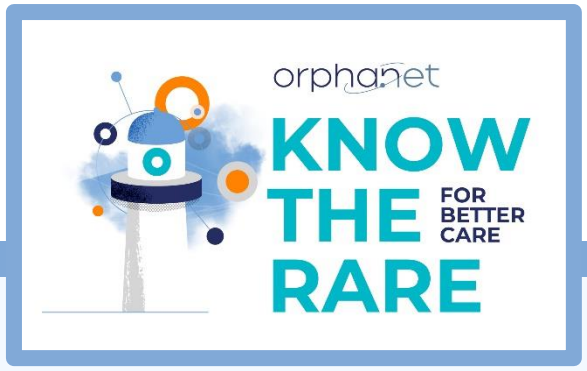

orphanet

2023 Activity Report

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Abbreviation list

BNDMR: French Rare Diseases Data Repository
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
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 (ORPHAcode), 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 in 2023 within Europe and across the globe.

1.1. Orphanet's missions

Since its creation in 1997, 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:

- **Contribute to making rare diseases visible in health and research information systems by producing, distributing and supporting the implementation of the Orphanet rare disease nomenclature (ORPHA codes) as 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, ICD-11, SNOMED-CT, MedDRA, UMLS, MeSH, GARD, so as to ensure the interoperability of databases and health information systems. Moreover, Orphanet provides tools and support to ensure the actual implementation and use of the ORPHAcodes in hospitals and in registries by the creation

of a Network of National Nomenclature hubs in 20 countries and a dedicated space in Orphadata.com.

- **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 32 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 9 languages of the database (Czech, 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.com platform and as structured vocabularies for rare diseases, the Orphanet Ontology of Rare Diseases (ORDO) and the HPO-ORDO ontological module (HOOM). 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. Orphanet is thus a reference resource enabling understanding and analysis of RDs in all their aspects

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 (Orphadata Science) as an ELIXIR Core Data Resource and a Global Core Biodata 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 French Orphanet Guides mobile application, the Orphanet data download platform Orphadata (www.orphadata.com), the API (application program interface) https://api.orphacodes.org, API Maladies Rares (ORPHAcode) - api.gouv.fr (https://api.gouv.fr/les-api/api-orphacode) and https://api.orphadata.com 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 the International Classifications of Diseases (ICD-10, ICD-11), 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 the Human Phenotype Ontology (HPO), epidemiological data and their functional consequences based on the International classification of functioning (ICF).
  - An encyclopaedia with textual information on rare diseases, presented in the form of a definition, an abstract or an automatically generated text for 9,884 entities in the Orphanet database. For 6,810 clinical entities summary texts are available, 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, Polish, and Czech. For certain selected diseases and emergency guidelines are produced in French and then translated.An inventory of

high-quality articles published by other journals or learned societies. At the end of 2023 4,967 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 32 member countries and providing information on: specialised expert centres and centres of expertise, medical laboratories, research projects, clinical trials, patient registries and variant databases, networks, technological platforms and patient organisations.
- A Newborn Screening Bibliographical Database indexing scientific articles and reglementary texts on newborn screening across the world, based on an ongoing literature review. Users can filter results by a range of features, such as the name of the disease, ORPHAcode, type of text, language, geographical region, and more. A search function is also available.

    - 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 ressources are available via a mobile app:**
    - **Orphanet Guides:** an app in French giving access to information on French national support mechanisms for patients and their families, information concerning the functional consequences rare diseases and the related standards of care, as well as recommendations for emergency practitioners concerning rare diseases. The app is available for iOS and Android. This app replaced the Orphanet app in 2021.
    - **RDK Rare Disease Knowledge™**: an app in French and English available in France launched by Orphanet and Tekkare/As We Know, aimed at reducing the diagnostic odyssey by allowing health professionals to obtain an orientation to an appropriate centre of expertise through a search by clinical sign assistant. Available in a web app, and for iOS and Android.

The Orphadata platform (www.orphadata.com) provides high-quality datasets related to rare diseases and orphan drugs, in a reusable and computable format.

- Freely available datasets (Orphadata Science): 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, data concerning the functional consequences of rare diseases;
- Datasets available via Data Transfer Agreement/Licence: Textual information, catalogues of patient organisations, expert centres, clinical laboratories and diagnostic tests, orphan drugs, and research activities.
- Ontologies (see below)

- Tools and services: A range of tools are available and others, such as APIs, are forthcoming to ease re-use of Orphanet data. For the moment the ORPHAcode API is available, as well as an ORPHAcodes Dataviz, FAIR Datapoint, ORDO SPARQL Endpoint and HOOM SPARQL Endpoint, and OrphaPackets.

- **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, such as epidemiological figures by geographical region. ORDO provides integrated, re-usable data for computational analysis. In obo and OWL formats

- **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 2023

Launch of RDK Rare Disease Knowledge™

At a joint press conference on 20 June 2023, Orphanet, Tekkare® and As We Know® launched RDKRare Disease Knowledge ™, a one-of-a-kind application designed to combat the diagnostic odyssey for people living with rare diseases. RDK allows primary care practitioners to search for rare diseases by name, or by a combination of clinical signs. Patients can also be directed to expert centres in France that manage specific diseases, overall helping to shorten the diagnostic process. Orphanet's rare disease data and expertise, coupled with Tekkare's technical know-how, make RDK a veritable fount of knowledge, putting the power of information on more than 6200 rare diseases right at? hand.

While primarily dedicated to healthcare professionals, this Class 1 medical device is freely available to all in both French and English, without the need for prior registration. When performing a search based on clinical signs, the application yields a list of possible diseases, ranked based on a weighted score which considers the clinical features of each disease. The user can then access information on each disease. This includes data from Orphanet, as well as best practice tools such as emergency guidelines and national diagnostic and care protocols, which enable patients to be monitored long-term.

To continue to improve the application, a call for sponsors has been launched and a growing number of sponsors now support the application. This will enable the addition of new features, and broaden the available information on expert centres beyond France. Sponsors have no influence on the content or editorial choices.

RDK can be accessed on the web, or downloaded to mobile devices and is available in French and English.

Orphanet was honoured to join As WeKnow, at the Prix Galien 2023 Awards in New York, to celebrate As We Know's nomination as best start-up of the year thanks to the RDK app. This prestigous prize recognises therapeutic innovations in the health care field since the 1970s.

In early 2024 the French Agency for Digital Health (ANS) awarded RDK with the annual 'Talents de la e-santé 'award 2023 for Best eHealth Innovation in the category 'innovation numérique en ville'.

FEDER Prize for Orphanet's "Undiagnosed" ORPHAcode

On 16 March 2023, Orphanet was honoured by the Spanish Federation for Rare Diseases (FEDER) with an award for the creation of a specific ORPHAcode for undiagnosed patients. The awards were presented to Ana Rath, director of Orphanetby Her Majesty Queen Letizia of Spain at a ceremony celebrating Rare Disease Day. The ORPHAcode in question, 616874, was developed in 2021 in the framework of the RD-CODE project and is assigned to patients left without a definitive diagnosis following a full investigation by rare disease experts. The existence of such a code improves the visibility of the experiences of undiagnosed patients, enables more precise epidemiological information about people living without a diagnosis and about rare diseases more broadly, and will allow in the future to bring them to coordinated research pathways as recommended by IRDiRC.

