1,731 diseases mapped to MeSH
3,756 diseases mapped to GARD

Genes:
5,544 genes linked to 3,856 rare diseases
5,539 genes interfaced with HGNC
5,037 genes interfaced with OMIM
4,955 genes interfaced with Genatlas
5,064 genes interfaced with UniProtKB
5,498 genes interfaced with Ensembl
779 genes interfaced with IUPHAR-DB
4,147 genes interfaced with Reactome



2,207 diseases interfaced with a **Pubmed** query



3,842 diseases indexed with **HPO terms** (clinical signs)

493 clinical entities indexed with CIF-derived terms

6,197 **external links** for 4,081 diseases

The Orphanet encyclopaedia contains the following summary texts:

5,899	English
4,072	French
5,091	Spanish
3,825	Italian
3,301	German
3,773	Dutch
1,163	Portuguese
1,252	Polish
421	Greek
245	Russian
166	Finnish
113	Japanese
103	Slovak

In-house produced texts: 122 **articles for the general public** in French, **103 emergency guidelines** in French, translated in German, English, Spanish, Italian, Portuguese, and Polish. **80 Disability factsheets** in French

Link to external RD literature

527	Review articles
727	Clinical genetics reviews
468	Clinical practice guidelines
154	Guidance for genetic testing
1,679	General public articles
293	Emergency guidelines

Figure 7 The disease database content as of January 2020

3.3.2. GENERAL PUBLIC ENCYCLOPAEDIA

The general public encyclopaedia was initially a French project supported by the First French National Plan for Rare Diseases in 2005 intended to give complete, reliable, and up-to-date information to patients and their relatives on the diseases that concern them. Since 2011, the general public encyclopaedia texts have been enriched with paragraphs on the functional consequences of rare diseases, including disabilities resulting from the disease, medical and social measures to prevent/limit them and consequences of these disabilities in daily life.

One hundred and twenty-one in-house French texts are available online. Ten have been translated into Spanish. In 2016, because of the lack of dedicated funding, the production of Orphanet's in-house general public encyclopaedia was interrupted. However, Orphanet disseminates high quality texts intended for the general public that are produced by third parties (see sections Links to External Rare Disease Literature).

3.3.3 DISABILITIES ENCYCLOPAEDIA

As part of the collaboration between CNSA (French National Solidarity Fund for Autonomy) and INSERM, Orphanet provides since 2013 a collection of texts named "disability factsheets" in the Orphanet Encyclopaedia of Disability devoted to the disabilities associated with each rare disease. This collection is addressed to the professionals in the field of disability as well as to the patients and their families. These texts have been elaborated in order to better understand and to assess 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.

Each text contains a description of the disease (adapted from the corresponding summary text from the Orphanet encyclopaedia for professionals) and a focus on disability-related measures and consequences in everyday life (taken from the corresponding text of the Orphanet general public encyclopedia). Since 2016 these texts are produced as stand-alone texts, independent of the General public encyclopaedia.

These texts are available on the Orphanet website via the link "Disability factsheet" at the bottom of the page describing the disease as well as from the "Encyclopaedia for professionals" and "Disability" tabs. Eighty-one of these texts were available online at the end of 2019 and they are also available in the Orpha Guides app. They have been downloaded approximately 235,477 times in 2019 (Figure 8). This represents an increase of 236% increase compared to approximately 68,900 downloads in 2018. Translations into Spanish of these texts started in June 2016, with 35 translated at the end of 2019.

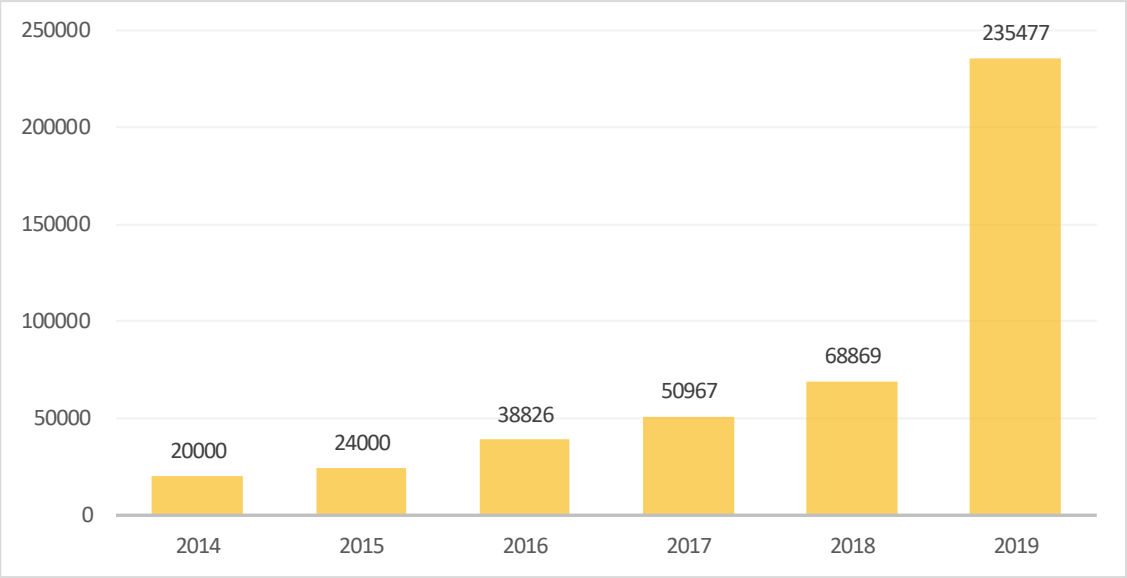


Figure 8 Evolution of number of downloads per year of the French Disability factsheets in since 2014

3.2.4. DIAGNOSTIC CRITERIA

Information on diagnostic criteria is presented in 26 concise documents intended to avoid serial misdiagnosis and to facilitate early therapeutic management. This information, identified as being recognised by experts in the field as a reference in the domain, is extracted from peer-reviewed journals, with a reference to the original paper given at the top of the page.

3.2.5. LINKS TO EXTERNAL RARE DISEASE LITERATURE

With the purpose of disseminating high quality articles through the Orphanet website, Orphanet identifies and assesses articles produced by peer-reviewed journals and learned societies in any of the languages of the Orphanet consortium. Articles are evaluated according to a set of quality criteria. Authorisations from the copyright holder are requested so as to give access to the full text. Numbers of external texts per category are presented in Table 5.

We can distinguish seven distinct externally produced texts accessible from the Orphanet website:

- **Review articles**

527 review articles (of which 241 were published in the Orphanet Journal of Rare Diseases) were online at the start of 2020.

- **Clinical Genetics Review**

These are peer-reviewed disease descriptions focusing on genetic aspects with an implication in the diagnosis, management, and genetic counselling of patients and families with specific inherited conditions. The clinical genetic review collection comprises 727 articles from GeneReviews (as of January 2020).

- **Clinical practice guidelines**

These guidelines are recommendations for the management of patients, issued by official organisations. There are two kinds of best practice guidelines: anaesthesia guidelines and clinical practice guidelines. They are both produced by learned societies or expert networks and published either in scientific journals or on the learned societies' or health agencies' websites. A methodology of assessment has been developed to review the guidelines based on the AGREEII instrument in order to disseminate only the most accurate ones, after permission of the copyright holder is obtained[6]. The Orphanet website gives access to 468 best practice guidelines at the start of 2020.

- **Guidance for genetic testing**

This collection comprises summary guidance intended to disseminate the best practices in genetic testing. They include Gene Cards (published in the *European Journal of Human Genetics*). 154 guidance documents are available via the website at the start of 2020.

- **Articles for the general public**

Dissemination of general public-intended texts in all languages, externally produced by expert centres or patient organisations (produced in compliance with a reliable methodology), are now selected. 1,679 articles were available on the website at the start of 2020. The breakdown by language is presented in Table 5.

- **Practical genetics articles**

This collection was co-produced by Orphanet and the *European Journal of Human Genetics* (EJHG), the official journal of the *European Society of Human Genetics*. 38 freely-accessible articles are published in the *EJHG* (Nature Publishing Group) and are accessible via Orphanet.

- **Emergency guidelines**

Orphanet has established a collaboration with the British Inherited Metabolic Disease Group (BIMDG) to provide links to the emergency guidelines that they produce.

- **Disability factsheets**

2 disability factsheets are available in Danish, produced by Sjaeldenborger, the Danish Rare Diseases alliance.

[6] *Clinical Practice Guidelines for Rare Diseases: The Orphanet Database,* Sonia Pavan , Kathrin Rommel, María Elena Mateo Marquina, Sophie Höhn, Valérie Lanneau, Ana Rath, PLOS One, Published: January 18, 2017, https://doi.org/10.1371/journal.pone.0170365

	Article for general public	Review article	Clinical practice guidelines	Guidance for genetic testing	Clinical genetics review
Croatian	28	-	-	-	-
Czech	29	-	-	-	-
Dutch	28	-	2		
English	232	423**	135	151	727
Finnish	14	-	-	-	-
French	217*	30	142	1	-
German	123	27	155	2	-
Greek	36	-	-	-	-
Hungarian	27	-	1	-	-
Italian	57	34	1	-	-
Polish	33	-	-	-	-
Portuguese	34	-	1	-	-
Romanian	33	-	-	-	-
Russian	37	-	1	-	-
Slovak	26	-	-	-	-
Spanish	72	12	29	-	-
Swedish	311	-	-	-	-

***including 241 Orphanet Journal of Rare Diseases reviews*

** not including the in-house produced articles*

Table 5 Total number of Orphanet external content (February 2020): type of text per language

3.3. Orphanet content: Orphanet catalogue of expert services

Orphanet provides a catalogue of:

- Centres of expertise/genetic counselling clinics and networks of centres of expertise
- Medical laboratories and diagnostic tests
- Patient organisations and umbrella organisations
- Patient registries
- Mutation databases
- Biobanks
- Ongoing research projects
- Clinical trials
- Platforms and infrastructures

The Orphanet catalogue of expert services is produced by collecting data either from official national sources, or proactively from non-official sources by information scientists in each country of the Orphanet consortium. Data follows a validation process before publication, and is quality controlled. The aim of this multi-step process is to generate high-quality, accurate and robust data: complete, valid, consistent, unique, and uniform with the other data of the database.

For data from official sources, no pre-release validation is required, but quality control is performed for consistency and added-value annotations are curated (i.e. link to the Orphanet classifications and characterisation of expert services). When issued from non-official sources, data is submitted to a pre-release validation process that is defined by each country following rules established at the national level and eventually with health authorities, to ensure data relevance for the rare disease community. A second round of validation is performed at the Orphanet coordination level to make sure data meets the criteria of relevance for rare diseases, to check coherence across the database and to ensure proper linking with the disease classification system. A third round of quality control is carried out on online published data following a process defined at national level (i.e. annual revision by the Scientific Advisory Board, or by competent authorities). At least once a year, professionals are invited to verify and update the expert services they are involved in.

The 35 countries in which Orphanet members collected data in 2019 are the following:
Armenia, Austria, Belgium, Bulgaria, Canada, Croatia, Czech Republic, Estonia, Finland, France, Georgia, Germany, Hungary, Ireland, Israel, Italy, Latvia, Lithuania, Luxembourg, Malta, the Netherlands, Norway, North Macedonia, Poland, Portugal, Romania, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey, the United Kingdom and Japan.

Data collection outside the Orphanet network:
Patient organisations in countries outside the Orphanet network can be registered in the database if they are an alliance and/or a member of EURORDIS and if they have a legal status or they are registered in an official journal. However, Orphanet does not ensure the regular update of this information. A disclaimer informing the users of this is available on the resource page of the website.

Research related resources (research projects, clinical trials, patient registries, biobanks and mutation databases) funded by funding agencies in countries outside of the Orphanet network are collected by the coordinating team if the funding agency is a member of the IRDiRC consortium. Patient registries outside of the Orphanet consortium can also be registered if they fulfil inclusion criteria (Please refer to the technical procedures for an exhaustive list of inclusion criteria).

The catalogue of expert services in the Orphanet network contains the following data:

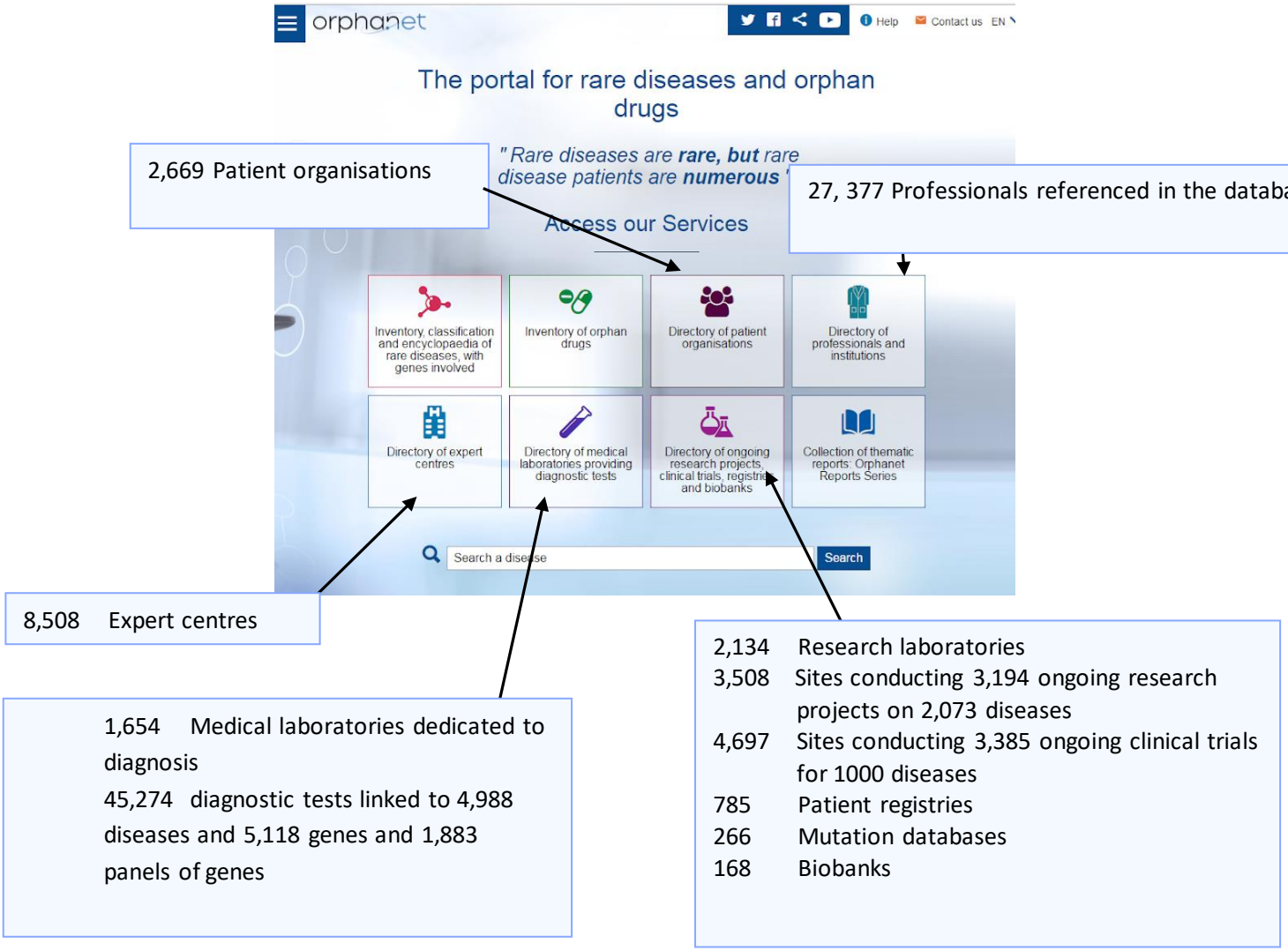


Figure 9 Directory of expert services (January 2020)

3.3.4. DATA QUALITY VALIDATION OF MEDICAL LABORATORIES

Medical laboratories listed in Orphanet are those offering tests for the diagnosis of a rare disease or a group of rare diseases, and those performing genetic testing whatever the prevalence of the disease. Information on quality management for medical laboratories and diagnostic tests is provided in Orphanet. Medical laboratories can be accredited and this involves a procedure by

which an authoritative body gives formal recognition that a body or person is competent to carry out a specific task (ISO 9000: 2000 Quality management systems – fundamentals and vocabulary). Moreover, medical laboratories can undergo an external quality assessment (EQA) whereby a set of reagents and techniques are assessed by an external source and the results of the testing laboratory are compared with those of an approved reference laboratory (WHO). This allows a laboratory to compare its performance for an individual test or technique against those of other laboratories.

Information on EQA participation is provided annually by Cystic Fibrosis Network, Cytogenetic European Quality Assessment Service (CEQAS) and European Molecular Genetics Quality Network (EMQN) with the consent of the concerned laboratories. For other EQA providers, information on participation can be provided by the laboratory itself.

3.3.5. ADDITIONAL FUNCTIONALITIES IN 2019

From 2019 onwards, patient organisations belonging to an alliance or a federation as shown as such on the Orphanet website.

A logo has been added to the expert centre pages when a centre belongs to an ERN.

3.4. Orphanet content: Orphanet inventory of orphan designations and drugs

The list of orphan designations and drugs includes all those substances that have been granted an orphan designation for a disease considered as rare in Europe, whether they were further developed to become drugs with marketing authorisation (MA) or not. The Orphanet database also includes drugs without an orphan designation as long as they have been granted a marketing authorisation issued by the European Medicines Agency (EMA - centralised procedure) with a specific indication for a rare disease. Some drugs (substance and/or trade name) are also included in the database because they have been tested in a clinical trial performed on a rare disease without such 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). Orphanet also collects information on Orphan Drugs from Food and Drug Administration in the USA (FDA).

Orphan drugs are published on the Orphanet website, under the Orphan drugs tab and data is also released within an Orphanet Report Series that is updated every trimester.

The database of orphan drugs and substances contains the following data (as of the end of 2017):

For Europe:

- **2126** Orphan Designations linked to **1583** substances and covering **655** diseases

- **334** Marketing Authorisations (of which **104** have an Orphan Designation and **230** without Orphan Designation), covering **313** diseases

For the USA:

- **806** Orphan Designations linked to **644** substances and covering **445** diseases

- **428** Marketing Authorisations (of which **419** have an Orphan Designation and **9** without Orphan Designation), covering **389** diseases

3.5. Orphanet products: Orphanet Report Series

Orphanet Reports (ORS) are a series of documents providing aggregated data covering topics relevant to all rare diseases. New reports are regularly put online and are periodically updated. These texts are published as PDF documents accessible from the homepage and from every page of Orphanet's website. New versions of these publications are advertised in OrphaNews. Orphanet also provides access to its procedures for data collection and curation in the scope of its Quality Management System.

The ORS and procedures are heavily downloaded: in 2019, more than 430,000 ORS and procedures were downloaded (Table 6).

	English	French	German	Spanish	Italian	Dutch	Polish	Portuguese
List of rare diseases in alphabetical order	30,146	77,420	23,676	17,171	39,434	8,034	43,580	10,011
Prevalence of rare diseases by alphabetical list	24,431	3,685	6,229	2,030	2,039	397	NA	1000
List of orphan drugs in Europe	15,758	1,838	1,181	1,235	1,277	278	NA	376
Prevalence of rare diseases by decreasing prevalence or cases	5,625	5,629	3,450	6,639	5,375	446	NA	1,972
Registries for RD in Europe	8,870	NA	NA	NA	NA	NA	NA	NA
Orphanet ICD10 coding rules	5,354	NA	NA	NA	NA	NA	NA	NA
Orphanet linearisation rules	911	NA	NA	NA	NA	NA	NA	NA
Research Infrastructures for rare diseases in Europe	1,596	NA	NA	NA	NA	NA	NA	NA
Vivre avec une maladie rare en France	NA	37,301	NA	NA	NA	NA	NA	NA

(N.A. = ORS not available in this language)

Table 6 Number of downloads of selected Orphanet Report Series in 2019 by language

3.6. Orphanet's IT infrastructure

The whole IT infrastructure is under the responsibility of Inserm. The production servers are located in one of the largest civil data centres in France, the CINES (Centre Informatique National de l'Enseignement Supérieur). To ensure structural security, the development servers are located in another Inserm building close to the CINES and linked to it by a fiber optic connection. This allows an excellent connectivity between production servers, development servers and backup environments. The architecture of the servers is represented in Figure 11.

No major problems were encountered in 2019 and the www.orpha.net website was highly available despite an increasing amount of visitors, which now reaches around 3 million pages viewed per

month. The uptime measurement, represented in Figure 10, by Nagios supervision for www.orpha.net in 2019 was 359d 19h 25m 10s 98.578%. This is slightly less than 2018 due to issues occurred during week-ends, which are not covered by administration supervision. Nevertheless the overall architecture, managed by the Inserm Department of Informatics (Inserm DSI), will need more updates in the coming months, especially concerning PHP versions which are now outdated (PHP lifecycle is now based on 7+ version, this needs several modifications on the web applications servers and web applications codes).
We also have added external cloud components to improve data analysis capabilities, using ElasticSearch Cloud solution with Dashboards based on Data visualisation tools Kibana. This component is accessible from the Orphanet's backoffice for Orphanet teams.

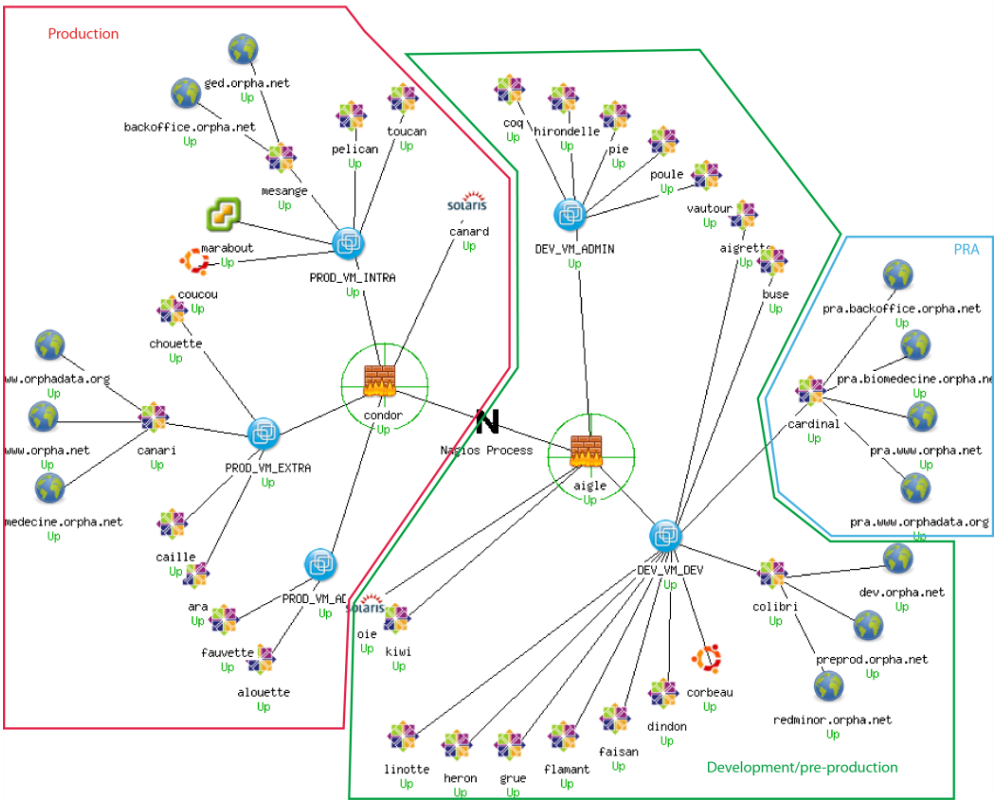


Figure 10 Orphanet's IT architecture in 2019

3.7. Orphanet services: The Orphanet website

The Orphanet website provides a user-friendly homepage with ergonomics that have been designed to provide easier access to the numerous services offered by Orphanet and to enhance usability, with specific emphasis on improving accessibility for visually impaired users (Fig 11). Indeed, the typeface is magnified and information is organised in easy-to-spot blocks with distinctive icons that allow users to more readily navigate the site. The disease search function is in the centre of the homepage.

Figure 11 The Orphanet portal homepage

Professionals and patient organisations can provide updates and add activities to the catalogue of expert resources via a secure account: these registrations are manually processed by the Orphanet local teams and undergo a quality control. Furthermore, the Orphanet website allows users to reach other Orphanet services: Orphadata, OrphaNews, Orphanet Report Series, and to interact with Orphanet, either through the expert registration service, or through the suggest and update functionalities.

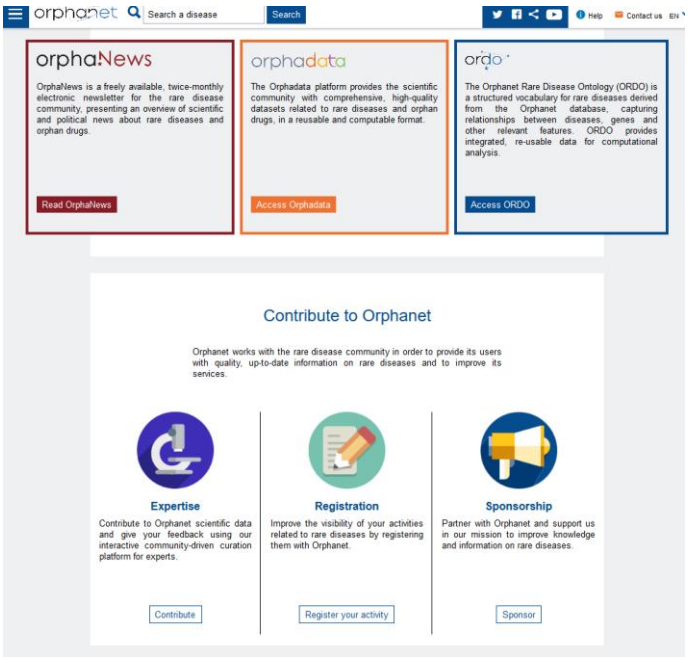


Figure 12 Access to Orphanet services and services for interaction with the curation team

3.7.4. INDEXATION BY SEARCH ENGINES

According to Google, the prominence of the www.orpha.net site can be assessed by the number of results obtained by using the site name as a query, for which there are 2,100,000 responses.

Users mainly access the www.orpha.net site through search engines, namely organic searches (92% of sessions according to Google Analytics), and Google alone is the source of 92% of consultations (Figure 13). Organic searches correspond to listings on search engine results pages that appear because of their relevance to the search terms, as opposed to them being from advertisements.

Around 6% of visits come from users directly visiting Orphanet, without passing by a search engine, other site referral or social media referrals, for example.

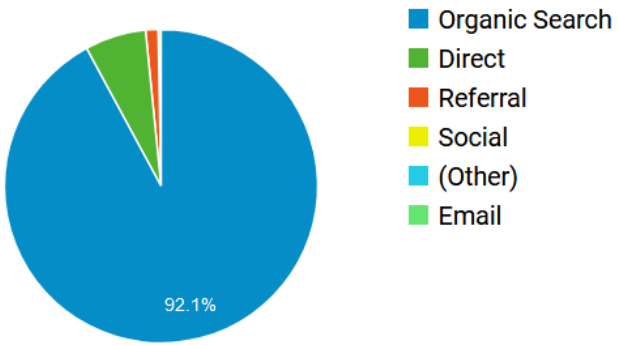


Figure 13 Distribution of the traffic sources
(Source: Google Analytics, 1st of January 2019 to 31st of December 2019)

The wealth of information available on our site attracts a substantial number of visits due to a sizable corpus of keywords (rather than just certain predominant keywords). The keyword primarily used to access our site is simply "Orphanet". The indexation of our site is of the "long tail" type: more than 85'000 keywords generated traffic to the site in 2019 according to Google Analytics

Google Analytics allows users to trace visits made from mobile devices (Smartphone, tablets): these visits represented 66% of all visits during 2019, an increase when compared to other years (61% in 2018, 54% in 2017, 28% in 2016, 20% in 2015 and 2014, and 23% in 2013). The newest version of Orphanet has a responsive design and so provide a much better adaptation to any mobile device.

3.7.5. THE WEBSITE'S AUDIENCE

ORPHANET IN NUMBERS

- 46 million pages viewed
- 10.4 million PDFs downloaded
- Visits from 236 countries

In 2019, around 46 million pages were viewed (14 million more than in 2018), thus on average around 126'000 pages were viewed per day (Figure 14).

The Google Analytics tool does not include direct access to PDF documents. However, PDF documents are an important entry point and generate a consistent volume of visits: 10.4 million PDFs were downloaded from the site in 2019.

The users come from 236 countries. The top ten countries are: Italy, France, Brazil, Germany, Spain, Mexico, United States, Argentina, Colombia, Belgium.

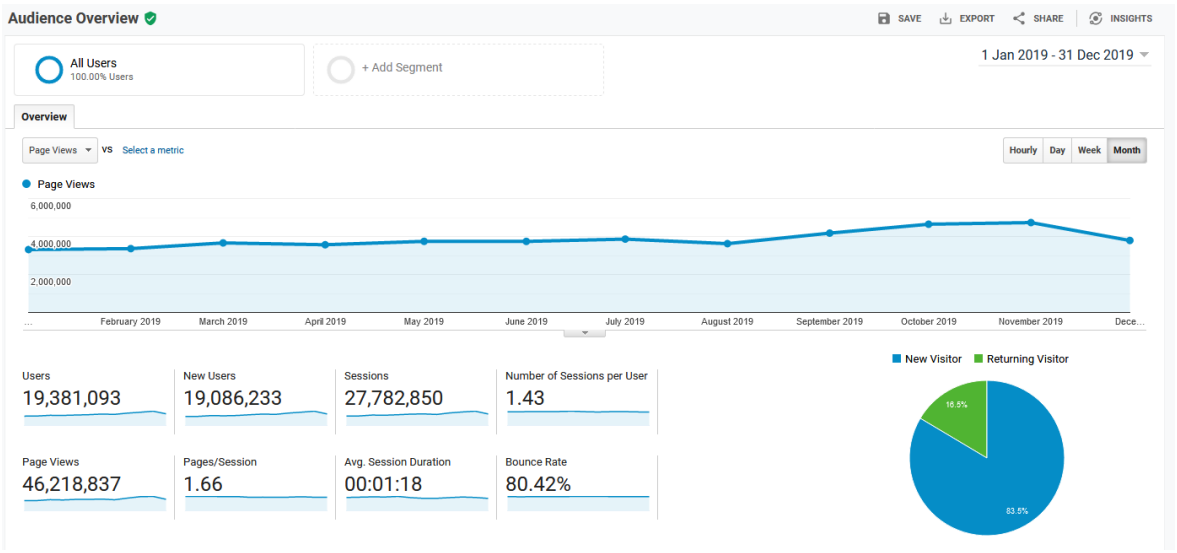


Figure 14 Orphanet website consultations in 2019

(Source: Google Analytics, 1st January 2019 to 31st December 2019)

The tool that is used to track our audience is Google Analytics. It allows 3 parameters to be monitored: sessions, users and page views (this shows a substantial ratio of page views / visitors). It should be noted that the current way in which users and sessions are counted is liable to change. For example, in 2014, the CNIL (*Commission nationale de l'informatique et des libertés* : the French data protection authority) recommended that websites inform users of the measurement tools used on the website, such as Google Analytics. During the summer of 2014 we developed a pop-up that requires users to accept this measurement. In case of refusal or inaction (no change of page for example), the user and the session are not properly recognised by the tool.

There was an increase in the number of around 9 million sessions in 2019 from 2018 (Figure 15), and there was an increase in users (7 million more than in 2018); the number of pages per session increased from 1.50 to 1.66, the average session duration decreased by 6 seconds for the second year in a row.

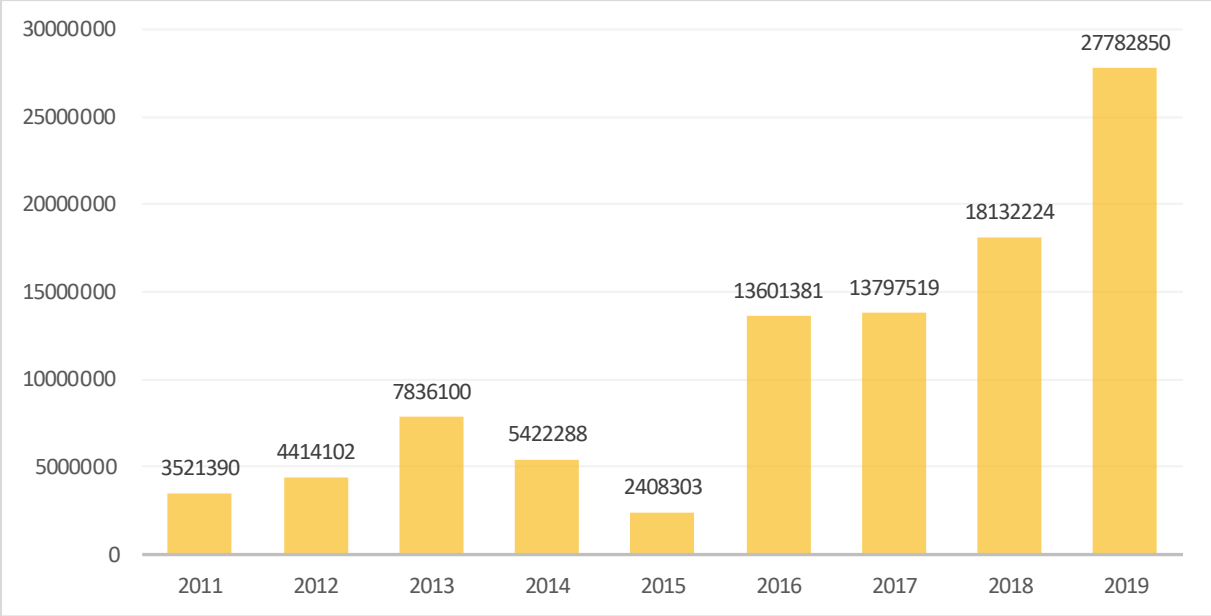


Figure 15 Evolution of number of sessions since 2011 (Source: Google Analytics)

3.7.6. ORPHANET NATIONAL WEBSITES

National websites dedicated to each partner country enable them to have an entry point in their national language(s). The national pages include information on national events, news and access to national policy documents concerning rare diseases and orphan drugs. Beyond the scope of national information, these pages provide access to the international database in seven languages. As of 31 December 2019, 37 national websites are online. Some of these national websites are published completely in their national language while for other countries, the layout of the national webpage is in English and the mandatory texts (General Information) are in their respective national language.

3.8. Orphanet services: Orphanet Rare Diseases Ontology & HPO-Orphanet Ontological Module

The **Orphanet Rare Disease ontology (ORDO)** is available on three websites Bioportal, Orphadata and the EBI Ontology Lookup Service.