Implementing ORPHAcodes in routine disease monitoring: Results from the RD-CODE project

In 2023 results of a study conducted in five European countries were published in the Orphanet Journal of Rare Diseases which demonstrated that ORPHAcoding shows strong potential to improve the quality of healthcare available to rare disease patients.

ORPHAcodes are the unique identifiers assigned to rare diseases in the Orphanet nomenclature of rare diseases. They were developed as a rare disease-specific nomenclature system, which would help improve the visibility of RD in health systems and facilitate research and monitoring activities. The Orphanet nomenclature is aligned with other dominant codification systems, such as ICD-10, ICD-11, SNOMED-CT, OMIM, UMLS, and MeSH.

In the context of the RD-CODE project, ORPHAcodes were incorporated into routine coding systems in the Czech Republic, Malta, Romania, Spain, and the Veneto region of Italy on a trial basis from January 2019-September 2021. In total, 3133 different ORPHAcodes were used to describe diagnoses, with more than half describing diseases with very low prevalence. Of these, it was found that 83.4% of the ORPHAcodes used described their disorder more precisely than the corresponding ICD-10 code.

Overall, the results of this study showed that the Orphanet nomenclature is a robust, versatile resource for the coding of rare diseases. In particular, it has promise for improving

data interoperability and cross-border research if implemented on a larger scale throughout the European Union.

The RD-CODE project ran from January 2019-December 2021, and aimed to support EU Member States in improving data collection on rare and undiagnosed diseases through the implementation of ORPHAcodes.

Orphanet Newborn Screening Bibliographical Knowledgebase

A Newborn Screening Bibliographical Knowledgebase was made available on the Orphanet website in 2023. The new knowledgebase indexes scientific articles and reglementary texts on newborn screening across the world, based on an ongoing literature review. Users can filter results by a range of features, such as the name of the disease, ORPHAcode, type of text, language, geographical region, and more. A search function is also available.

This resource was developed thanks to support from the AFM-Téléthon, and includes data drawn from the review carried out by the French High Authority for Health (HAS). Further information on neonatal screening panels in specific countries is available from the International Society for Neonatal Screening. It is hoped that this new source of knowledge will provide a centralised source of established knowledge in the field for stakeholders.

Additional HTA information for France available via Orphanet

The Orphanet orphan drug database has been updated to include information on appraisal and reimbursement in different countries around the world. The new "Appraisal/reimbursement" section of the drug pages was launched in 2023 and can be found under Additional information. This section now contains links to the French national health authority's "Historique des avis" when available. This provides an overview of the assessments which have been conducted in France. For general information on processes in other countries, there is also a link to the Impact-HTA project's Country Vignettes page.

Health Technology Assessment, or HTA, is the multidisciplinary process of evaluating new health technologies or interventions, to determine their value and involve policy, particularly with regards to pricing and reimbursement. It is a key part of transparent, evidence-based policy making in health.

As previously, information on specific drugs can be found by searching either by substance name, or by the name of the disease for which they are indicated. This update represents a total of 480 new pieces of data which have been added to the Orphanet database. The information will continue to be updated on an ongoing basis as the results of new evaluations are made available.

Orphanet Data for Rare Diseases Direct Grants

The Orphanet Data for Rare Diseases Direct Grant (OD4RD) was a one-year project co-funded by the European Commision's EU4Health programme that started in 2022 which was followed up in 2023 by the OD4RD2 Direct Grant for a three-year period.

The aim of OD4RD was to increase the visibility of rare diseases in Health Information Systems by achieving the implementation of ORPHAcodes in hospitals, to increase the quality of data generated about RD patients by disseminating best practices for coding with ORPHAcodes, and to provide the means to generate accurate data for exploitation and analysis by European Reference Networks (ERNs), hospitals and decision makers, notably to improve their understanding of RD activities. The project also aimed to contribute to the EU Health Data Strategy by connecting the dots with structuring initiatives around EHR formats and health data spaces (EHDS) both for primary use in order to achieve better diagnosis and care of RD patients, (for example for the assessment of current practices and results against gold standards of care), as well as for secondary use, to inform policy decision-making and research

The project maintained the update of the Orphanet nomenclature and classification of RD, the development of the Orphanet knowledge and information base around RD in collaboration with ERNs, the development of national Orphanet nomenclature hubs to ensure optimal implementation at national level, and support to the EC in its ERN strategy through dedicated IT systems. Training sessions and a help desk have been provided over the project's run (ending mid 2023). A full repository of deliverables is available.

OD4RD was followed in mid-2023 by the Orphanet Data for Rare Diseases 2 (OD4RD2) 3-year Direct Grant. This project builds and expands on the achievements of the previous OD4RD project, taking advantage of Orphanet's specific expertise and its organisation as a long-lasting, well-established network, to fulfil the following general objectives:

- To contribute to the generation of standardised, interoperable data on RD diagnosis for primary and secondary use, by maintaining and supporting the implementation of the Orphanet nomenclature of RD, in collaboration with the ERNs.
- To contribute to the harmonisation of data collection across settings (health records, registries) and amongst countries, by the dissemination of coding good practices at the data source level.
- To contribute to supporting evidence-based decision-making in the frame of the European strategy around ERNs, by supporting the exploitation of reference corpuses of data and information on RD.

The OD4RD2 Kick Off meeting was an online event held on April 13th and 14th, 2023.

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 wishes to make their major achievements in the rare diseases field sustainable after the Third Health Programme (2014-2020); 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. A SGPP Focus Group dedicated to the question of Orphanet's sustainability was established at the end of 2019 with a mandate to present different scenarios for a sustainable future, as well as a business plan for Orphanet in 2020. Following the delivery of this work a Sustainability Task Force in the Orphanet Network worked on new tools to help Orphanet Network Members make Orphanet better known and advocate at National level for support towards its sustainability goals. These tools include a new slogan reflecting Orphanet's missions and objectives ("Know the rare for better care"), associated visuals, slideshows for different audiences, and a short, animated video presentation to convey Orphanet's missions as regards its end users.

In 2023 work started within the Orphanet Sustainability Task Force towards the construction of an AIBSL structure for the Orphanet Network. This work will continue in 2024.

Collaboration with European Reference Networks (ERNs)

In order to improve rare disease knowledge generation and dissemination, Orphanet collaborates with European Reference Networks (ERNs) for rare diseases. This common endeavour aims to improve rare diseases patients' lives by increasing knowledge and providing equal access to the pool of expertise provided by the ERNs. Collaboration between Orphanet and ERNs are facilitated by EU-funded projects (OD4RD/OD4RD2, ERICA) and individual collaborations (OrphaID with ITHACA); these mechanisms provide a framework for synergies between, ERNs (networks of expertise on RD) and Orphanet (network of information and knowledge).

In 2023 work between Orphanet and the ERNs focused on the following activities;

- **Improve the Orphanet nomenclature of rare diseases to provide 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: a full list of the status of ongoing collaborations with ERNs is available in our GitHub (updated every six months).
- **OrphaID platform** (https://id-genes.orphanet.app/ithaca/): launched in 2022 to provide access to curated intellectual disability related genes and phenotypes, resulting from a collaboration between ITHACA and Orphanet.

- **Revise and enlarge the Orphanet encyclopedia of rare diseases:** in 2023, 74 texts have been revised in collaboration with ERNs.
- **Prove a directory of healthcare, patient support and research activities related to RD**: work continued to represent all ERNs' activities. In particular, to build a repository of clinical research conducted by ERNs in the framework of the ERICA project.
- **Communicate on ERN activities to the RD community**: a dedicated section of OrphaNews International provides a showcase, with an edition dedicated to resources provided by ERNs concerning COVID-19 and RD and resources provided by the ERNs for refugees/displaced persons.

Collaborative work with ERNs will continue in the context of the JARDIN Joint Action (Joint Action on Integration of ERNs into National Healthcare Systems) from 2024, which will produce recommendations, and implementation pilots in the main fields of action, such as patient pathways, national reference networks, and data management for rare diseases. These pilots constitute a promising way to provide EU Member States with directly implementable solutions for their healthcare systems

European Joint Co-fund 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 Orphanet Network and coordination team are key partners, and co-leads activities around coordinated access to data and services within this programme.

- Orphanet co-coordinates the Pillar on coordinated access to the research data ecosystem, delivering the Virtual Platform of resources and data sources for RD research
- Orphanet provides a web-based RD research analysis platform including funded research projects curated by the Orphanet Network. This platform is open to Orphanet partners and IRDiRC funders.
- Orphanet developed and delivered a train-the-trainers programme around the Orphanet nomenclature and ontologies for registries and research-oriented repositories. This programme resulted in 100 training sessions, organised by 15 of the national hubs, followed by 2,800 participants from 23 European Reference Networks.

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 INSERM leads the work package in charge of collecting standardised genetic and phenotypic information concerning unsolved rare diseases cases from ERN cohorts, 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. The Orphanet team has within this project developed the Rare Disease Case Ontology (RDCO), co-designed similarity algorithms for a phenotypic-similarity based variant prioritisation pipeline, currently implemented in the RD-Connect Genome-Phenome Analysis Platform (GPAP), and organised a series of jamborees with ERNs to discuss results of the application of this methodology to complex diagnostic cases. All deliverables are available on the Solve-RD website, and the WP1 led by Orphanet published a paper on their work in early 2024.

X-eHealth

INSERM, Orphanet's coordinating team is involved in the X-eHealth project (finished in 2023), an EU CSA (Coordination and Support Action) project to support the eHealth expert group in which MS are represented to decide on an eHealth strategy in the EU for EHRs, ePatient summary and ePrescription. The group proposed specifications to the European Commission's eHealth Network in which ORPHAcodes were included based on RD use-cases developed in this project. This is extremely important for the RD community at it allows to be identified as RD patients when facing unplanned cross-border medical situations.

Orphanet in the European Health Data Space (EHDS)

Orphanet was involved in the TEHDaS Joint Action, that helped prepare the European legislative acts framing the European Health Data Space (EHDS). Orphanet was involved in tasks intended to harmonise national data access procedures, and ito promote interoperability standards, in particular ORPHAcodes. In 2022 Orphanet became part of the European Health Data Space Pilot 2, providing expertise on metadata models and access to an international network of experts in RDs in the Orphanet network, in particular the EJP RD Virtual Platform, so as to contribute building the RD European data ecosystem.

ERICA

The overarching goal of the project is to is to build on the strength of the individual ERNs and create a platform that integrates all ERNs research and innovation capacity. In this project Orphanet co-leads WP3 which has the general aim of facilitating the Europe-wide implementation of standardised Patient-Centred Outcome Measures (PCOMs) and Patient Reported Outcome Measures (PROMs) for rare diseases. Orphanet contributes to this work with the Disabilities annotations and collaboration with MAPI Research Trust in order to assess what PCOMs and PROMs are already available and what are the gaps, and which could be exploited for more than one disease. Orphanet also contributes to WP6, which is intended for Integration, outreach and dissemination. Orphanet contributes with the Orphanet database of ERNs' CPGs and clinical trials.

In August 2022 the first version of the Patient Reported Outcome Measures (PROMs) Repository was launched, with a further update in 2023, with the aim of improving patient

centred care, clinical research, and to inform generally health policy. The Repository is an open-access tool which provides a centralised point of access for information on patient-centred outcome measures of relevance for rare disease research. PROMs refer to measurement tools used by patients to provide information on their own health status and quality of life. They are a key part of patient-centred research and care, and can be used both to inform care pathways at the patient level, and more broadly to support research and policy-making. The repository can be accessed on ERICA's website.

Collaboration with the World Health Organization

Orphanet contributes to the enrichment of ICD-11 with rare disease terms, as part of the French WHO Collaborating Center since 2021. Orphanet has already curated and distributes ORPHAcodes-ICD11 semantic alignments for over 5,500 rare disorders, and this effort continues.

Collaboration with SNOMED International

In October2023 Orphanet (Inserm) and SNOMED International released an updated SNOMED CT to Orphanet map, with the objective of improving the visibility of rare diseases in terminologies and promoting interoperability among different codification and terminology systems.
The SNOMED CT to Orphanet Map Release is the product of a joint project carried out under the renewed 2020 Inserm and SNOMED International collaboration agreement, initiated in 2015. Based on an agreed priority set, new concepts for rare diseases as defined in Orphanet (clinically defined entities occurring in less than 1 in 2,000 inhabitants) have been added to SNOMED CT, and a map created from SNOMED CT to Orphanet.

One of the key use cases for this standardised map is to meet European Union (EU) requirements to implement ORPHA codes in health systems for Rare Diseases epidemiology and research, including use in registries, enabling linkage from SNOMED CT enabled Electronic Health Records (EHRs), and supporting cross-border interoperability with International Classification of Disease (ICD)-based coding systems.

The two organisations plan to continue publishing the SNOMED CT to Orphanet map annually in the October timeframe. The map will be extended over the coming years to include further Rare Diseases included in the Orphanet nomenclature.

Access to the human readable map and accompanying release notes is made available from Orphanet via the Orphadata platform, and the RF2 version from SNOMED International for Members and Affiliates from the organisation's Member Licensing and Distribution Service.

Gene Curation Coalition

The Gene Curation Coalition (GenCC), composed of several groups and resources providing information on validity of gene-disease relationships of which Orphanet is a founding member, has created a database bringing together manually curated gene-disease relationships submitted by GenCC member organisations, including Orphanet. Orphanet is numerically one of the largest contributors of disease-gene relationships with 5330

submissions. GenCC provides harmonised definitions for different levels of gene–disease validity based on existing resources. In 2023, Orphanet has participated to a series of meetings aimed at reviewing gene-disease relationships. This work will help progress towards an easier way to update the GenCC database with Orphanet gene-disease relationship through an online submission tool.