Initially, ORDO was jointly developed in 2013 by Orphanet and the European Bioinformatics Institute (EMBL-EBI) to provide a structured vocabulary for rare diseases, capturing relationships between diseases, genes and other relevant features which will form a useful resource for the computational analysis of rare diseases. It is derived from the Orphanet database. It integrates nosology (classification of rare diseases), relationships (gene-disease relations, epidemiological data) and connections with other terminologies (MeSH, UMLS, MedDRA, GARD), databases (OMIM, Universal Protein Resource Knowledge Base (UniProtKB), Human Genome Organisation Gene Nomenclature Committee (HGNC), ensembl, Reactome, IUPHAR, Genatlas) or classifications (ICD-10), complete epidemiological data, mappings and genetic annotations. The ontology is maintained by Orphanet and further populated with new data. Orphanet classifications can be browsed in the EBI's ontology lookup service (OLS). ORDO is updated twice a year and follows the OBO guidelines on deprecation of terms. It constitutes the official ontology of rare diseases. The availability of such relationships between medical terminologies allows RDs to be used as a "pivot" to connect different biological, clinical or genetic ontologies. This interoperability allows for the association of new content and the establishment of new research hypotheses on data that were not initially related to each other. In 2018 French and Spanish translations of ORDO were launched, with German and Dutch launched in 2019.

Orphanet provides phenotypic annotations of the rare diseases in the Orphanet nomenclature using the Human Phenotype Ontology (HPO). **HOOM, the HPO-Orphanet Ontological Module.** launched in 2018, is a module that qualifies the annotation between a clinical entity and phenotypic abnormalities according to a frequency and by integrating the notion of a phenotype being a diagnostic criterion. In ORDO a clinical entity is either a group of rare disorders, a rare disorder or a subtype of disorder. The phenomes branch of ORDO has been refactored as a logical import of HPO, and the HPO-ORDO phenotype disease-annotations have been provided in a series of triples in OBAN format in which associations, frequency and provenance are modelled. HOOM is provided as an OWL (Ontologies Web Languages) file, using OBAN, the language used for the Orphanet Rare Disease Ontology (ORDO), and HPO ontological models. HOOM provides extra possibilities for researchers, pharmaceutical companies and others wishing to co-analyse rare and common disease phenotype associations, or re-use the integrated ontologies in genomic variants repositories or match-making tools.

In 2019, ORDO was downloaded 11,171 times, a decrease of 11% as compared to the previous year.

3.9. Orphanet services: Orphadata

Since Orphanet has become increasingly well known as the reference source for documentation on rare diseases, a growing number of requests for its high-quality data are received. To meet the needs of massive data extraction, Orphadata was created. Orphadata is intended to contribute to accelerating R&D and to facilitate the global adoption of the Orphanet nomenclature. Orphadata was designated as an ELIXIR Core Data Resource at the start of 2019.

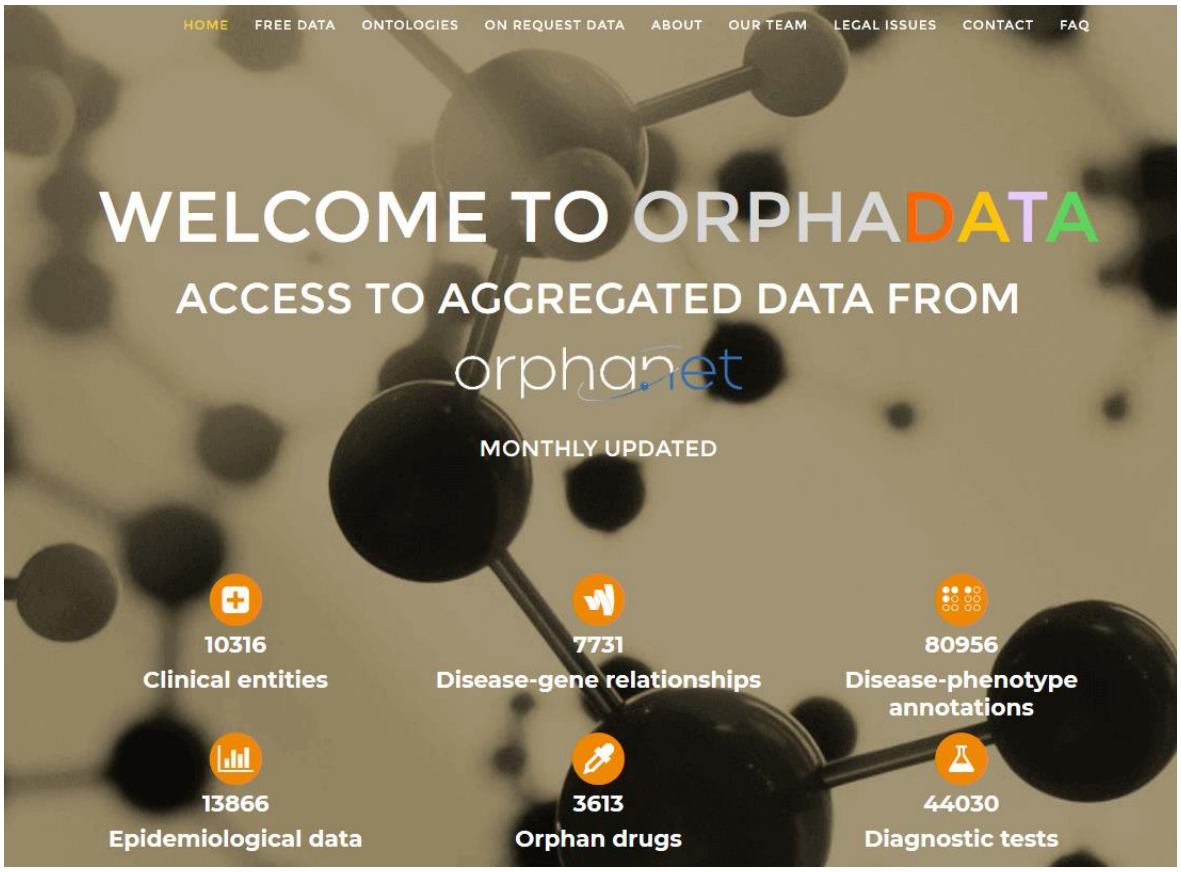


Figure 16 Screenshot of the Orphadata platform

Via this platform Orphanet datasets have been made directly accessible in a reusable format since June 2011. The data sets are available in seven languages: English, French, German, Italian, Portuguese, Spanish, Dutch, Polish and in Czech (available from 2018). Part of the datasets are available freely via a Creative Commons licence (CC BY 4.0 from the start of 2019), and some are available via signature of a Data Transfer Agreement for academic research (Table 7) or a licence agreement for for-profit organisations/companies (Table 8).

• An inventory of rare diseases, cross-referenced with OMIM, ICD-10, MeSH, MedDRA, UMLS, GARD and with genes in HGNC, OMIM, UniProtKB, IUPHAR and Genatlas. Annotations on typology of diseases and genes and of gene-disease relationships. Definitions for RD, XML and JSON format.
• A classification of rare diseases established by Orphanet, based on the literature and expert consensus classifications.
• Epidemiological data related to rare diseases based on the literature (point prevalence, birth prevalence, lifelong prevalence and incidence, or the number of families reported with respective intervals per geographical area, type of inheritance, interval average age of onset and age of death).
• Phenotypes associated with rare disorders (annotations using HPO terms), as well as their frequency.
• Linearisation of RD : for analytical purposes, each disorder is attributed to a preferred classification (linearisation) by linking it to the head of classification entity.
• Orphanet Rare Diseases Ontology (ORDO)
• HPO-ORDO Ontological Module (HOOM)

Table 7 Products freely accessible on Orphadata (ELIXIR Core Data Resources)

• An inventory of Orphan Drugs at all stages of development, from EMA orphan designation to market authorization, cross-linked with diseases.
• Summary information on each rare disease in seven languages (English, French, German, Italian, Spanish, Portuguese, Dutch, Polish).
• URLs of other websites providing information on specific rare diseases
• A directory of specialised services, providing information on centres of expertise, medical laboratories, diagnostic tests, research projects, clinical trials, patient registries, mutation databases, biobanks and patient organisations in the field of rare diseases, in each of the countries in the Orphanet network.

Table 8 Products accessible on Orphadata after signature of a Data Transfer Agreement/licence agreement

Orphadata also gives access since 2019 to the "Nomenclature pack": this data set is specifically for use in coding setting and provides the computable information necessary to achieve the implementation of ORPHAcodes in Health Information Systems. These files are generated and made available once a year, in 9 different languages: Czech, Dutch, English, French, German, Italian, Polish, Portuguese and Spanish.

Orphadata provides a documentation for users that defines and describes the elements of the dataset and gives access to Orphanet procedures relevant to the users of the data, such as the *procedure for producing the nomenclature*, the *methodology of alignment of ICD10 coding rules for rare diseases* and the *methodology of linearisation*.

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.

In 2019, **Orphadata products (free and on request) were downloaded more than 120,000 times**. This represents a decrease of 24% compared with 2018 (Figure 17).

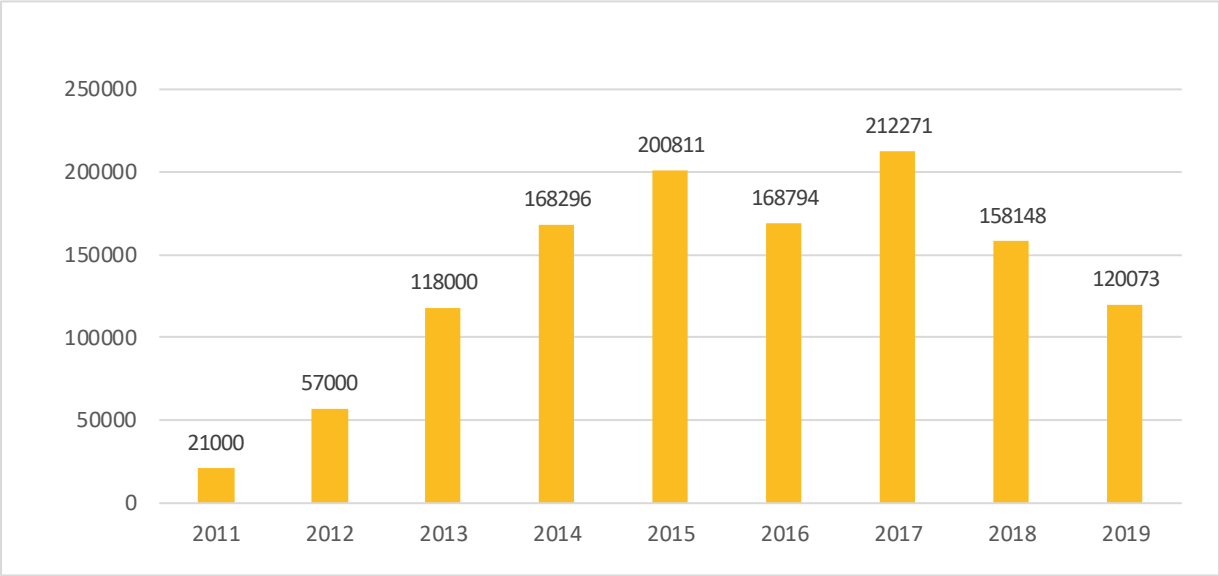


Figure 17 Number of downloads from the Orphadata website since mid-2011

The most requested Orphadata product in 2019 were the classifications of rare diseases (Figure 18 and 19).

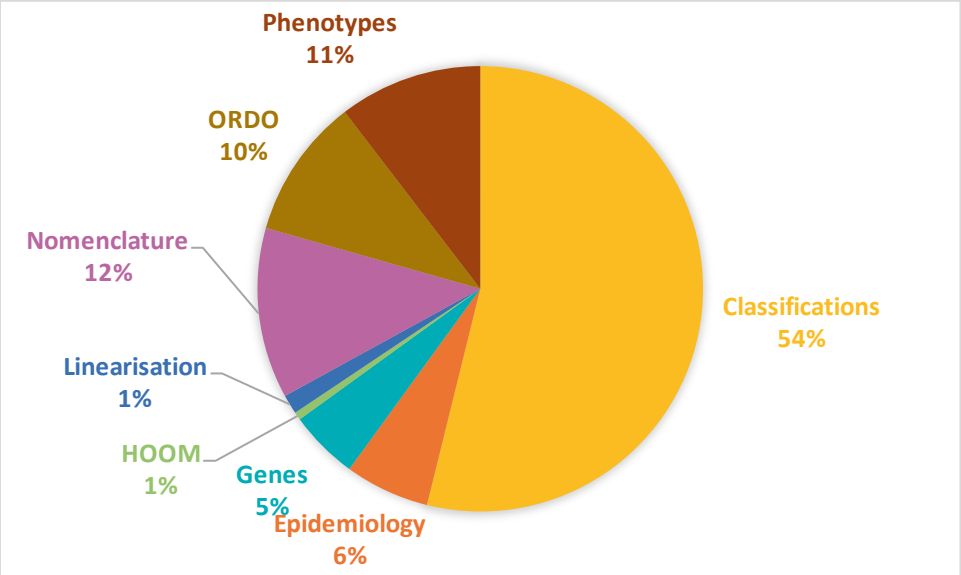


Figure 18 Distribution of the downloads of Orphadata freely available datasets in 2019. [total 110,762 downloads]

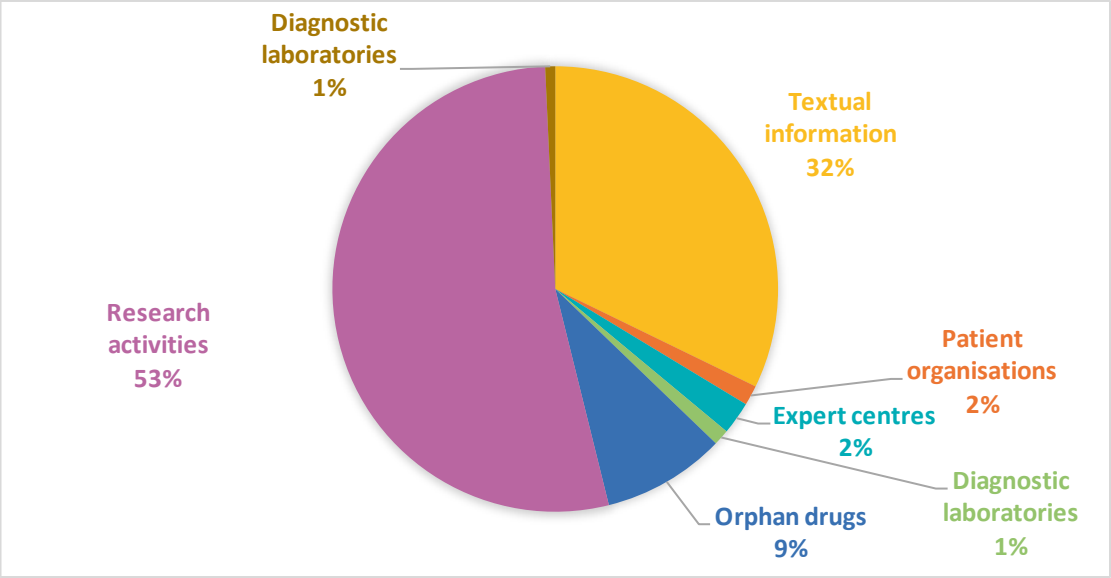


Figure 19 Distribution of the downloads of Orphadata Datasets accessible on demand in 2019 [total of 2,350 downloads]

3.9.4. ADDITIONAL FUNCTIONALITIES IN 2019

In 2019, Orphadata launched a new product on the platform, the "Nomenclature pack", adata set geared specifically for use in coding setting and provides the computable information necessary to achieve the implementation of ORPHAcodes in Health Information Systems. These files are generated and made available once a year, in 9 different languages: Czech, Dutch, English, French, German, Italian, Polish, Portuguese and Spanish.

The XML models for Orphadata products, and UML schema for ORDO were published on Orphadata for the first time in 2019. A number of communication documents were also produced in order to explain to users the contents of each of the datasets, as well as ORDO and HOOM, and thus facilitate the use and reuse of the data and tools available via the platform.

ORDO was generated in German, Dutch, Spanish, French, Italian and Polish, in addition to English for the first time in 2019. This means that ORDO is available in all the Orphanet languages that have an Orphanet nomenclature in national language except Portuguese and Czech.

3.10. Orphanet Services: The OrphaNews Newsletter

OrphaNews is a bimonthly newsletter for the rare disease community, presenting an extensive overview of scientific and political news about rare diseases and orphan drugs. Subscription to this newsletter is free. A literature survey is performed twice a month in order to update the Orphanet database and to collect both scientific and political news to report in OrphaNews. The selection of articles for the newsletter is validated by a multidisciplinary editorial board. News is also submitted from contact points in each of the Orphanet consortium countries.

OrphaNews International is supported by the European European Commission's DG SANTE (PP-1-2-2018-Rare 2030 . OrphaNews France is supported by the French Muscular Dystrophy Association (AFM), while OrphaNews Italy is supported by Genzyme.

Figure 20 OrphaNews homepage

In 2019 OrphaNews in English had 12,100 subscribers. OrphaNews in French had 7,400 subscribers and OrphaNews in Italian had 5,200 subscribers.

3.11. Orphanet Services: Mobile applications

Orphanet data is available via two mobile apps.

Figure 21 Orphanet mobile app and Orpha Guides mobile app

Orphanet is an app allowing users to access the list of rare diseases, textual information concerning the disease and associated services (expert centres), as well as Emergency Guidelines. The app was retired in 2020, as redundant with the new, responsive Orphanet website.

Orpha Guides was an app in French giving access to information on French national support mechanisms for patients and their families, as well as information concerning the functional consequences of rare diseases. A revision of the application is underway and will be launched in 2021.

3.12. Orphanet Journal of Rare Diseases

Orphanet Journal of Rare Diseases (OJRD) is an open access, online journal that encompasses all aspects of rare diseases and orphan drugs. The journal publishes high quality reviews on specific rare diseases. In addition, the journal may consider articles on clinical trial outcome reports, either positive or negative, and articles on public health issues in the field of rare diseases and orphan drugs. OJRD was indexed in Medline at the end of its first year of existence (2006) and was selected by Thomson Scientific after only two years of being in publication. Its 5-year impact factor is 4.029. Articles have been downloaded over 1,700,000 times. Springer Nature, the publishing house hosting the OJRD, has signed the San Francisco Declaration on Research Assessment (DORA) that intends to halt the practice of correlating the journal impact factor to the merits of a specific scientist's contributions.

4. Users: 2019 satisfaction survey

The 2019 satisfaction survey was conducted in one phase launched in February 2020 via a po-pup window added to the first page users landed on. The survey was translated into the 8 languages of the website (i.e. English, French, Spanish, Italian, Portuguese, Dutch, German and Polish) and was displayed in the language of consultation via the pop-up. The survey covers the mode of discover of Orphanet, the user's profile and their opinion of the services proposed by Orphanet. The survey was closed after 5 weeks of display on the website. This survey was made of 14 questions split into 3 sections. The results were analysed and presented in a dedicated Orphanet Report, and the highlights are presented here

Question 1: To what extent do you agree or disagree with the following statement?

This question aimed to find out whether users found Orphanet website user friendly, easy to use and if the information found was easily understandable. Respondents were asked to rate (++, +, -, --), to what degree:

- the site is easy to navigate,
- the information was easy to find,
- the information found was easy to read and understand.

Respondents were asked to provide answers concerning the three statements but an answer was not required. 6330 respondents replied to this question.

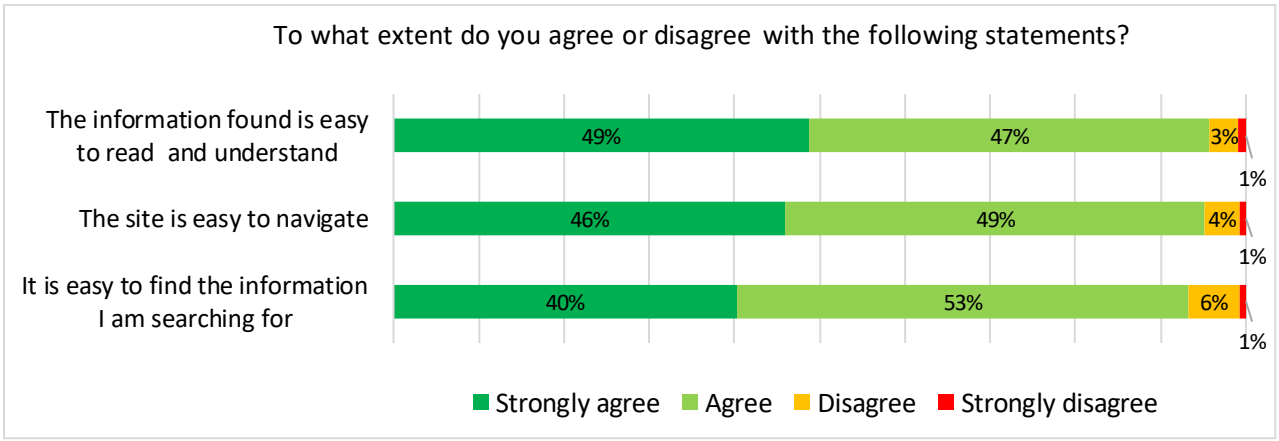


Figure 22: Repartition of the respondents' rate on the ease to use the Orphanet website and to understand the information found (n=6330)

These results show that most of the respondents (more than 90%) find that the Orphanet website is user-friendly, that the information is easy to find and that once it is found the information is easy to read and understand (Figure 22). A minority of respondents (4 to 7%) disagree or strongly disagree with these statements. This is more than in the last survey (around 2%) but this can be explained by the fact that in the last survey we proposed an intermediate category showing that 13 to 19% of respondents are ambivalent.

Question 2: How useful would you rank the following Orphanet services for your own use?

This question aims to determine the utility and users' knowledge of the various services/products offered by Orphanet. Respondents were asked to rate (++, +, -, --) each service/product or to specify that they did not know this service/product.

An answer was not required and 5413 respondents replied to this question, i.e. 37% of the total respondents (the total of regular user respondents being 48%).

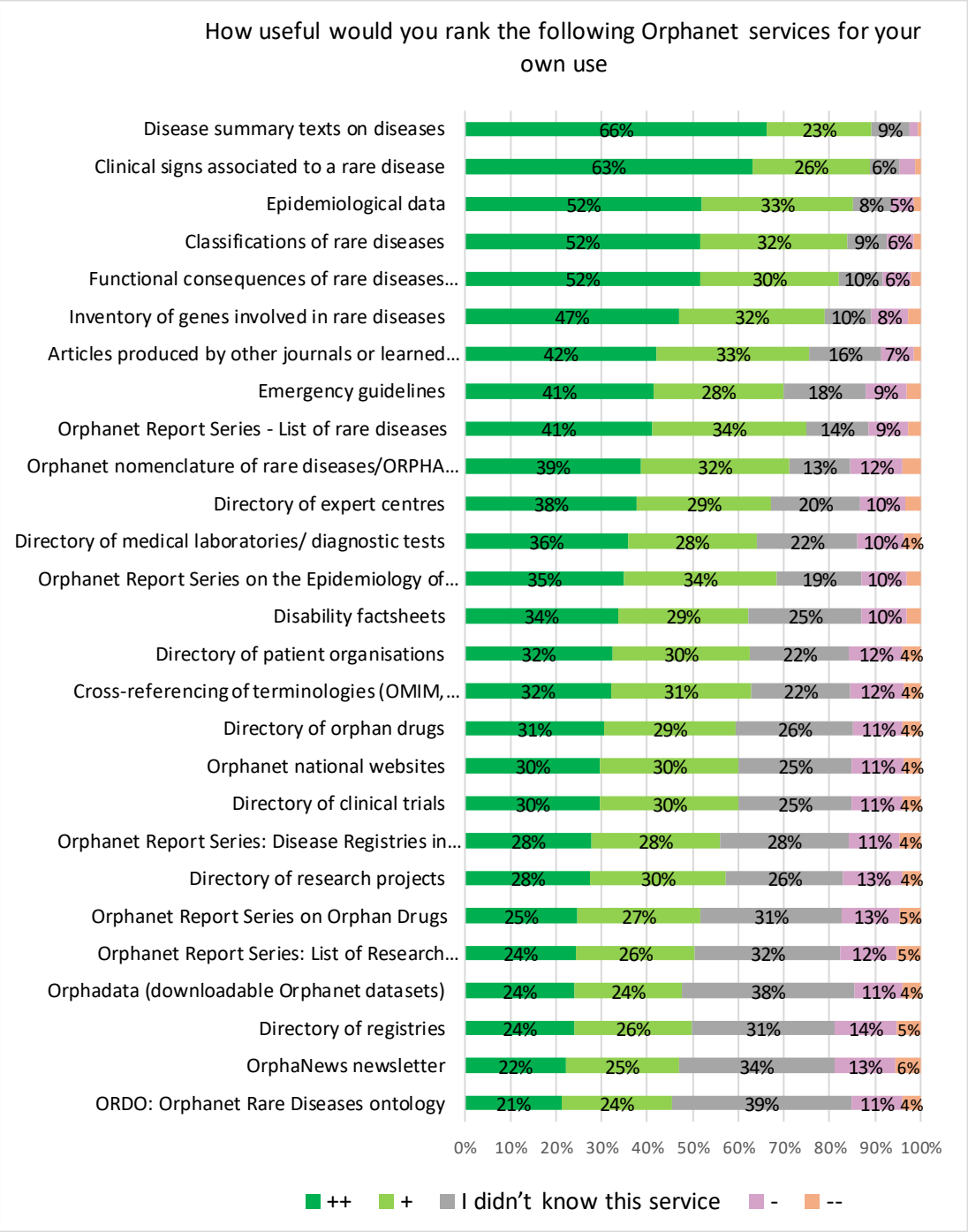


Figure 23 : Repartition of the respondents rate on utility and or knowledge of services/products offered by Orphanet (n=5413)

The most useful services for respondents (almost 90%) are disease summary texts and clinical signs associated with a rare disease (Figure 23) followed by epidemiological data, classifications of rare diseases, functional consequences of rare diseases (disabilities) and the inventory of genes involved in rare diseases (around 80%).

Articles produced by other journals and published on the Orphanet website, Orphanet nomenclature of rare diseases / ORPHAcodes and emergency guidelines are also very useful services for Orphanet users (at around 70%).

4 to 15% of respondents do not find certain products/services useful for their needs. These results should, however, be considered in the light of the results of question 11, where we asked what Orphanet could do to better serve its users : it emerges from this question that detailed information would be more useful for some users.

Overall, the services/products offered by Ophanet are more useful than not for respondents.

The Orphanet Report Series on Registries, Orphan Drugs and Research Infrastructures and also the OrphaNews newsletter are not well known to our users (around 30%). Orphanet should therefore increase the visibility of these products and services.

Orphadata (downloadable Orphanet datasets) and Orphanet Rare Disease Ontology (ORDO) are the least known products (almost 40%) maybe due to the fact that these services have their own access in addition to the Orphanet website and that people who need these services do not come to the Orphanet website to find them.

Question 3: Overall, how satisfied are you with Orphanet?

The global satisfaction of Orphanet website users was evaluated through this question. An answer was not required and 5262 respondents replied to this question, i.e. 36% of the total respondents, the total of regular user respondents being 48%.

Only one answer was possible plus a non-mandatory free field to add any comment that could explain the answer. Comments were aimed at ascertaining in more detail what people think of Orphanet and were provided by 598 individuals.

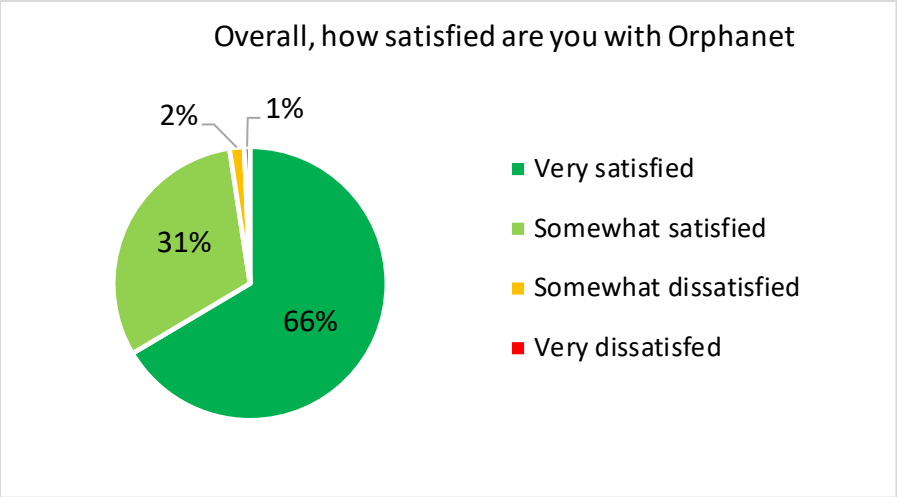


Figure 24: Global satisfaction of the Orphanet website users (n= 5262)

The vast majority of respondents were either very satisfied or satisfied with Orphanet with a total of 97% responding positively (Figure 24), increasing by 4 points compared to the last survey (93%, n=4369).

The free comment field helped us to understand the reasons for satisfaction or dissatisfaction (Figure 14):

- 57% considered that information provided by Orphanet is useful and accurate, showing the same trend as in the last survey.
- 2% of respondents were dissatisfied and 1% were very dissatisfied. The main free comments explained that the information is not detailed enough and not updated enough, and the website is not user-friendly enough.

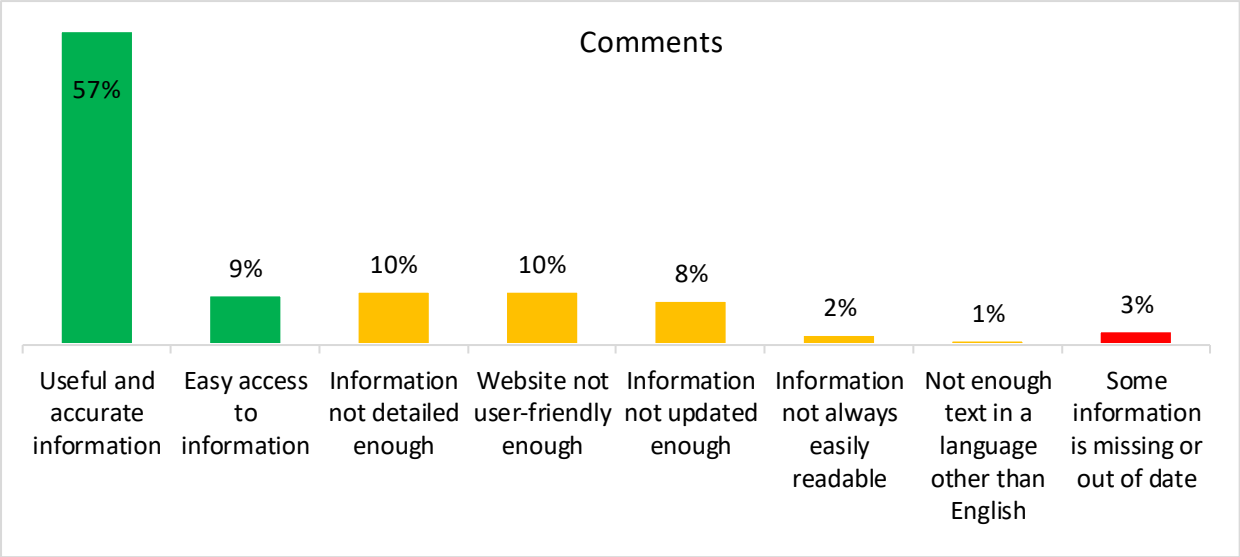


Figure 25: Free comments of the Orphanet website users (n= 598)

Question 4: How likely is it that you would recommend Orphanet to a friend or a colleague?
This question was asked in order to determine Orphanet's Net Promoter Score (NPS), which measures the likelihood, on a 1-10 scale, that someone will recommend a company to someone else. The Net Promoter Score was calculated by subtracting the percentage of customers having ranked this probability from 0 to 6 from the percentage of customers having ranked this probability from 9 to 10. Thus, results can go from -100 to +100.

An answer was not required and 5299 respondents replied to this question, i.e. 37% of the total respondents, the total of regular user respondents being 48%.

Almost 63% of those responding turned out to be promoters as they responded with a score of 9 or 10, 29% were passive (score of 7 or 8) and 8% were detractors (score of 0 to 6). This gives a NPS of 54.3 (Figure 26).

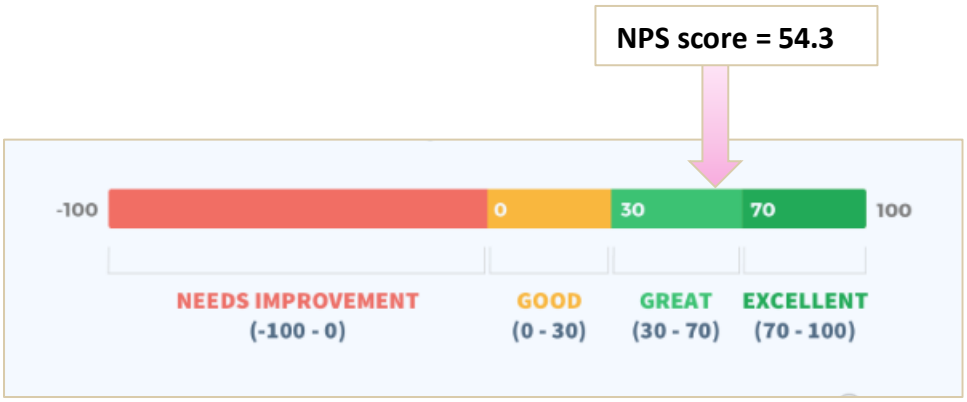


Figure 26: Orphanet Net Promoter Score (NPS) (n= 5299)

To our knowledge, Orphanet is the only service dedicated to providing free information on rare diseases and orphan drugs, that publishes its NPS. Thus, we cannot compare this score to other similar services but is useful in measuring our customer satisfaction when tracked. This score increased by 6.5 points compared to the last survey in 2018 (47.8, n=4199).

It is noteworthy that according to these results 63% of the respondents would recommend using Orphanet while only 8% would not.

5. Networking: Orphanet's national and international collaborations

Orphanet believes in the effectiveness of sharing data and expertise in order to achieve a deeper understanding of rare diseases and to address the specific needs of different stakeholders.

Thanks to the internally produced, expert-reviewed scientific information that Orphanet offers on rare diseases, Orphanet is often solicited by many different projects to contribute its expertise.

It is for these reasons that new collaborations and partnerships are developed regularly, resulting in the intense scientific collaborative activity described below.

5.1 National plans or strategies for rare diseases

Orphanet teams actively participate in the preparation of National Plans or Strategies for Rare Diseases as they are recognised as experts at the national level.