Improving quality, transparency and traceability

- In addition to the general SOPs available online and annually updated since 2013, the following procedures were available online in 2023:

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, classification and ontology 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) and Portuguese (2021) and Russian (2021)
  Nomenclature production in national language
- Linearization rules for Orphanet classifications

- Collaboration with networks of expertise for the revision of the Orphanet nomenclature and classification of rare diseases

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
- Translation of the Disease Summary Texts of the Orphanet Encyclopedia for Professionals
- Collection and dissemination of disease information for health professionals and the general public

2) Expert ressources

- Glossary and representation of terms related to diagnostic tests

- Data collection and registration of medicinal products intended for rare diseases in Orphanet
- Data collection and registration of expert centres in Orphanet

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

- Data collection and registration of biobanks in Orphanet

Orphanet published **a dedicated Orphanet Report Series crediting the experts having contributed to the update of scientific data in Orphanet** in 2022. An edition crediting the experts contributing in 2023 is due Autumn 2024.

- **Application of the General data protection regulation (GDPR) to Orphanet data:** this regulation is applicable since 25 of May 2018 across Europe. Orphanet, having as a legal basis the INSERM's public interest missions, collects personal information of professionals declaring their activities and /or contributing 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 exerce their modification or suppression rights concerning their personal data in Orphanet 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. A dedicated mail address is available for any GDPR-related issue: gdpr.orphanet@inserm.fr. Our legal notice on the Orphanet website has been updated. The online data registration and update the Orphanet registration tool was updated in order to make notice of users' rights more explicit. From 2021 on, all network members were invited to sign a Confidentiality Agreement, accompanied by updated best-practice documentation for the handling and storage of data.

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

- **Resources for refugees and displaced persons**: In response to the humanitarian crisis resulting from the war in Ukraine, we have compiled and made available via Orphanet a list of resources for people living with rare diseases affected by the situation. These are updated as necessary.
- **COVID and Rare Diseases Resource:** The COVID-19 pandemic has particularly impacted the rare disease community and expert information is, as ever, of high importance. In

order to help professionals and people living with rare diseases find expert recommendations and services concerning COVID-19 and rare diseases, Orphanet published a **list of resources** available in different languages from March 2020. This list includes resources curated by the European Reference Networks and EURORDIS and is updated regularly, most recently integrating recommendations concerning vaccination. These are updated as necessary.

- **The Orphanet Report Series have been updated:** 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).* **A leaflet presenting Orphanet's activities and latest developments has also been produced in English.**

Orphadata

- **Orphadata datasets were updated** during the year, with an update of the annual Orphanet nomenclature pack in July 2023.
- **The Orphadata catalogue of datasets available on request was updated.**

Users satisfaction and key user statistics

- **Users are satisfied with the services provided by Orphanet:** in the satisfaction survey carried out at the start of 2023, 97 % of respondents stated that they were very satisfied or satisfied with Orphanet, stable compared to 2022.
- **2.9 million PDF documents were downloaded in 2023.**
- **Around 16 million visitors came last year from 236 countries.**

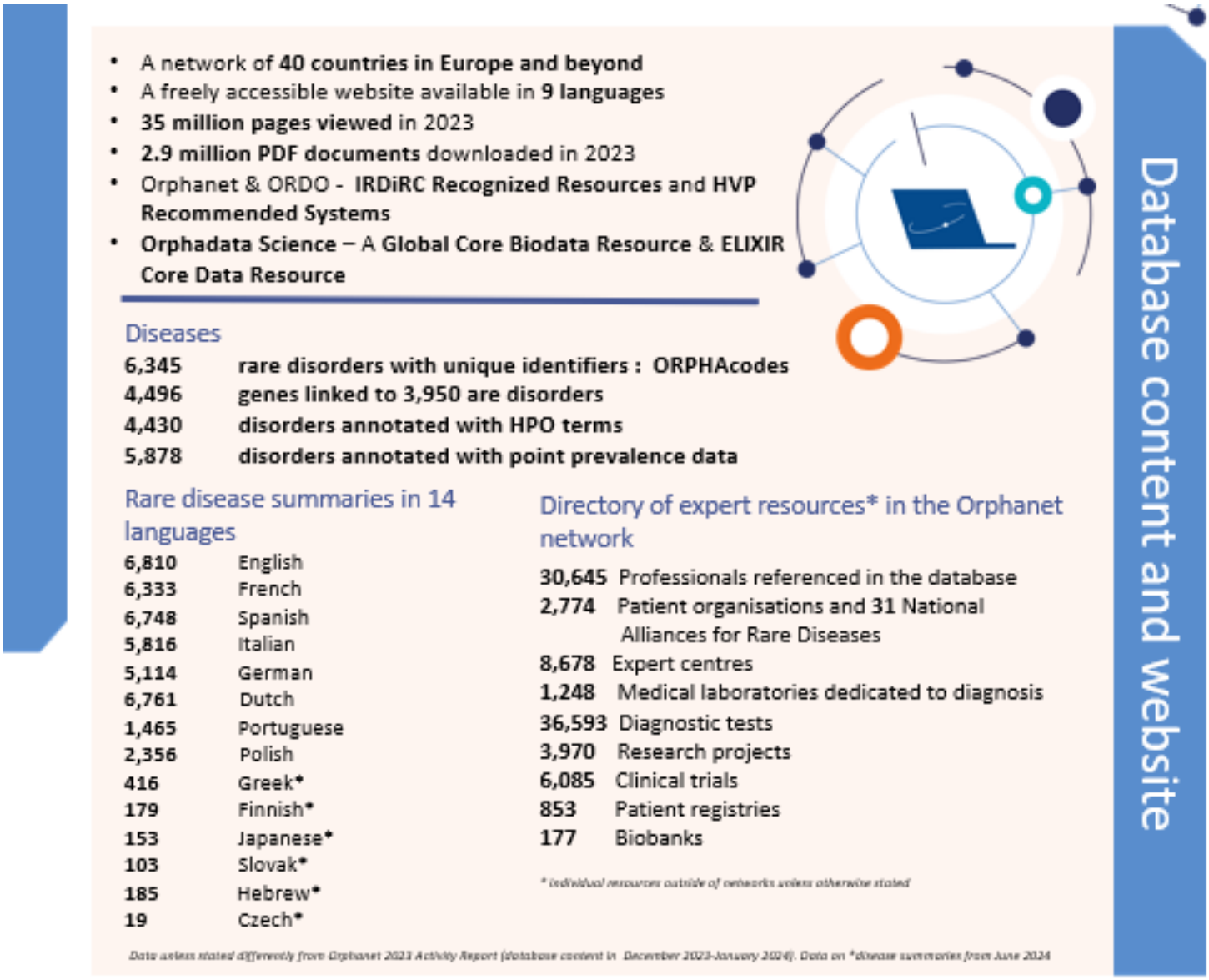


Figure 1 Orphanet in numbers (January 2024)

2. Orphanet network

2.1. The 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).

Following on from the Orphanet Direct Grant (2018-2021), the Orphanet Data for Rare Diseases Direct Grant (OD4RD) was one-year project that started in 2022 co-funded by the European Commision's EU4Health programme that follows up on the work of the previous Direct Grant.