Orphanet is mentioned either as the reference portal for rare diseases or main source of information on rare diseases in the recommendations and proposed measures of the majority of national plans or strategies adopted to date. The countries below have provided additional information concerning support to Orphanet in national plans and strategies for rare diseases.

Czechia

Orphanet is part of the Third National Plan for Rare Diseases, in particular citing support for the Orphanet nomenclature in Czech to improve coding for rare diseases in health information systems.

Germany

Orphanet Germany was involved in two activities that received financial support from the German Ministry of Health in 2017: (1) SE-ATLAS, a joint project by the Universities of Mainz, Orphanet-Germany, and the Centers for Rare Diseases in Frankfurt and Tübingen, aiming to innovate the presentation of health care facilities for patients with rare diseases in Germany by featuring an interactive geographical map. This service has not recently been maintained. 2) PORTAL-SE is a sister project by the Universities of Hannover, Freiburg and Mainz, the Chamber of Physicians of Lower Saxony, and Orphanet-Germany, to conceptualise a central information portal facilitating access to information on all aspects of rare disease care in a user-group specific manner. Both of these projects do not intend to create new databases. Orphanet Germany will, according to the German Action Plan on Rare Diseases, remain the central information platform in this respect.

The Netherlands

The Minister of Health, Welfare and Sport in the Netherlands appointed the NFU, the Netherlands Federation of University Medical Centres, to coordinate the identification and registration of Dutch centres of expertise for rare diseases together with Orphanet Netherlands and the VSOP (Dutch national patient umbrella organization for rare and genetic disorders). A procedure was developed

in which an independent designation committee evaluates potential centres of expertise according to the EUCERD criteria established at the European level. These criteria include the presence of guidelines, protocols, standards and indicators of care, and equally evaluate scientific research, the relationship with patient organization(s) and how the continuity of the centre is ensured within the institute. A description of the evaluation procedure is published on the NFU website (in Dutch; https://www.nfu.nl/patientenzorg/complexezorg/procedure-expertisecentra/). Since the start of this project, three rounds of evaluation have taken place in which potential centres from both University Medical Centres and non-university major "top-clinical" hospitals were assessed. From all three rounds, the minister assigned medical centres as official Dutch centres of expertise. These officially designated centres can be found on the Orphanet website and the Erfocentrum website www.erfelijkheid.nl.

Italy

The **Italian Health Ministry included Orphanet as a reference** in the new version (July 2016) of the Ministerial Decree of December 09, 2015, on Prescription Appropriateness (Italian title of the Decree: "Condizioni di erogabilità e indicazioni di appropriatezza prescrittiva delle prestazioni di assistenza ambulatoriale erogabili nell'ambito del Servizio sanitario nazionale"). The Decree sets up specific conditions for laboratories performing genetic tests in Italy ("Condizioni di erogabilità", as reported in "Allegato 1" of the Decree). In particular, with regard to genetic tests, the document contains the following reference to Orphanet database: "In order to identify single genes, refer to genes reported in the Orphanet database with diagnostic value"). This reference to Orphanet into the Italian legal framework marks an important milestone in its consolidation as a legitimate source of information on rare diseases in Italy. Orphanet was also highly mentioned in the National Plan for Rare Diseases 2013-2016 and the Ministry of Health identified Orphanet as a reference source of information for rare diseases and orphan drugs.

Portugal

The Ministry of Health of Portugal was recommended by the Assembly of the Republic to implement the Integrated Strategy for Rare Diseases, based on an interministerial, intersectoral and interinstitutional cooperation, which makes a complementary use of medical, social, scientific and technological resources.

The Integrated Strategy for Rare Diseases has the mission of developing and improving:

1) Coordination of care;
2) Access to early diagnosis;
3) Access to treatment;
4) Clinical and epidemiological information;
5) Research;
6) Social integration and citizenship.

This Interministerial Commission aims to combat the vulnerability of this population group by reducing the dispersion of information on these diseases, increasing access to diagnostic and therapeutic interventions as well as better referral in the health system. It also aims to improve health literacy of patients, families and caregivers.

Orphanet was recognised as a reference portal and credible source of information on rare diseases, their characteristics, diagnostic and possibilities of treatment, thus being an instrument for improving clinical and epidemiological information on rare diseases.

Under this strategy, a Card of People with Rare Diseases (CPRD) was implemented:

- To ensure access to relevant clinical information, to health care professionals, specially focusing on good practice recommendations in acute care;
- To improve the integrated management of the disease to avoid delay, error and harmful procedures;
- To guarantee the correct referral to Reference Centres;
- To improve continuity of care, between all the levels of care;

This card includes the name and the ORPHAcode of the rare disease, and the name and contact of the Reference Centre. The card is available at the national web-based patient clinical record.

Over the past 5 years, health professionals and facilities have been increasingly interested in requesting CPRD, and up to December 2018, 6112 CPRD were requested. Recognising that coding rare diseases through ORPHA codes is constantly evolving, along with genetic research, the catalogue of rare diseases available at the CPRD was updated during 2018, allowing higher accuracy and updates of the rare disease diagnosis. Additionally, in 2018 a Manual to Support People with Rare Diseases was published which compiles a set of information dispersed in several public institutions, relevant for people with rare diseases.

5.2. Nomenclature and terminologies

5.2.4. Adoption of the Orphanet nomenclature in health information systems

To improve the traceability of rare diseases in health information systems and to increase the recognition of each rare disease in national health and reimbursement systems, Orphanet has developed an evidence-based standardised nomenclature: the ORPHA nomenclature. It is composed of a unique and stable ORPHA number for each entry of the inventory. The ORPHA number can be used for codification purposes.

In 2014, the Commission Expert Group on Rare Diseases adopted a recommendation on ways to improve codification for rare diseases. In this document, Member States are encouraged to consider and explore the feasibility of the use of ORPHA codes at a national level and to include the codification of rare diseases as an area of their national plans/strategies for rare diseases. Support for the large number of Member States who have already expressed their interest in using ORPHA codes (as a complement to existing coding systems) is provided via a dedicated work package (WP5) of the Joint Action for rare diseases RD-ACTION (www.rd-action.eu). This work package has notably produced a survey of current codification situations in the Member States, a review document of

existing technical implementations for RD coding, and a Standard procedure and guide for coding with Orphacodes, as well as a beta version of a master coding file, and specifications for the implementation of this file. Specifications for an integrated coding application with Orphacodes have also been produced. Finallya mapping exercise of the use of ORPHA codes in Europe was carried in 2017.

A new two year project, RD-CODE (www.rd-code.eu/), co-funded by the Third health Programme, will start on January 2019 and will end in June 2021. The objective of this project is to support Member States in improving gathering information on rare diseases by implementation of ORPHA codes. The implementation process will be guided by the "Standard procedure and guide for the coding with Orphacodes" and the "Specification and implementation manual of the Master file" both developed in the framework of the previous Joint Action on Rare Diseases RD-ACTION (2015-2018).

The aim of the RD-CODE project is to promote the use of the Orphanet nomenclature, which has been recognised as a best practice by the Steeting Group for Health Promotion and Prevention at the European Commission, for implementation into routine coding systems. This enables a standardised and consistent level of information to be shared at European level. Starting with countries that have no systematic implementation of ORPHA codification yet, but that are already actively committed to doing so, this project will demonstrate real-world implementation to guide other countries in the future.

A number of countries have already taken some concrete steps in implementing ORPHA codes in their healthcare systems (Portugal, Germany, France, Belgium, Italy, Norway, Latvia, Czech Republic, Hungary, Cyprus, Switzerland) and national Orphanet teams are playing a key role in particular in the following countries:

Czech Republic

Orphacodes are utilised in collaboration with Czech Society of Medical Genetics and Genomics and the General Health Insurance Company for the pilot reimbursement of extra funding for members of the Czech members of the European Reference Networks for Rare Diseases and for reimbursement of next generation sequencing in rare diseases.

France

In 2012, it was decreed that the French hospital system database would use ORPHA codes to code all hospitalised patients. The aim is to better identify patients in the healthcare system so as to improve knowledge of their healthcare pathways. The ORPHA code has been added in a dedicated part of the coding system, in addition to the ICD-10 derived code. Also because of the development of electronic health records in France, the French Ministry of Health set up in 2015 an advisory committee for the codification of RD in which Orphanet plays a major role. A governmental memo was released in January 2016[7], aimed at centres of reference and centres of competence, making the codification of rare disease patients with ORPHA codes mandatory in the French Rare Diseases

[7] http://circulaire.legifrance.gouv.fr/pdf/2016/01/cir_40460.pdf

Data Repository BNDMR. Orphanet and the BNDMR have developed guidance documents for the codification of rare diseases in the BNDMR. The French Networks of Expertise (Filières de santé maladies rares) are in charge of producing coding guidelines in order to improve quality and consistency of coding in their disease fields. ORPHA codes are being implemented in electronic health records progressively.

Germany

In July 2013, a 3-year project started to revise the German ICD-10 (ICD-10GM), which was prolonged with a second funding period until 31st October 2019. Orphanet Germany is a partner of this project by supplying the DIMDI (German Institute of Medical Documentation and Information) with the German translation of rare disease terms. The project intends to integrate the Orphanet classification of diseases by adding ORPHA codes and it also serves to expand the inventory of rare diseases within the ICD-10GM. Alignment of German disease terms within both database systems should lead to more congruence between both systems.

The Netherlands

The RIVM, the National Institute for Public Health and the Environment, that coordinates this project on behalf of the Ministry, started to compare the disease classification of the World Health Organization (WHO; WHO-FIC Update and Revision Committee) with the Orphanet classification. RIVM project leaders are working in close collaboration with Orphanet Netherlands on this subject within the work package 5 of the RD-ACTION project.

Italy

In 2017, ORPHA codes have been integrated into the health and research information systems of eight Italian regions.

Portugal

The ORPHA nomenclature supports the registration of rare diseases at all NHS levels of care, being the mandatory classification to be used by all rare disease reference centres and by CPRD. The Portuguese Health Information System of the Ministry of Health purchased a licence for the use of SNOMED-CT in the country since January 2014. This licence allows its distribution and use free in Portugal. Access is available to health professionals, the Information and Communication Technologies (ICT), researchers, and all those who are interested in using the terminology.

5.2.5. COLLABORATION WITH THE WHO

The World Health Organisation (WHO) and Orphanet collaborate on the revision of the International Classification of Diseases (ICD-11).

Orphanet has been entrusted as the operating institution to prepare the proposal for ICD-11 related to rare diseases. The Rare Diseases Topic Advisory Group (RD-TAG) has therefore managed the

process of the preparation and peer-review of proposals in order to include rare diseases in every relevant chapter of the electronic version of ICD-11. In 2013, the beta version of ICD-11 was released. To date, 57% of RD in Orphanet are represented in the ICD Joint Linearisation for Mortality and Morbidity Statistics . Expert links to Orphanet are transmitted to maintain up-to-date definitions. A mapping file between ICD11 and ORPHA numbers is under production and will be released by Orphanet in 2021.

A collaboration is also underway with the WHO's ICTRP (International Clinical Trials Registry Platform) (https://www.who.int/ictrp/en/) and Orphanet. ICTRP aims to offer a complete view of clinical research, which is accessible to all those involved in health care decision-making. It includes therefore rare diseases. The collaboration is aimed at making clinical trials on rare diseases easily identifiable and findable, thus improving knowledge on rare diseases. ICTRP and Orphanet will work to identify and flag all rare disease related clinical trials in the ICTRP database for its users. Rare disease related clinical trials are identified using the Orphanet nomenclature of rare diseases. Clinical trials for rare diseases are exported into the Orphanet database, where additional information is available, in particular the rare disease concerned, the category of clinical trial, and the medicinal product in development, amongst other information. ICTRP users will be able to see all RD-related clinical trials in the Orphanet and IRDiRC countries and to visit Orphanet to gather detailed information. This will contribute to raising awareness of rare diseases and facilitating access to the most recent information on clinical trials in the field of rare diseases. This collaboration strengthens Orphanet's position as a reference database in the field of rare diseases by providing an exhaustive clinical trials registry, and will assure that ICTRP users can easily identify clinical trials for rare diseases (http://apps.who.int/trialsearch/).

5.2.6. COLLABORATION WITH SNOMED INTERNATONAL

A collaboration with SNOMED International is ongoing in order to include RD lacking in SNOMED-CT, and to provide alignments between ORPHA codes and SNOMED-CT terms. It will help with the identification of patients with RD in health information systems in countries having adopted SNOMED-CT. The alignment file will be available in 2020, distributed alongside SNOMED CT by SNOMED, and by Orphanet via Orphadata.

5.2.7. COLLABORATION WITH NIH-NCATS' GENETIC AND RARE DISEASE INFORMATION CENTER

A partnership was established between Orphanet and the Genetic and Rare Disease Information Center (NIH-NCATS) in 2016. One of the aims of this partnership was to mutualise efforts so as to provide the audiences of both sites with the most complete and up-to-date information on rare diseases. In a first step, the Orphanet and GARD nomenclatures were aligned, so as to allow cross-referencing between the two resources. These alignments can be visualised on the disease identity card on the Orphanet website, and are also included in the nomenclature and cross-references file available on Orphadata.

5.3. Catalogue of services

5.3.4. Collaboration with RD-Connect

A partnership has been established between Orphanet and RD-Connect. The latter is a European funded project (2012-2018) aimed at creating an integrated platform connecting databases, registries, biobanks and clinical bioinformatics for rare disease research. This partnership is focused on sharing data on biobanks and registries between Orphanet and RD-Connect in order to enrich both databases. RD-Connect as a project ended in 2018, and the scope of the collaboration continues currently in the framework of the EJP-RD.

5.3.5. Portail Romand des Maladies Rares

A collaboration is in place with the Swiss 'Portail Romand des maladies rares' (www.infomaladiesrares.ch) in order to improve the visibility of expert centres on rare diseases registered in Orphanet in Romandy.

5.4. Scientific collaborations and partnerships

5.4.4. Partnership with International Union of Basic and Clinical Pharmacology (IUPHAR)/ Guide to Pharmacology

A partnership was established with **IUPHAR/Guide to Pharmacology** at the end of 2011 to cross-link Orphanet with the IUPHAR/Guide to Pharmacology database and the cross-linking is ongoing. This project is being expanded in order to take into account the evolutions of the IUPHAR database.

5.4.5. Partnership with The International Rare Diseases Research Consortium

IRDiRC was launched in April 2011 to foster international collaborations in rare disease research. IRDiRC united researchers and organisations investing in rare disease research in order to achieve two main objectives, namely to deliver 200 new therapies for rare diseases and the means to diagnose most rare diseases by the year 2020. In 2017, such considerable progress was made towards these goals that three new goals were adopted, namely: all patients coming to medical attention with a suspected rare disease will be diagnosed within one year if their disorder is known in the medical literature, 1000 new therapies for rare diseases will be approved, and methodologies will be developed to assess the impact of diagnoses and therapies on rare disease patients.
Orphanet collects data on research-related activities funded by IRDiRC members, which are research funding agencies. This requires the expansion of data coverage to new countries such as the United States and Japan.

Orphanet also provides regular data analysis for the following indicators on the IRDiRC website: number of new RD on a monthly basis, number of genes linked to RD, number of RD for which there is a genetic test available and number of medicinal products with an orphan designation and marketing approval for the treatment of RD in the US and/or Europe.
Orphanet hosted the IRDiRC Scientific Secretariat from 2011 to 2018 under the Support-IRDiRC contract. The scientific secretarit was then transferred to another service at the Inserm (ITMO GGB), in the framework of the European Joint Programme on Rare Diseases (EJP-RD). In the context of this new organisation, Orphanet remains responsible for the curation of the database of research projects and clinical trials, as well as for the production of indicators.

5.4.6. PARTNERSHIP WITH RARECARENET & JOINT ACTION ON RARE CANCERS (JARC)

Since mid-2013, Orphanet has had a partnership with **RareCareNet**, providing them with information on expert centres and rare cancer patient organisations. RareCareNet in return provides Orphanet with information on the epidemiology of rare cancers, and a common effort is currently performed in order to agree on the classification of rare cancers. This work continues in the context of the EU Joint Action on Rare Cancers, which ran from 2016 to 2019 (www.jointactionrarecancers.eu). This Joint Action aimed to integrate and maximise efforts of the European Union (EU) Commission, EU Member States and all stakeholders to advance quality of care and research on rare cancers. Orphanet was involved in a number of the work packages, in particular on issues such as the collection of epidemiological data of rare cancers, information on expert centres for rare cancers, clinical practice guidelines, and nomenclature and classifications. Cross-talk with the European Joint Action on Rare Diseases, RD-Action, coordinated by Orphanet, was also been assured. The Joint Action issued ten recommendations for the future of rare cancers in its "Rare Cancer Agenda 2030".

5.4.7. COLLABORATION WITH THE EUROPEAN BIOINFORMATICS INSTITUTE

Collaboration was established with the **EMBL - EBI** at the end of 2011 to cross-link Orphanet's database with their genomic and their biological pathway data resources (ensembl and Reactome) and is currently ongoing, with cross-references being regularly updated.

Orphanet and EMBL-EBI have jointly developed the **Orphanet Rare Disease Ontology** (ORDO) and in 2014, a new version of this ontology was launched (ORDO 2.0) in collaboration with the EBI; subsequent versions have been produced by Orphanet. The Ontology is updated twice a year.

5.4.8. COLLABORATION WITH THE FRENCH INSTITUTE OF BIOINFORMATICS – ELIXIR FRANCE

Orphanet is the French Institute of Bioinformatics' 30th platform. The IFB is a national bioinformatics infrastructure bringing together platforms from the main players in research in France: CNRS, INRA, INRIA, CEA and the INSERM, as well as the Curie and Pasteur Institutes and French universities. At the moment, 32 platforms are members, grouped into six regional centres across France. The IFB's primary mission is to provide the basic services and resources in the field

of bioinformatics for scientists and engineers working in life sciences. Notably, IFB is the French node of the European research infrastructure ELIXIR.

ELIXIR is a distributed infrastructure for life-science information, uniting Europe's leading life science organisations in managing and safeguarding the massive amounts of data being generated every day by publicly funded research. ELIXIR coordinates and develops life science resources across Europe so that researchers can more easily find, analyse and share data, exchange expertise, and implement best practices. This makes it possible for them to gain greater insights into how living organisms work. As a platform of the IFB, Orphanet is also part of this European research infrastructure, offering data and a bio-ontology of rare diseases to advance research in this field.

Orphanet has participated in the ELIXIR pilot use case on rare diseases in the context of the EXCELERATE project: in 2016 Orphanet contributed to this use case by producing a report on the role of Orphanet, in particular the Orphanet nomenclature, as a vector for interoperability in the field of rare diseases. This project aims to build an ELIXIR registry of data resources and analysis tools that are critical for the development of rare disease research, implement a technical framework for the comparison and standardisation of services useful for rare disease communities, and collaborate with rare-disease communities in organising and running their training courses, workshops and jamborees. One of the principal goals of ELIXIR is to work towards the sustainability of resources and tools such as those offered by Orphanet, which makes this a strategic step in the right direction for Orphanet's future. In this context, Orphanet and ORDO are already cited in the ELIXIR Biosharing platform, a curated, informative and educational resource on inter-related data standards, databases, and policies in the life, environmental and biomedical sciences, and at the start of 2019 the free-access datasets from the Orphanet database provided on Orphadata were designated as an ELIXIR Core Data Resource. The knowledge bases singled out as Core Resources, to which Orphanet now belongs, work as « conceptual authorities » with a clear role in the standardisation of evolving concepts. Orphanet will play this role for rare diseases within the scientific community. The Core Data Resources are also at the core of ELIXIR's long-term sustainability strategy as a European infrastructure for information and life sciences data. ELIXIR aims to ensure that these resources are available long-term and that the life-cycles of these resources are managed such that they support the scientific needs of the life-sciences, including biological research. As a Core Data Resource Orphanet will pursue its work to develop and maintain quality standards for its scientific data and will move forward to adopt FAIR data principles.

5.4.9. Collaboration with NIH-NCATS Genetic and Rare Disease Information Center (GARD)

A partnership between Orphanet and the Genetic and Rare Disease Information Center (NIH-NCATS) was established in 2016. The aim of this partnership is to mutualise efforts so as to provide the audiences of both sites with the most complete and up-to-date information on rare diseases. In a first step, the Orphanet and GARD nomenclatures were aligned, so as to allow cross-referencing between the two resources. In a second step, summary texts from Orphanet (along with a link to the relevant Orphanet disease page and the Orphanet logo) have been included in GARD for the diseases for which GARD does not have a text. This cross-Atlantic partnership will improve the

visibility of Orphanet in the United States and is just one of the ongoing efforts to integrate the Orphanet nomenclature, in particular, into the different rare-disease related resources maintained by the NIH (e.g. UMLS, ClinVar, MedGen, GTR).

6. Funding

Orphanet's budget was approximately 2.97 million Euros in 2019, originating from 8 different contracts for the core activity funding and from various other contracts in some of the participating countries (Figure 27).

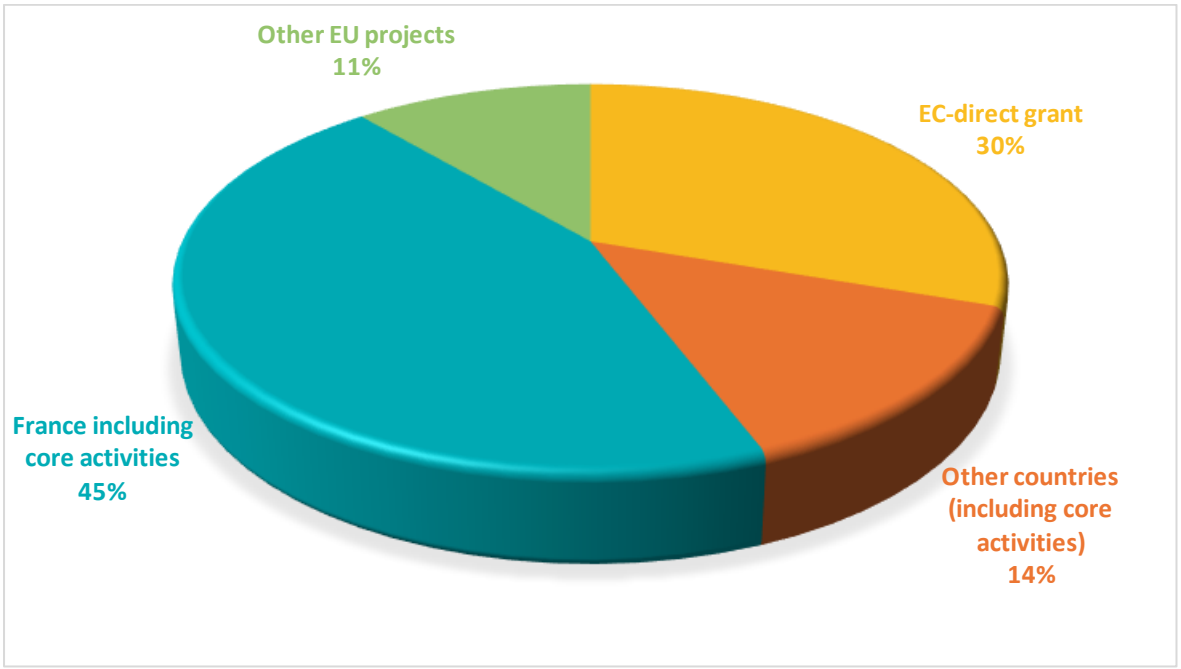


Figure 27 Orphanet's global budget 2019

6.1 Orphanet's core activity funding

Orphanet's core activities include the infrastructure, the coordination activities (management, management tools, quality control, rare disease inventory, classifications, scientific annotations and production of the encyclopaedia, SMQ) and communication. It excludes the collection of data on expert resources in the participating countries.

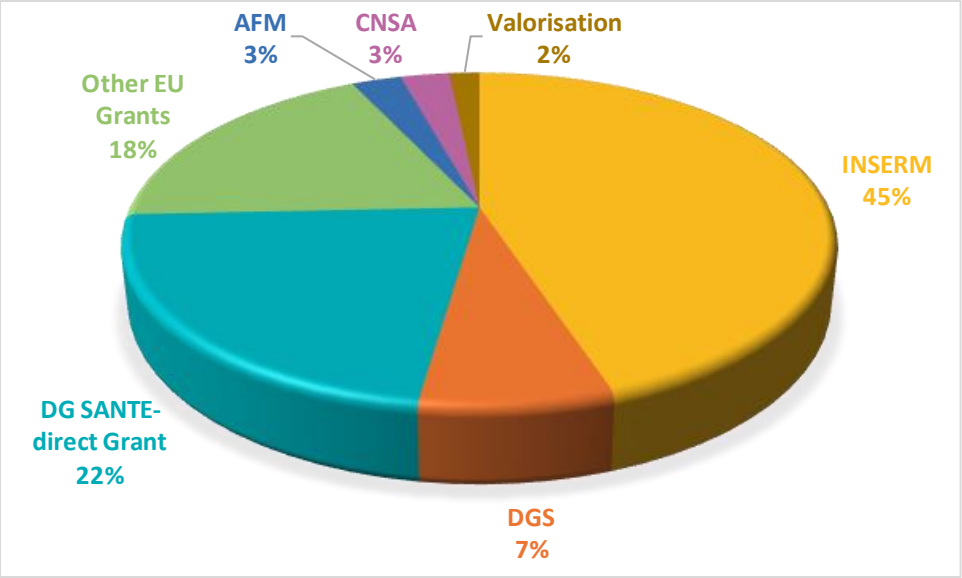


Figure 28 Orphanet core activities funding 2019

This budget (approx 1.78 million Euros) excludes the costs of infrastructure (office space) which are essentially covered by INSERM (Figure28).

6.2.4. EUROPEAN FUNDING

The European Commission funds the inventory of rare diseases, the encyclopaedia, and the collection of data on expert services in European countries (since 2000, DG Health and Consumers Protection grant N°s S12.305098; S12.324970; SPC.2002269-2003220, 2006119, 20091215 and since 2004, DG Research and Innovation grant N°s LSSM-CT-2004-503246; LSHB-CT-2004-512148; LSHB-CT-2006-018933; Health-F2-2008-201230, HEALTH-F2-2009-223355, DG Santé grant 20133305-Operating Grant Orphanet). In 2014, the DG Santé grant 20102206 (Orphanet Europe Joint Action) was extended for one year without additional funding. In 2015, Orphanet participated in the ECRIN Integrating Activity (ECRIN-IA, 284395), funded by the European Union Framework Program 7. From 2016 Orphanet coordinated the HIPBI-RD project (E-Rare3 ERA-NET joint call). Orphanet was also involved in the ELIXIR-EXCELERATE Project (H2020 Project N° 676559). From 2018, Orphanet participates the Rare2030 participatory foresight project (DG SANTE PP-1-2-2018-Rare 2030), in the H2020 project Solve-RD (N° 779257), and is co-pillar leader in the Horizon 2020 European Joint Programme Co-Fund on Rare Diseases (N°825575)

Orphanet network was most recently funded by the DG Santé grant RD-ACTION Joint Action 677024 (2015- May 2018) and the Orphanet Direct Grant 831390 (2018-2020).

6.2.5. OTHER CURRENT FINANCIAL PARTNERSHIPS FOR CORE ACTIVITY FUNDING

Instituts thématiques Inserm Institut national de la santé et de la recherche médicale	The "Institut National de la Santé et de la Recherche Médicale" finances Orphanet's core activities. *Inserm Transfert* is in charge of supporting Orphanet in providing access to its data to Industry and in providing advice concerning intellectual property.
Liberté • Égalité • Fraternité RÉPUBLIQUE FRANÇAISE MINISTÈRE DES AFFAIRES SOCIALES ET DE LA SANTÉ	The French Directorate General for Health (DGS) finances Orphanet's core activities.
Co-funded by the Health Programme of the European Union	The European Commission finances the database of diseases and the encyclopaedia in English, as well as the coordination, communication (including OrphaNews International) and IT of the project through the EU Health Programme.
AFMTÉLÉTHON INNOVER POUR GUÉRIR	The "Association Française contre les Myopathies" finances OrphaNews France and International, the scientific literature survey, as well as data collection on clinical trials.

Table 9 Other current financial partnerships for core activity funding

6.2.6. CURRENT NON-FINANCIAL PARTNERSHIPS FOR CORE ACTIVITY

Non-financial partners are those that provide services in kind and/or share their expertise for Orphanet core activities.

World Health Organization	Collaboration with the World Health Organisation (WHO) in the process of revising the International Classification of Diseases, and with the International Clinical Trials Registration Platform (ICTRP) in order to improve the visibility of RD clinical trials.
hpo	HPO and Orphanet collaborate on disease-phenotype annotations.
GENATLAS	Cross-referencing with Genatlas which collaborates in updating the data on genes involved in rare diseases.
UniProt	Cross-referencing with UniProt KB which collaborates in updating the data on genes linked to proteins involved in rare diseases.
HGNC HUGO Gene Nomenclature Committee	Cross-referencing with HGNC which collaborates in updating the data on genes involved in rare diseases.
OMIM® Online Mendelian Inheritance in Man®	Cross-referencing with OMIM (The Online Mendelian Inheritance in Man).

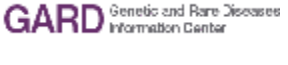
	Cross-referencing with Reactome.
	Cross-referencing with Ensembl.
	Cross-referencing with The International Union of Basic and Clinical Pharmacology DataBase (IUPHAR-DB)/ Guide to Pharmacology.
	The LOVD (Leiden Open Variation Database) platform includes links to Orphanet's gene pages, and Orphanet cross-links to LOVD from gene pages.
	EuroGentest financed the creation of a thesaurus of clinical signs to harmonise international phenotype nomenclatures. EuroGentest collaborates with Orphanet in the field of quality management of medical laboratories.
	Orphanet and RD-Connect shared information on biobanks and patient registries. Orphanet provides RD-Connect with the nomenclature of RD.
	Orphanet and EMBL-EBI have developed ORDO and in 2014, a new version of this ontology was launched (ORDO 2.0).
	Collaboration with Snomed International is ongoing in order to include RD lacking in SNOMED-CT, and to provide alignments between ORPHA codes and SNOMED-CT terms
  	Orphanet is the 30th bioinformatics structure of the French Institute of Bioinfomatics, which is the French node of ELIXIR. Orphanet participates in the ELIXIR Use Case on Rare Diseases in the framework of the H2020 EU Project ELIXIR-EXCELERATE project N°676559. Orphadata is an ELIXIR Core Data Resource.
	Orphanet works with the Genetic and Rare Disease (GARD) Information Center, hosted by NIH-NCATS, in order to align their nomenclatures and improve the provision of textual information on rare diseases.

Table 10 Current non-financial partnerships for core activity

6.2. Financial and non-financial partnerships for national activities

Orphanet's national activities are also supported by national institutions, specific contracts and/or contributions in kind. In European countries, data collection at the national level is also supported by the European Commission. Globally this budget reaches 1.19 million Euros. Please refer to Figure 3 for an overview of funding of national activities.

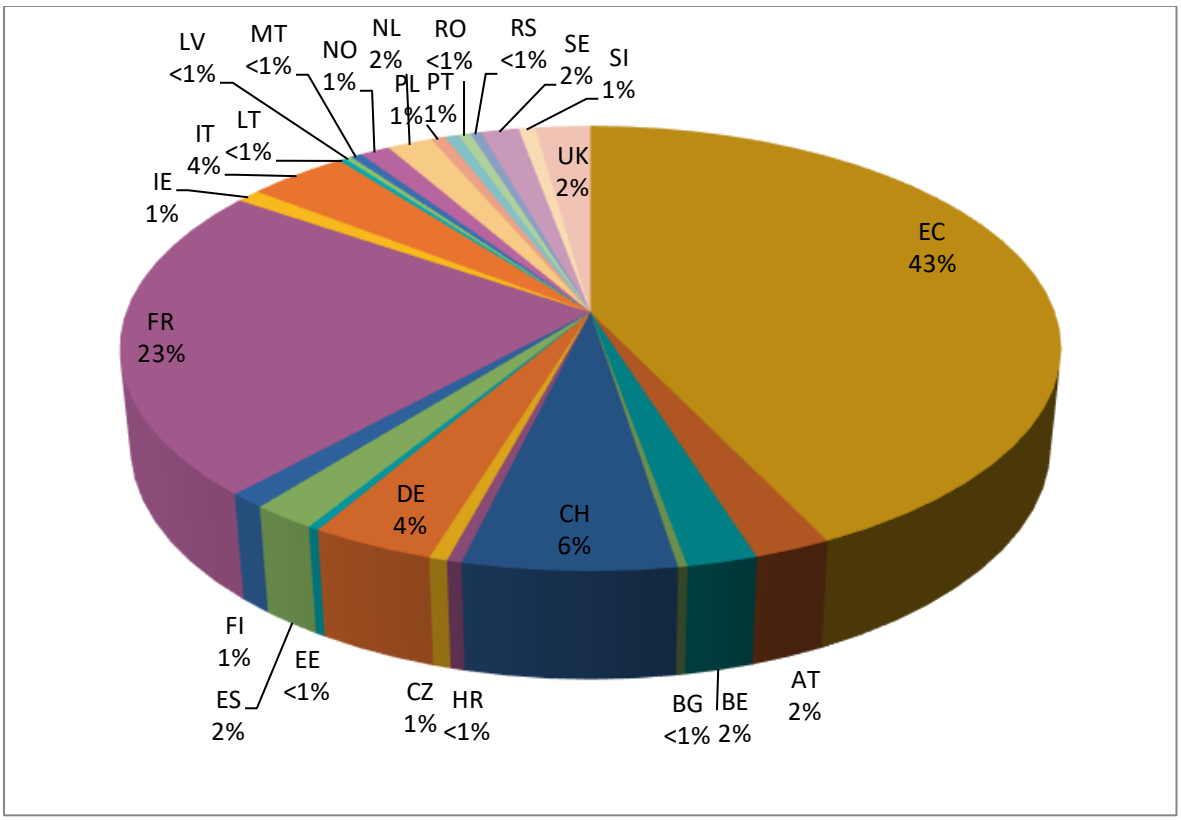


Figure 29 Funding sources for national activities in 2019

6.2.7. PARTNERSHIPS PROVIDING FUNDING FOR NATIONAL ACTIVITIES

Institutional partners host Orphanet's national team activities and contribute to the project by allocating a budget and the time of some of their professionals.

AUSTRIA	
MEDIZINISCHE UNIVERSITÄT WIEN	The Medical University of Vienna is a beneficiary of Orphanet Network 831390 (until 2018: RD-ACTION 677024) and hosts Orphanet Austria since 2004. It further provides part-time funding (in kind) for the work of the country coordinator.
Bundesministerium Arbeit, Soziales, Gesundheit und Konsumentenschutz	The Austrian Ministry of Labour, Social Affairs, Health and Consumer Protection has provided funding to Orphanet Network 831390 from 2018 onwards.