The aim of OD4RD was to increase the visibility of rare diseases in Health Information Systems by achieving the implementation of ORPHAcodes in hospitals, to increase the quality of data generated about RD patients by disseminating best practices for coding with ORPHAcodes, and to provide the means to generate accurate data for exploitation and analysis by European Reference Networks (ERNs), hospitals and decision makers, notably to improve their understanding of RD activities. The project also aimed to contribute to the EU Health Data Strategy by connecting the dots with structuring initiatives around EHR formats and health data spaces (EHDS) both for primary use in order to achieve better diagnosis and care of RD patients, (for example for the assessment of current practices and results against gold standards of care), as well as for secondary use, to inform policy decision-making and research.

The project maintained the update of the Orphanet nomenclature and classification of RD, the development of the Orphanet knowledge and information base around RD in collaboration with ERNs, the development of national Orphanet nomenclature hubs to ensure optimal implementation at national level, and support to the EC in its ERN strategy through dedicated IT systems. Training sessions and a help desk have been provided over the project's run (ending mid 2023). A full repository of deliverables is available.

OD4RD was followed in April 2023 by the Orphanet Data for Rare Diseases 2 (OD4RD2) 3-year Direct Grant. The Network of National Nomenclature Hubs expanded from 13 to 19 countries. This project will build and expand on the achievements of the previous OD4RD project, taking advantage of Orphanet's specific expertise and its organisation as a long-lasting, well-established network, to fulfil the following general objectives:

- To contribute to the generation of standardised, interoperable data on RD diagnosis for primary and secondary use, by maintaining and supporting the implementation of the Orphanet nomenclature of RD, in collaboration with the ERNs.
- To contribute to the harmonisation of data collection across settings (health records, registries) and amongst countries, by the dissemination of coding good practices at the data source level.
- To contribute to supporting evidence-based decision-making in the frame of the European strategy around ERNs, by supporting the exploitation of reference corpuses of data and information on RD.

The OD4RD2 Kick Off meeting was an online event held on April 13th and 14th, 2023. The first day gathered 70 participants and was restricted to OD4RD2 project partners and Orphanet Network members.

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 guides 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 the Orphanet 'culture' amongst all consortium members, and to determine how to move towards a more effective bilateral communication within the network. This empowers Orphanet as a network, achieving 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.

A number of boards were developed in the framework of the OD4RD project (2022-2025). In 2022, a Data Advisory Board was created in order to advise on the ORPHAcodes and Orphanet knowledge base implementation and exploitation. Terms of reference can be found here. In 2022, an ERN Board to provide advice on the strategy addressing the ORPHA

codification and implementation needs, and for facilitating the collaboration between ERN groups and Orphanet team in improving the Orphanet nomenclature and the production of RD information. The ERN Board acts as the forum in which different kinds of Orphanet-ERNs collaboration will be presented to promote synergies across ERNs.

From 2018 onwards, Orphanet full-member countries sign a Network Agreement. The Network members are institutions endorsed by the Ministry of Health or Ministry of Research of the member country. The current signatories are: Austria; Belgium; Bulgaria; Czech Republic; Estonia; Finland; France; Germany; Georgia; Ireland; Israel; Italy; Latvia; Lithuania; Netherlands; Norway; Poland; Romania; Serbia; Slovenia; Spain; Sweden; Switzerland; Georgia; and Japan. In 2019, 3 additional countries joined the Network: Luxembourg, North Macedonia, Turkey. In 2020, Russia and Kazakhstan joined the network (Russia has been temporarily suspended from 2022 as a result of the geopolitical situation). Nine countries complete the network as contact points: Armenia, Canada, Cyprus, Morocco, Malta Tunisia, Argentina, Australia, Slovakia. Two countries are observers whilst they renew their membership Croatia;and United Kingdom.

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 40 countries 2023.

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

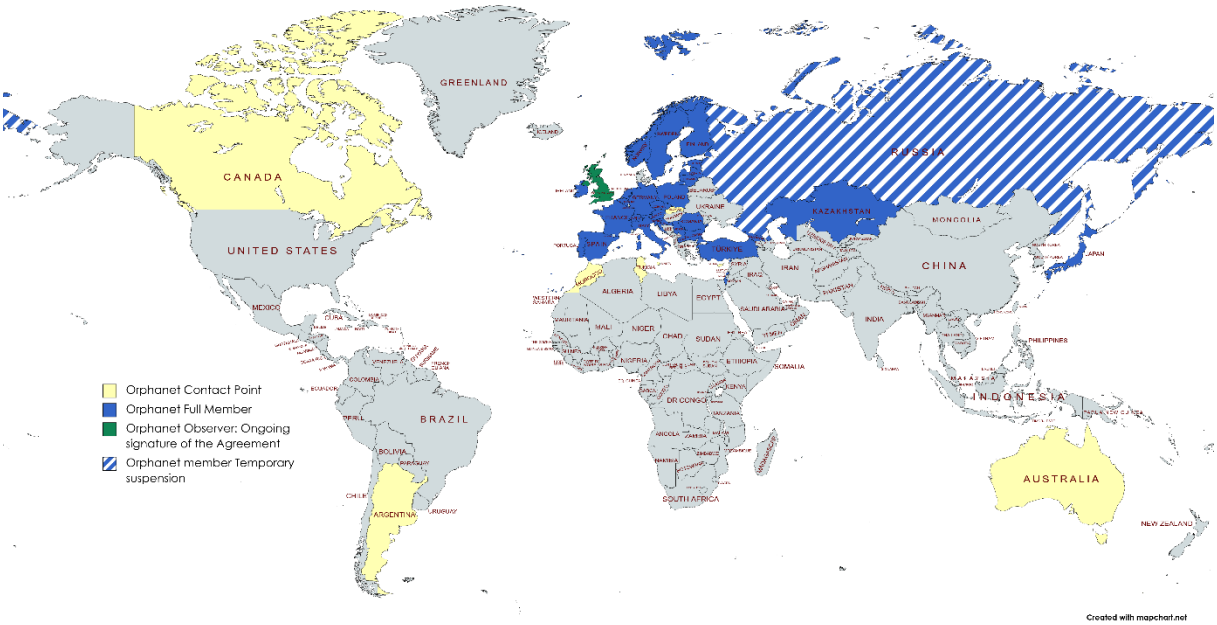


Figure 2 Orphanet Network Members (December 2023)

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.

2.4.2. Orphanet network 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 9 languages of the website, and also in Turkish and Chinese. 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. In 2020 work on a Czech translation of the Orphanet website started with the Czech version launched in 2021.

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 (the European Joint Action supporting the rare disease field and Orphanet, before the current Direct Grant) National teams can also participate in core database activities if resources are available, and since 2019 the quality control of the database as well. The Orphanet Ireland team has contributed to the IT developments, the Orphanet Austria tea contributes to the Encylopedia, and several teams contribute to the expert resources catalogue diverse task forces.

Since the beginning of the OD4RD project, 13 Orphanet network members developed a National Nomenclature Hub in order to provide local support and capacity building in local language to hospitals implementing the ORPHAcodes as well as to coders in hospitals and in registries. The number if hubs expanded to 19 in OD4RD2.

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 dissemination activities, notably to raise awareness of rare diseases, and Orphanet, in their country.