BELGIUM	
	Sciensano's service "Health Services Research" hosts the Orphanet Belgium team. At Sciensano, there is internal collaboration with Infectious Diseases Service to validate data on reference laboratories and screening tests for infectious disease.
	The Federal Public Service Health, Food Chain Safety and Environment has been a beneficiary in RD-ACTION 677024 (financial support from the European Health Program).
	The National Institute of Health and Disability Insurance (NIHDI) finances Sciensano to participate in the Orphanet project. The National Institute of Health and Disability Insurance provides information on the recognized reference centers working under a revalidation convention.
BULGARIA	
	The Bulgarian Association for Promotion of Education and Science (BAPES) hosts Orphanet Bulgaria's activities.
CANADA	
	The Canadian Institute of Health Research is the host institution of Orphanet Canada, finances a position for an information scientist and provides additional administrative support for the project.
	The Québec "Ministère de la Santé et des Services sociaux" finances a project manager position in Quebec and some administrative support.
	The Department of Medical Genetics of the McGill University Health Centre is the host institution of Orphanet-Quebec and provides the medical coordinator.
	Le "Regroupement québécois des maladies orphelines" provides the project coordinator and administrative support.
	Pfizer Canada finances different Orphanet-Canada outreach events (Café Scientifique, Booth, Presentation) and helps distribute Orphanet-Canada information through their network.
	Care4Rare finances a part-time position for an information scientist.
CROATIA	
	Rare Diseases Croatia was a beneficiary in RD-ACTION 677024.

CZECH REPUBLIC	
CHARLES UNIVERSITY	The Charles University Prague - 2nd School of Medicine was a beneficiary in RD-ACTION 677024.
česká asociace pro vzácná onemocnění	The Czech Association of rare diseases finances the activity of the Czech team since April 2012.
SPOLEČNOST LÉKAŘSKÉ GENETIKY ČLS JEP	The Czech Medical Genetics and Genomics Society (www.slg.cz) helps Orphanet CZ in the collection of information on DNA diagnostic laboratories in the country, information on rare diseases clinics - dysmorphology, genetic counseling and information on patient support groups. Genetics professionals work with the overarching Czech rare disease patient association (www.vzacna-onemocneni.cz) which represents more than 30 individual associations. They have a joint partnership for the development of the Czech National Plans for rare diseases following the Czech National Strategy from 2010. The first, second and third Czech National Plans (2012-2014, 2015-2017 and 2018-2020) have been developed under the auspices of the Ministry of Health - Department of Medical Services and in collaboration with the National Coordination Centre for Rare Diseases at UH Motol (www.nkcvo.cz).
ÚZIS ČR	CZ Orphanet team is collaborating together with the Institute of Health Information and Statistics of the Czech Republic on the RD-Code project.
ESTONIA	
TARTU ÜLIKOOL UNIVERSITAS TARTUENSIS 1632	The University of Tartu was a beneficiary in RD-ACTION 677024.
FINLAND	
RINNEKOTI -Säätiö	Rinnekoti Foundation was a beneficiary in RD-ACTION 677024.
FRANCE	
Liberté • Égalité • Fraternité RÉPUBLIQUE FRANÇAISE MINISTÈRE DES AFFAIRES SOCIALES ET DE LA SANTÉ	The French Directorate General for Health (DGS) finances the collection of data in France for the expert resources catalogue.
AFMTÉLÉTHON INNOVER POUR GUÉRIR	The “Association Française contre les Myopathies“ finances OrphaNews France.
FONDATION Groupama vaincre les maladies rares	The “Fondation Groupama pour la santé” contributes to the development of the Orphanet website and the mobile application.

	The “Agence de la biomédecine” finances the monitoring of the list of laboratories, the creation of tools for collecting, managing and monitoring annual activity, as well as funding the compilation of data collected in France.
	The ”Caisse nationale de solidarité pour l'autonomie” supports the annotation of rare diseases with the International Classification of Functioning, Disability and Health (ICF) and the Orphanet encyclopaedia of disabilities.
GERMANY	
	The Medical School of Hanover (MHH) supports data collection.
	Förderverein Orphanet Deutschland e.V., a charity founded by Orphanet Germany to support national activities, provides funding to the team.
	Leadiant GmbH, a pharmaceutical company, provided funding to support national activities 2018.
	Merck Family Foundation, a charitable limited company founded by the Merck Group, is supporting national data collection.
	Pfizer Pharma GmbH, a pharmaceutical company, provided funding to support national activities 2018.
	B.Braun Stiftung, a charity, is supporting the overall knowledge of the database by funding national training sessions for teaching experts on how to use the Orphanet database.
	MVZ Dr. Eberhard & Partner Dortmund (ÜBAG), a private company, provided funding to support national activities 2018.
	Selbsthilfe primäre Hyperoxalurie e.V., a patient association, donated money to support national activities in 2018.
HUNGARY	
	Orszagos tisztifoorvosi hivatal - OTH is a beneficiary in RD-ACTION 677024.
	Semmelweiss Egyetem is a beneficiary in RD-ACTION 677024.

ITALY	
	The Italian Health Ministry finances Orphanet-Italy activities through current research funding.
	The Bambino Gesù Children's Hospital is a beneficiary in RD-ACTION 677024.
	Genzyme, a Sanofi Company, finances OrphaNews Italia.
IRELAND	
	The Health Service Executive provides co-funding for Orphanet Ireland staff.
JAPAN	
	Japan Agency for Medical Research and Development (AMED) provides funding to the Orphanet Japan's core activities.
LATVIA	
	"Centre for Disease Prevention and Control of Latvia" (Slimību profilakses un kontroles centrs) was a beneficiary in RD-ACTION 677024.
LITHUANIA	
	The Vilnius University Hospital, "Santariškių Klinikos" Centre for Medical Genetics is a beneficiary in RD-ACTION 677024.
NETHERLANDS	
	The LUMC hosts Orphanet Netherlands and co-funds the work of project manager Dr Petra van Overveld and Prof van Ommen.
	The Centre for Medical Systems Biology is a joint activity of six institutions in the Netherlands, led by LUMC and including VUMC. The CMSB co-funds the rare disease

	work of project manager Dr Petra van Overveld and of the chair of the Dutch Scientific Advisory Board, Prof Cornel.
NFU	The Dutch Federation of University Medical Centers (NFU) funds the work of Dr Judith Carlier and co-funds Dr. Wendy van Zelst-Stams.
Radboudumc	The Radboudumc contributes to the project by allocating time of Dr. Wendy van Zelst-Stams.
NORWAY	
Helsedirektoratet	The Norwegian Directorate of Health hosts part of Orphanet Norway's activities and contributes to the project by allocating the time of some professionals.
Norwegian National Advisory Unit on RARE DISORDERS	The Norwegian National Advisory Unit for Rare diseases hosts part of Orphanet Norway's activities and contributes to the project by allocating the time of some professionals.
POLAND	
	The "Instytut Pomnik Centrum Zdrowia Dziecka" (Children's Memorial Health Institute) supports Orphanet Poland in all activities inside and outside the institution; e.g. organising conferences for professionals, parents and media; discussions on rare disease with all stakeholders; and improving access to orphan drugs.
Ministerstwo Zdrowia	The Polish Ministry of Health contributes to the translation of the Orphanet encyclopaedia in Polish and contributes to translation of the Orphanet international website.
PORTUGAL	
IBMC	IBMC - Institute for Molecular and Cell Biology hosted Orphanet-Portugal from 2009 to June 2015.
U.PORTO INSTITUTO DE CIÊNCIAS BIOMÉDICAS ABEL SALAZAR UNIVERSIDADE DO PORTO	ICBAS - Instituto de Ciências Biomédicas Abel Salazar, the Biomedical Sciences Institute at the University of Porto, funded Orphanet Portugal activities from 2009 till June 2015.
Direcção-Geral da Saúde www.dgs.pt Ministério da Saúde	DGS - The Directorate-General of Health, at the Portuguese Ministry of Health, is beneficiary in RD-ACTION 677024 and hosts the Orphanet Portugal team since June 2015.

ROMANIA	
	The “Universitatea de Medicina si Farmacie “Gr.T.Popa” Iasi“ was a beneficiary in RD-ACTION 677024.
SLOVAKIA	
	CUMS (UNIVERZITA KOMENSKEHO V BRATISLAVE) was a beneficiary in RD-ACTION 677024.
SLOVENIA	
	The University Medical Centre Ljubljana was a beneficiary in RD-ACTION 677024.
SPAIN	
	The Centre for Biomedical Network Research (CIBER), Area on Rare Diseases (formerly known as CIBERER), has been the partner for Orphanet in Spain since April 2010. CIBER (Institute of Health Carlos III, Ministry of Economy, Industry and Competitiveness) finances the salary of one full-time information scientist and 75% of the salary of a full-time project manager as well as the main activities of the Spanish team. CIBER financed in 2019the different expenses associated to Orphanet Spain activities, such as the production of fliers and attending meetings where the Orphanet team’s activities were disseminated.
SWEDEN	
	Karolinska University Hospital, Department of Clinical Genetics, Centre for Rare Disease was a beneficiary in RD-Action 677024.
SWITZERLAND	
	University Hospitals of Geneva is the host institution of Orphanet Switzerland and finances a part-time position for the coordinator and provides some administrative support for the project.
	The National Coordination of Rare Diseases (kosek) signed a cooperation agreement with Orphanet Switzerland in May 2019, allocating a budget for the recruitment of a project manager.

TURKEY	
AiFD	The Association of Research-Based Pharmaceutical Companies gives non-restricted support for the Turkish translation of the Orphanet webpage and the documents. They supported the creation of the Orphanet-Turkey website and help Orphanet Turkey to prepare and print leaflets for health care professionals and the general public.
UNITED KINGDOM	
Public Health England	The National Congenital Anomaly and Rare Disease Reg. Service (Public Health England) hosts Orphanet UK activities and contributes to the project by allocating the time of some professionals since August 2014.

Table 11 Partnerships providing funding for national activities

6.2.8. INSTITUTIONAL PARTNERSHIPS PROVIDING SERVICES IN KIND FOR NATIONAL ACTIVITIES

All the Institutions hosting the national Orphanet teams provide their office space, all the necessary supplies to run the team activities and allocate the time of some of their professionals.

ARMENIA	
	The Center of Medical Genetics and Primary Health Care hosts Orphanet-Armenia's activities and contributes to the project by allocating the time of some professionals.
AUSTRALIA	
Government of Western Australia Department of Health	The Office of Population Health Genomics, Department of Health, Western Australia hosts Orphanet Australia's activities and contributes to the project by allocating the time of some professionals.
CROATIA	
	The Zagreb Children's Hospital contributes to the project by allocating the time of the country coordinator
IRELAND	
Mater Hospital Dublin	The Mater Misericordiae University Hospital (MMUH) supports Orphanet Ireland by housing the National Rare Disease Office and Orphanet Ireland. The MMUH provides Clinical Geneticist hours to Orphanet Ireland, and provides Human Resources, Administrative, and IT support.

ISRAEL	
	Sheba Medical Center, Tel Hashomer of Israel hosts Orphanet Israel's activities and contributes to the project by allocating the time of some professionals since June 2014.
JAPAN	
	Foundation for Biomedical Research and Innovation at Kobe (FBRI) hosts the Orphanet Japan's activities and contributes to the project by allocating the time of some professionals.
MOROCCO	
	The National Institute of Hygiene hosts Orphanet Morocco's activities and contributes to the project by allocating the time of some professionals.
SERBIA	
	The Institute of Molecular Genetics and Genetic Engineering, University of Belgrade, hosts Orphanet Serbia's activities and contributes to the project by allocating the time of some professionals.
SPAIN	
	The Príncipe Felipe Research Center (CIPF) hosts Orphanet Spain's activities.
TURKEY	
	The Istanbul University hosts Orphanet Turkey's activities and contributes to the project by allocating the time of some professionals.

Table 12 Institutional partnerships providing services in kind for national activities

6.2.9. NON-FINANCIAL PARTNERSHIPS FOR NATIONAL ACTIVITIES

BELGIUM	
	A partnership exists with RaDiOrg.be, a EURORDIS member, which continued to play a role in the validation of data on Belgian patient organisations in Orphanet.

	The Orphanet team hosted by the Scientific Institute of Public Health collaborates internally with the Service "Infectious Diseases in the general population" to validate data on reference laboratories and tests for infectious diseases.
	The College of Human Genetics in Belgium, which represents the 8 recognized genetic centres, is collaborating with the Orphanet team to improve and simplify the process of registration and update of data on genetic testing activities in the Orphanet database.
	The National Institute of Health and Disability Insurance provides information on the recognized reference centres that work under a convention.
BULGARIA	
	The Association of Medical Students in Plovdiv has been actively promoting Orphanet use in its community. Together, BAPES and AMS-Plovdiv have organised a series of workshops, dedicated to Orphanet.
	The Bulgarian National Alliance of People with Rare Diseases has partnered with BAPES in order to promote Orphanet among rare disease patients in Bulgaria, as well as to list the Bulgarian patient associations on the Orphanet database.
CZECH REPUBLIC	
	The Ministry of Health of the Czech Republic officially supports Orphanet.
CROATIA	
	Rare Diseases Croatia cooperates with its member organisations and with the Medical Faculty of the University of Zagreb.
ESTONIA	
	The Ministry of Social Affairs of Estonia officially supports Orphanet.
FINLAND	
	The Ministry of Social Affairs and Health of Finland officially supports Orphanet.
	Terveysportti (www.terveysportti.fi) is a web service for medical professionals published by Duodecim Medical Publications Ltd, which is owned by the Finnish Medical Society Duodecim. Orphanet was included in Terveysportti's searches concerning the 300 "most common rare diseases". As a result, Orphanet will have a higher profile among the Finnish health care professionals.

FRANCE	
	The Ministry of Health and the Ministry of Research officially supports Orphanet in the framework of the French National Plan for Rare Diseases from 2018
	"Air France" provides a quota of airline tickets for patients to travel to medical experts or for experts to travel to patients with rare diseases. Orphanet provides expertise on the merits of applications when needed.
	Orphanet has delegated to "Maladies Rares Info Services", the French helpline for information on rare diseases - 0156538136, the role of replying to unsolicited electronic messages received by Orphanet.
GERMANY	
	The "Allianz Chronischer Seltener Erkrankungen e.V." (ACHSE) works together with Orphanet Germany on information services for patients.
	The "Kindernetzwerk e.V. - für Kinder, Jugendliche und (junge) Erwachsene mit chronischen Krankheiten und Behinderungen" provides data on associations in Germany.
	The "Deutsche Gesellschaft für Humangenetik e.V." supports Orphanet by supplying the German team with addresses and information on laboratories and diagnostics.
	Nationale Kontakt- und Informationsstelle zur Anregung und Unterstützung von Selbsthilfegruppen (NAKOS) officially supports Orphanet.
	The AWMF (Association of the Scientific Medical Societies in Germany) cooperates with Orphanet DE by supplying the web links of their clinical practice guidelines to the Orphanet encyclopaedia.
	DIMDI cooperates with Orphanet DE in including the disease terms from the German Orphanet nomenclature into the alpha-code of the ICD-10GM.

HUNGARY	
	The State Secretary of Health within the Ministry of Human Resources officially supports Orphanet.
IRELAND	
	The Department of Health officially supports Orphanet and provides governance of Orphanet Ireland.
	The National Rare Disease Office (NRDO) hosts the Orphanet Ireland team. Orphanet is the main source of rare disease resource information for the NRDO Information Line.
	The National Clinical Programme for Rare Diseases (which is a partnership between the Royal College of Physicians Ireland and the HSE provides clinical oversight for Orphanet Ireland through its Clinical Advisory Group.'
	'Rare Diseases Ireland (RDI), the Medical Research Charities Group (MRCG) and the Irish Platform for Patient Organisation, Science and Industry (IPPOSI) together form the Irish National Alliance for Rare Disease. They collaborate in the promotion of Orphanet and rare disease activities in Ireland.
ITALY	
	The "Istituto Superiore di Sanità" officially supports Orphanet.
	Telethon collaborates with Orphanet for the collection of data concerning research projects.
	Uniamo, the Italian Federation of support groups on rare diseases, collaborates with Orphanet in the organisation and promotion of events dedicated to rare diseases, in order to increase public awareness on this particular issue.
	Netgene collaborates with Orphanet for the diffusion of information on rare diseases.
	Farmindustria promotes Orphanet publications.
	Osservatorio Malattie Rare (O.Ma.R.) collaborates with Orphanet in disseminating information rare diseases and the promotion of events.

	The Italian Inter-regional Technical Board for Rare Disorders collaborates with Orphanet in collecting data concerning the Centres of Reference officially recognised in Italy.
LATVIA	
Ministry of Health of the Republic of Latvia	The Ministry of Health of the Republic of Latvia officially supports Orphanet.
	The Rare Diseases Society in Latvia aims to promote equal rights and opportunities for patients with rare diseases.
PALĪDZĒSIM.LV	Palidzesim.lv is a non-governmental organisation in Latvia which financially supports children and families to confirm a diagnosis of a rare disease by sending patients or medical samples abroad.
LITHUANIA	
MINISTRY OF HEALTH OF THE REPUBLIC OF LITHUANIA	The Ministry of Health of the Republic of Lithuania officially supports Orphanet.
NETHERLANDS	
Ministry of Health, Welfare and Sport	The Ministry of Health, Welfare and Sport of the Netherlands officially supports Orphanet Netherlands.
erfocentrum	The Erfocentrum provides information to the general public on mainly rare, genetic disorders. A collaboration was established to increase the number of Dutch rare disease summary texts available on both the Orphanet and Erfocentrum websites. In addition the Erfocentrum displays the list of Dutch designated rare disease expert centers for the general public.
VSOP	The VSOP (Dutch national patient *umbrella organization* for rare and genetic disorders) provides information regarding patient organisations dedicated to rare diseases and participates in the designation of Dutch centers of expertise for rare diseases.
BBMRI.nl Biobanking and BioMolecular resources Research Infrastructure The Netherlands	A collaboration was established with BBMRI-NL (Biobanking and BioMolecular resources Research Infrastructure The Netherlands) to increase the registration of Dutch biobanks with data and samples on rare diseases in both the Orphanet database and the BBMRI-NL catalogue.
POLAND	
PKU RD	The patient organisation, Ars Vivendi, provides patients and parents with information about Orphanet services and cooperates with Orphanet Poland.