3. Orphanet: Products and services

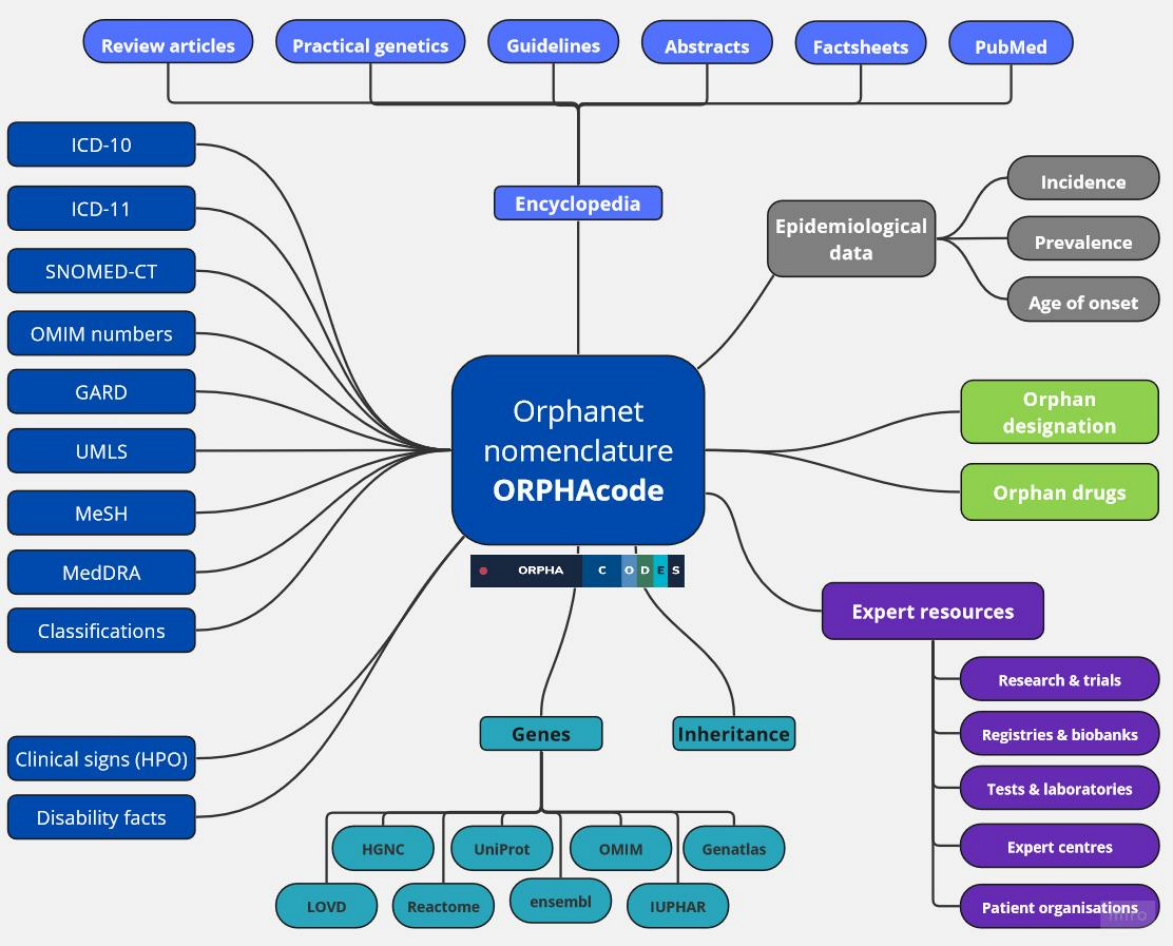


Figure 3 The Orphanet database

The Orphanet knowledgebase is an organised and dynamic collection of information and data about RD and Orphan Drugs. 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 the Orphanet website and in Orphadata.com. 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.

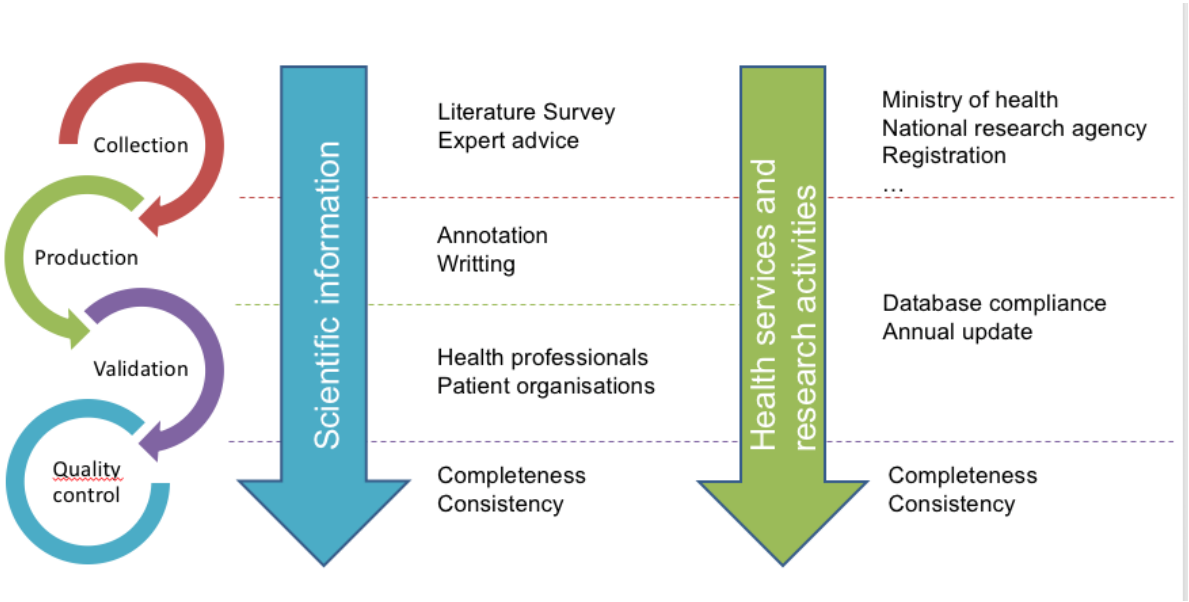


Figure 4 Orphanet data production methodology

The update of the scientific content of the database is performed using a four-step methodology (Figure 3) 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 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: nomenclature of rare diseases

Orphanet provides a comprehensive nomenclature 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).