	The Polish Association of Patients with Muchopolysaccharidosis and Rare Diseases provides patients and parents with information about Orphanet services and cooperates with Orphanet Poland.
ROMANIA	
Romanian Ministry of Health	The Ministry of Health collaborates with Orphanet Romania in updating data on the Romanian medical system. It officially supports Orphanet.
	Orphanet Romania collaborates with the Romanian Medical Association in updating data on health professionals.
SRGM Societatea Romana de Genetica Medicala	Orphanet Romania collaborates with the Romanian Society of Medical Genetics to set up programs for the development of a national network of diagnosis, investigation and prevention in Centres of Medical Genetics and to promote collaboration with associations of people with genetic/malformative diseases.
ASOCIATIA PRADER WILLI DIN ROMÂNIA	Orphanet Romania collaborates with the Romanian Prader Willi Association in order to bring together the efforts of patients, specialists and families to ensure a better life for all people with genetic diseases.
SLOVAKIA	
	The Ministry of Health of the Slovak Republic officially supports Orphanet.
SLOVENIA	
REPUBLIC OF SLOVENIA MINISTRY OF HEALTH	The Ministry of Health of Slovenia officially supports Orphanet.
SPAIN	
GOBIERNO DE ESPAÑA MINISTERIO DE SANIDAD, SERVICIOS SOCIALES E IGUALDAD	The Spanish Ministry of Health, Consumption and Social Welfare- Office for Health Planning and Quality officially supports Orphanet.
Fondo de Investigación en Salud Instituto de Salud Carlos III	The Institute of Health Carlos III (ISCIII) provides Orphanet with data on national research projects funded through the Health Strategic Action Calls.
entidad de utilidad pública feder FEDERACIÓN ESPAÑOLA DE ENFERMEDADES RARAS	The Spanish Federation for Rare Diseases (FEDER collaborates with Orphanet with the updating of Patient Organizations' information, the revision of some texts included in the disability factsheets and articles for the general public, and Orphanet resources dissemination.
SWEDEN	
REGERINGSKANSLIET Ministry of Health and Social Affairs, Sweden	The Ministry of Health and Social Affairs of Sweden officially supports Orphanet.

SWITZERLAND	
	The Health On the Net Foundation owns the domain wwww.orphanet.ch and supports the technical aspect of the Orphanet Switzerland online forms to collect data.
	ProRaris, the Swiss Alliance of patients with rare diseases has established a close collaboration with Orphanet Switzerland in order to identify relevant information services for patients and professionals and in the organisation and promotion of events dedicated to rare diseases, in order to increase public awareness on this particular issue.
	Orphanet Switzerland is member of the « Community of Interest for Rare Diseases » launched in August 2011. This community brings together all the relevant stakeholders in the field of rare diseases in Switzerland in order to support the adoption and the implementation measures of the National Concept on Rare Diseases by the Swiss federal Office of Public Health.
TURKEY	
	The Turkish Ministry of Health officially supports Orphanet. It collaborates with Orphanet Turkey for data collection and the dissemination of Orphanet in Turkey.
UNITED KINGDOM	
	The Department of Health officially supports Orphanet.
	Ataxia UK and Orphanet cooperate in the exchange of information, in the validation and online publication of research projects regarding ataxia and in the endorsement and boosting of Orphanet and Ataxia UK activities.
	Orphanet collaborates with Rare Disease UK in the sharing of data and expertise, in the endorsement and promotion of Orphanet and Rare Disease UK activities, and in the development of the UK Strategy for Rare Diseases.Rare disease UK is also a post-validator of information on Orphanet concerning UK PO.
	Orphanet collaborates with Genetic Alliance UK in the sharing of data and expertise, in the endorsement and boosting of Orphanet and Genetic Alliance UK activities, in seeking to raise awareness, improve the quality of services and information available to patients and families and to improve the quality of life for those affected by genetic conditions. Genetic Alliance is also a post-validator of information on Orphanet regarding UK PO.

Table 13 Non-financial partnerships for national activities

7. Communication

7.1. Communication documents

In 2019, A5-size flyers to present Orphanet and Orphanet services were updated when necessary and distributed:

- Orphanet in 4 languages (English, French, Spanish and German)
- Orphadata (English)
- Orphanet application for iPhone and iPad (English)
- ORPHA codes (English)
- Orphanet database structure and main products (English)
- Orphanet rare disease ontology (English)
- Registering your activity as a professional with Orphanet (English)
- Resources for ERNs (English)
- Orphanet tutorials

An A4 leaflet about Orphanet's global positioning and achievements in the previous year was also printed and distributed at congresses.

7.2. Invitations to give lectures at conferences in 2019

Orphanet representatives, as specialists in the field of rare diseases, were invited to give lectures and to participate with poster presentations in more than 30 conferences worldwide in 2019. These lectures were mostly focused on presenting the Orphanet database, public health policies ,and RD research. In addition to this, Orphanet was also represented in a range of national and international workshops and training sessions in raise awareness of Orphanet data and tools, and to liaise with other rare-disease focused projects.

7.3. Booths at conferences in 2019

Orphanet booths were held in 6 different congresses in 2019 as indicated in the list below:

- Rare Disease Symposium 2019, 28 February 2019, Hannover, Germany
- 'Bridging health and social care' Rare Disease Ireland 2019, 28 February 2019, Dublin, Ireland
- Rare Diseases Day 2019 Symposium, 28 February, Valencia, Spain

- European Society of Human Genetics, 15-18 June 2019, Göteborg, Sweden
- American Society of Human Genetics, 15-19 October 2019, Houston, USA
- Patientenuniversität der MHH: Gesundheitsbildung für alle - Kinderkrankheiten und Infektionen - Was ist heute noch wichtig?, 16 June 2019, Hannover, Germany

7.4. Articles in peer-reviewed journals

The Orphanet network produced one article in 2019:

- Nguengang Wakap, S., Lambert, D.M., Olry, A. *et al.* Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database. *Eur J Hum Genet* **28,** 165–173 (2020)

The network also contributed to the following articles:

- Sergouniotis, P. I., Maxime, E., Leroux, D., Olry, A., Thompson, R., Rath, A., ... & Dollfus, H. An ontological foundation for ocular phenotypes and rare eye diseases. Orphanet Journal of Rare Diseases, 14(1), 8. (2019).
- Melissa Haendel, Nicole Vasilevsky, Deepak Unni, Cristian Bologa, Nomi Harris,Heidi Rehm, Ada Hamosh, Gareth Baynam, Tudor Groza, Julie McMurry, Hugh Dawkins, Ana Rath, Courtney Thaxon, Giovanni Bocci, Marcin P. Joachimiak, Sebastian Köhler, Peter N. Robinson, Chris Mungall & Tudor I. Oprea. How many rare diseases are there?. Nature Reviews (5 November 2019)
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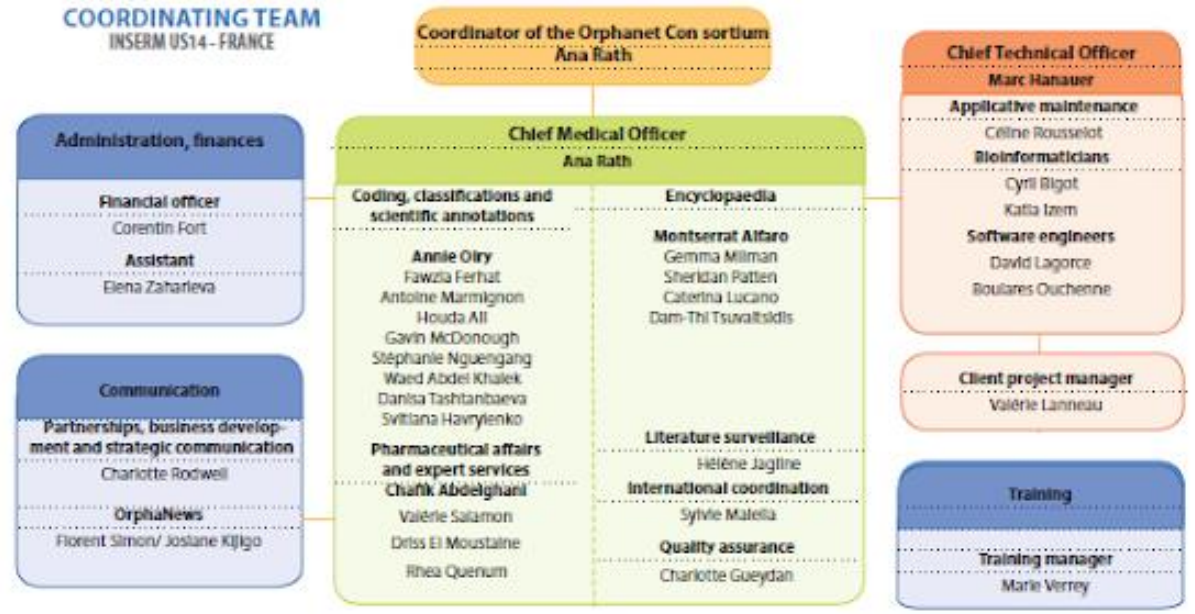
7.5. Social media

The Orphanet coordinating team maintains a Facebook page (5,565 followers) and a Twitter account (@orphanet : 4,728 followers) as well as the Orphanet Tutorials Youtube channel.

The Orphanet Italy team also maintains a Facebook page (14,447 followers) and a YouTube channel. The Orphanet Germany team maintains a Facebook page (367 followers).

8. The Orphanet team in 2019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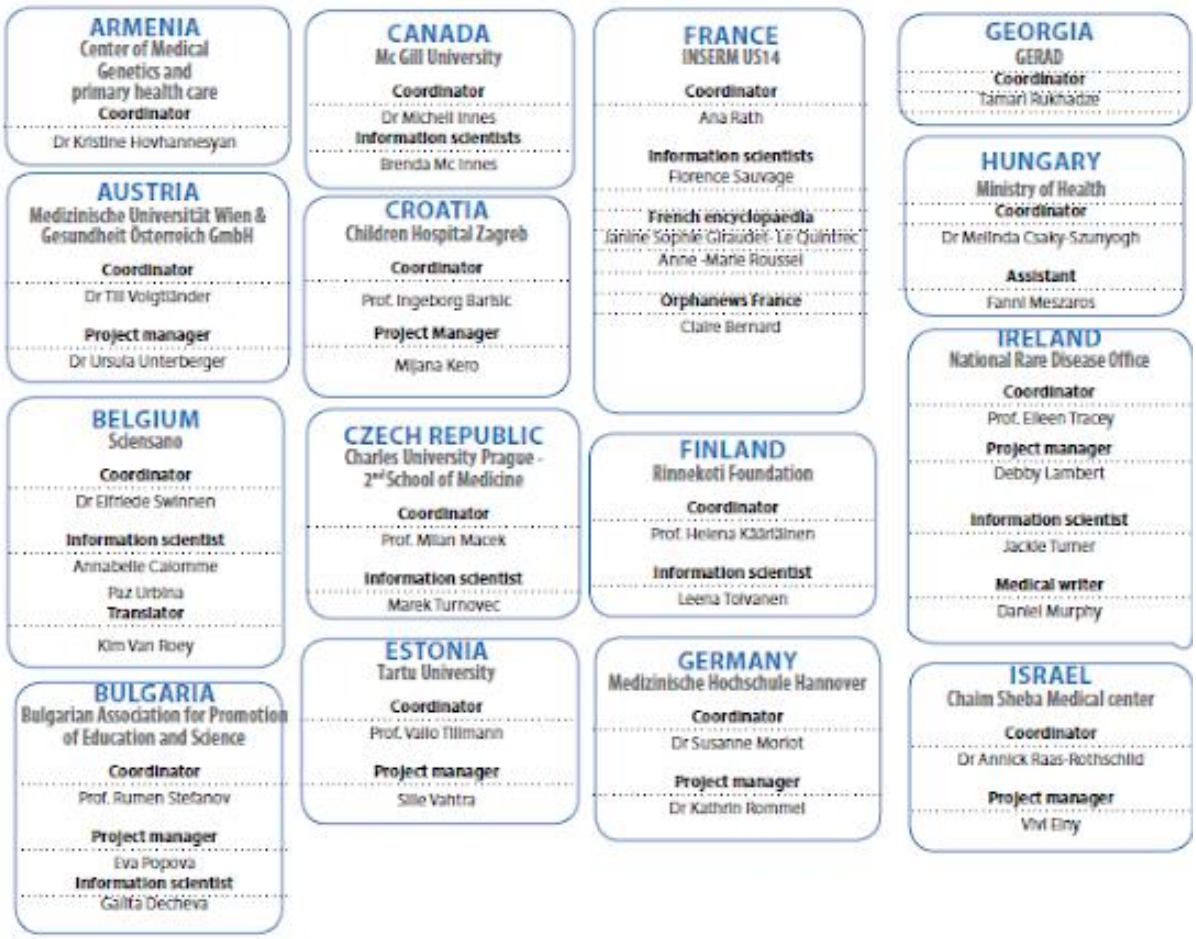
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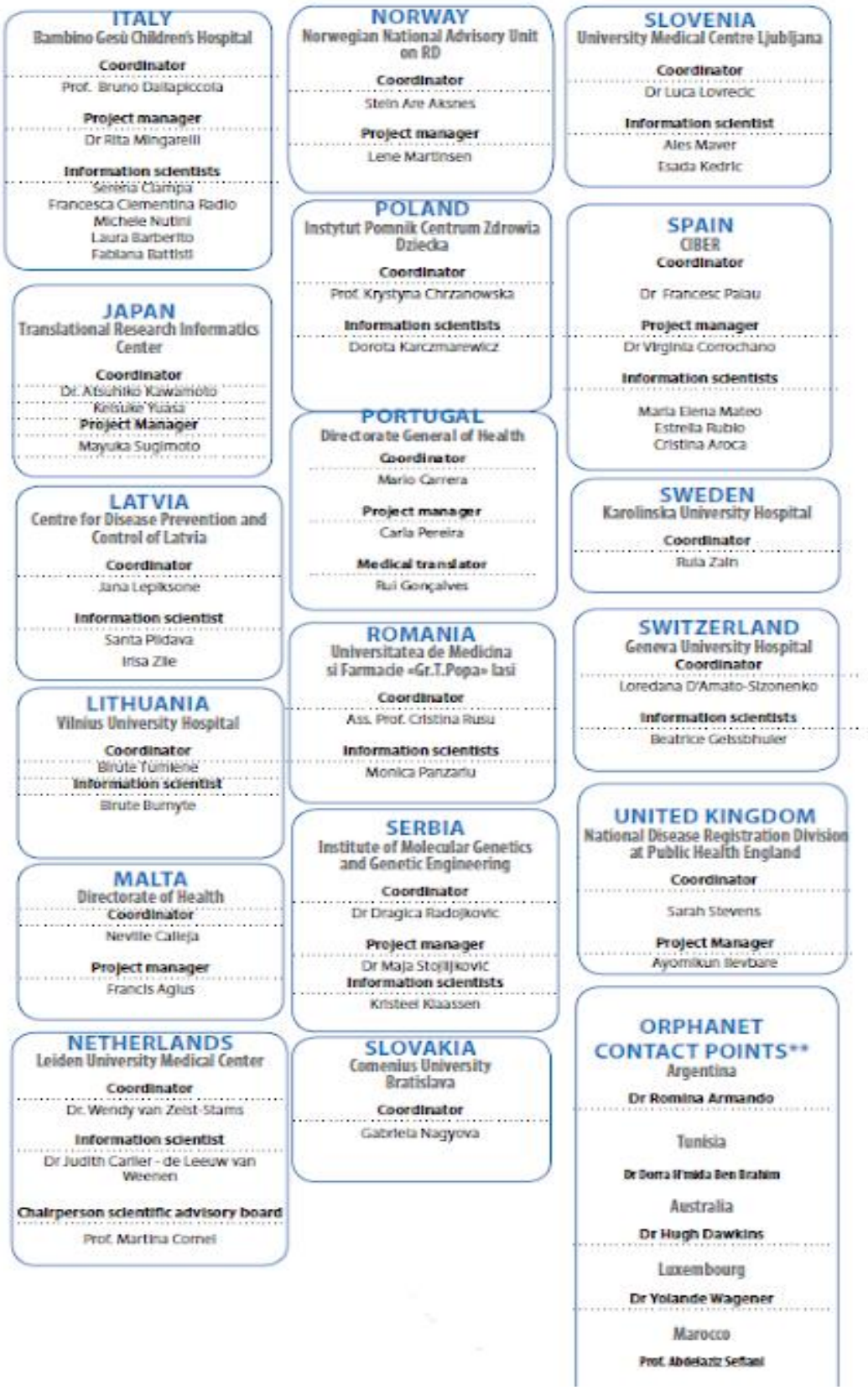

Figure 34 Organisational chart (December 2019)

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

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