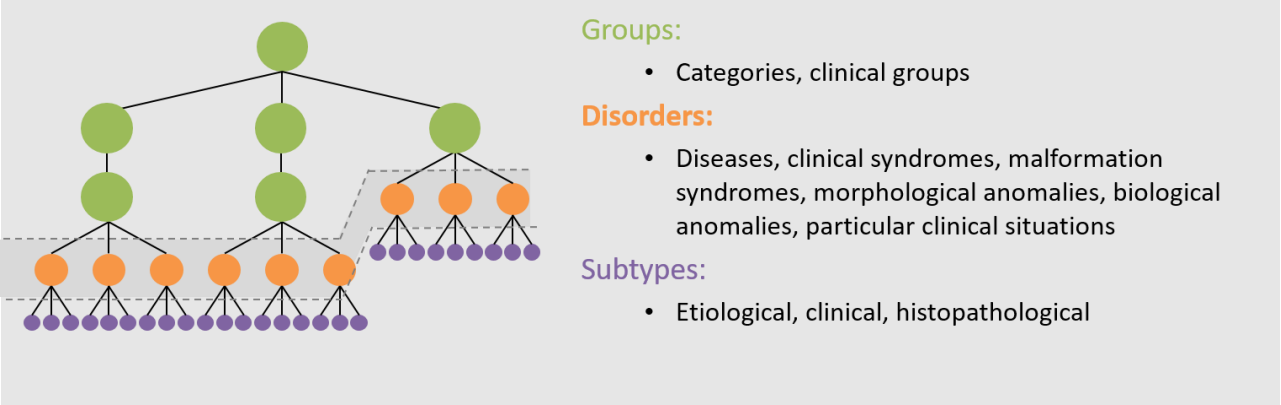


Figure 5 Schema of the Orphanet nomenclature and classifications

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 9,514 active clinical entities[1] and their synonyms (including 6,345 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 every July for routine codification in health information systems, as part of a Nomenclature Pack for implementation, developed in the framework of the RD-CODE project and expanded in the OD4RD/OD4RD2 projects. In this pack Orphanet provides a set of files in XML format, including the Orphanet nomenclature file, the Orphanet ICD-10 and ICD-

[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 2024.

[2] Diseases, malformation syndromes, morphological anomalies, biological anomalies, clinical syndromes, particular clinical situation in a disease or syndrome, data from January 2024.

11 mapping file, a directory containing the Orphanet classifications, and a PDF describing in details all files enclosed in the Orphanet nomenclature pack for coding, as well as a set of tools to facilitate the codification of RD.

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, and since 2023 ICD-11 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 codes
ICD-10	7,311
ICD-11	5,472

Table 1 Number of disorders, groups of disorders or subtypes aligned to ICD-10 codes (December 2023)

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 SNOMED International and were released as a Beta version in 2020 and a first official release was made available in October 2021 from SNOMED International, with a human readable file made available via Orphadata, updated every October each year. Mappings are carried out in a semi-automatic way and are manually curated. Updates follow UMLS releases once a year, however mapping UMLS meta-concepts and related terminologies (MeSH, MedDRA) was not continued in 2020 because a strategic decision was made to include ORPHAcodes in UMLS: the process is ongoing and was completed at the end of 2022.

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*	8,874
MeSH*	3,154
SNOMED CT*	6,552
MedDRA*	1,589
OMIM**	4,709
GARD**	3,583

Table 2 Number of mapped clinical entities (groups of disorders, disorders and sub-types) per terminology (December 2023) *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, 4,430 [3] disorders, groups of disorders or subtypes of disorders are annotated with HPO terms. Further annotations to HPO are being carried out. Based on these annotations, the Rare Disease Knowledge (RDK) app was launched in 2023 to help reduce the diagnostic odyssey (see introduction).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.com

[3] As of January 2024.

Natural history data	Number of groups of disorders, disorders and sub-types
Average age of onset	6,496
Mode of inheritance	5,500

Table 3 Number of disease (groups of diseases, disorders and sub-types) per natural history data *(December 2023)*

Epidemiological data	Number of groups of disorders, disorders and sub-types
Point prevalence	5,878
Prevalence at birth	567
Lifetime prevalence	47
Annual incidence	657

Table 4 Number of diseases (groups of disorders, disorders and sub-types) per epidemiological data *(January 2024)*

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 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 1,057 clinical entities with functional consequences annotated[4].

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

[4] As of Janaury 2024

IUPHAR/BPS Guide to Pharmacology databases (see Figure 6 for details). 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.

3.2.1. Additional functionalities in 2023

ICD-11 alignments with the Orphanet nomenclature of rare diseases were made available in 2023, and were also included for the first time in the Orphanet nomenclature pack.

The Orphanet Nomenclature Pack was updated in July 2023.

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 9,884 entities in the database had one of these forms of textual information) at the start of 2024.

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/ definition for 6,687 rare diseases, subtypes of RD or groups of RD was available online at the start of 2024.

They are progressively translated into the seven other languages of the website (French, Italian, Spanish, German, Polish, Portuguese, Czech and Dutch). In addition, 180 abstracts are translated in Finnish, 419 in Greek, 534 in Russian, 151 in Japanese, 185 in Hebrew and 103 in Slovak: they are available as PDFs (“Summary information”) via the bottom of the

corresponding disease page. For an additional 3, 074 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).

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 end of 2023, 110 emergency guidelines in French were available concerning 456 diseases online with 3 new guidelines produced in 2023. They are being translated into the following six languages: English, German, Italian, Portuguese, Spanish and Polish. 45 emergency guidelines are available in English (including those contributed by BIMDG), 44 in Italian, 24 in German, 52 in Spanish, 17 in Portuguese, and 16 in Polish. Emergency guidelines were downloaded 404,308 times in 2023.

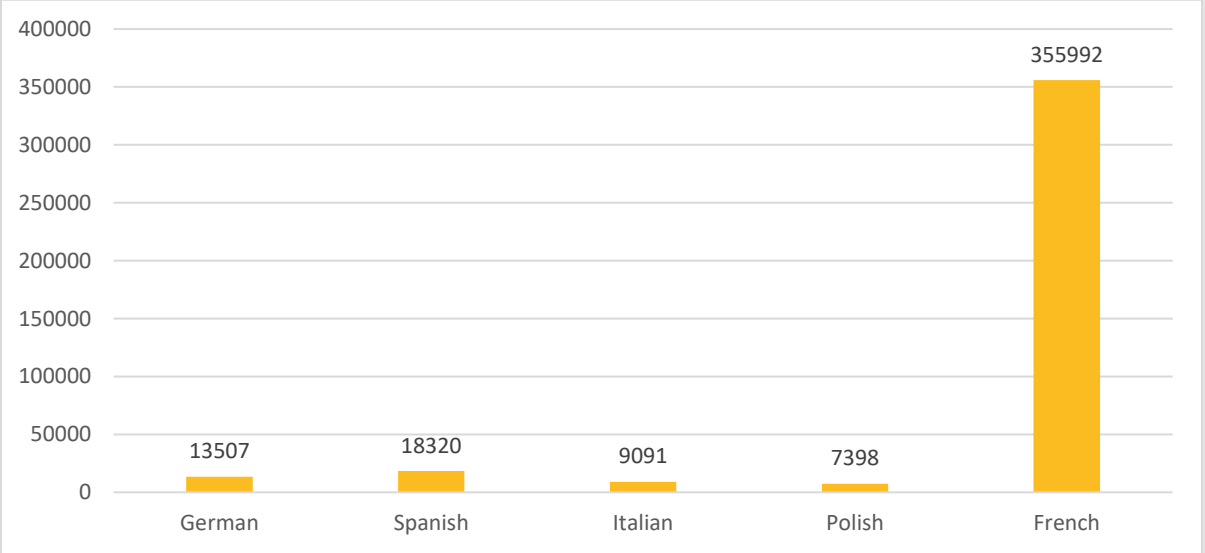


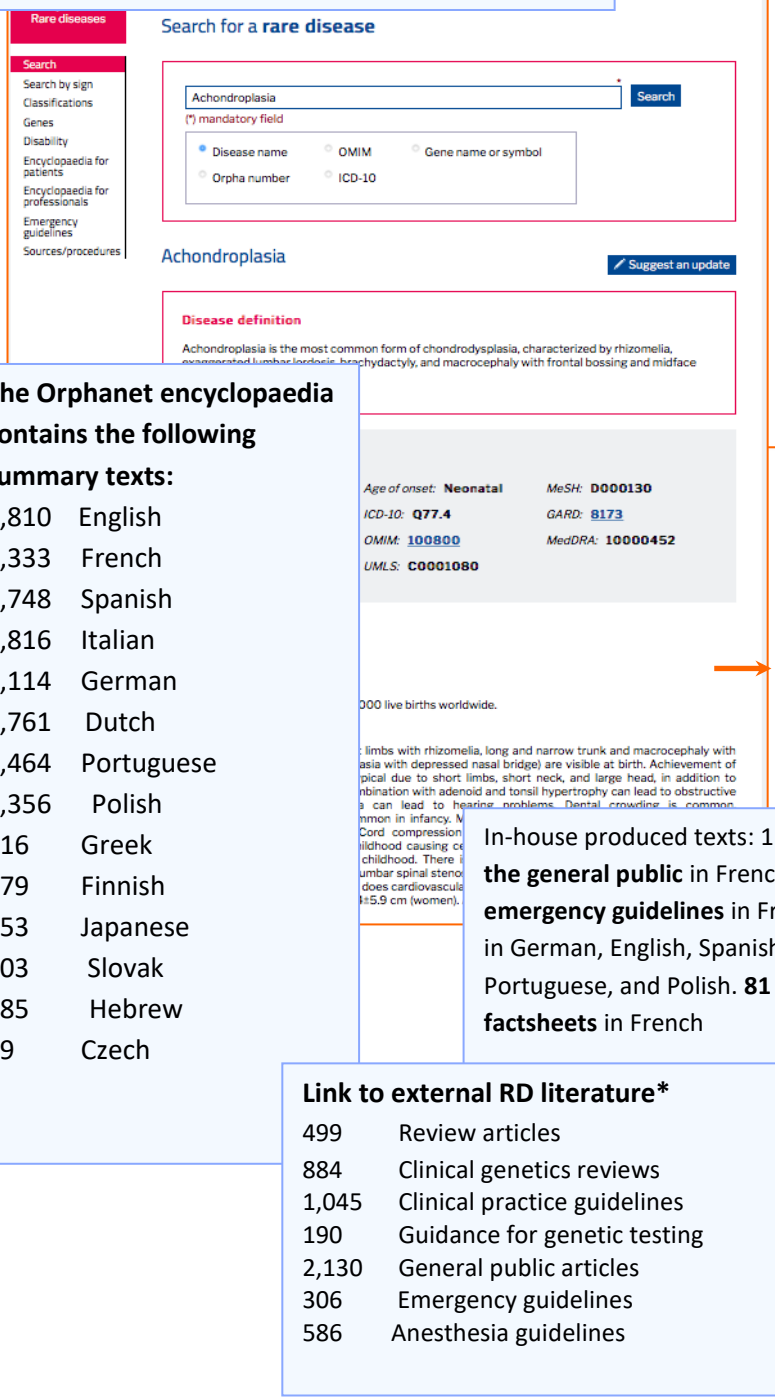
Figure 6 Downloads of Orphanet Emergency Guidelines in 2023 by language

Epidemiology:
5,878 diseases annotated with point prevalence data

Natural history:
5,500 diseases annotated with mode of inheritance
6,496 diseases annotated with age of onset

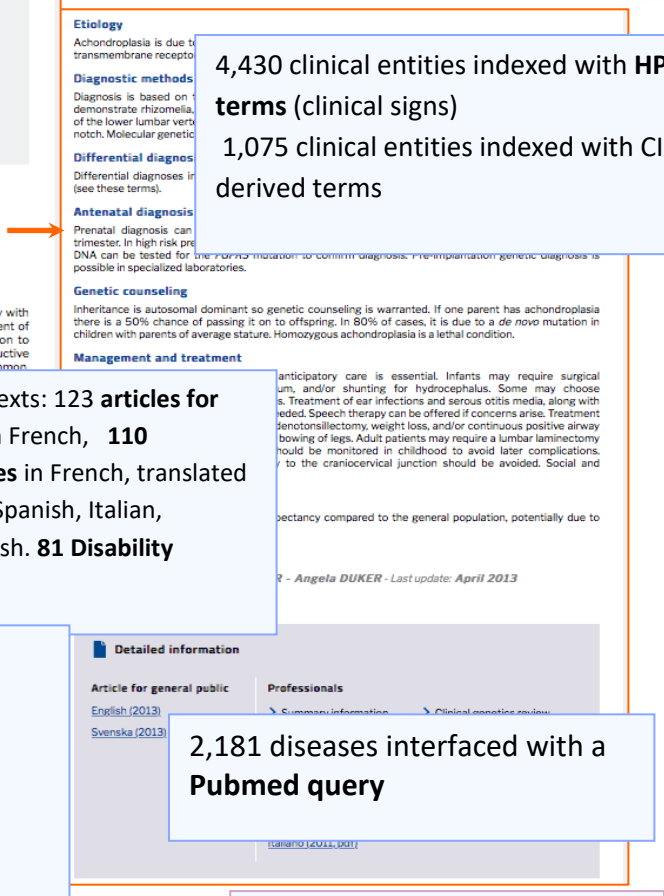
Mappings:
7,311 diseases mapped to ICD-10
5,472 diseases mapped to ICD-11
4,709 diseases mapped to OMIM
8,874 diseases mapped to UMLS
1,589 diseases mapped to MedDRA
3,154 diseases mapped to MeSH
3,583 diseases mapped to GARD

Genes:
- 4,496 genes linked to 3,950 rare diseases
- 7,275 genes interfaced with HGNC
- 7093 genes interfaced with OMIM
- 4,954 genes interfaced with Genatlas
- 7,194 genes interfaced with UniProtKB
- 7,231 genes interfaced with Ensembl
- 1,680 genes interfaced with IUPHAR-DB
- 4,426 genes interfaced with Reactome



The Orphanet encyclopaedia contains the following summary texts:

6,810	English
6,333	French
6,748	Spanish
5,816	Italian
5,114	German
6,761	Dutch
1,464	Portuguese
2,356	Polish
416	Greek
179	Finnish
153	Japanese
103	Slovak
185	Hebrew
19	Czech



4,430 clinical entities indexed with **HPO terms** (clinical signs)
1,075 clinical entities indexed with CIF-derived terms

In-house produced texts: 123 **articles for the general public** in French, **110 emergency guidelines** in French, translated in German, English, Spanish, Italian, Portuguese, and Polish. **81 Disability factsheets** in French

Link to external RD literature*

499	Review articles
884	Clinical genetics reviews
1,045	Clinical practice guidelines
190	Guidance for genetic testing
2,130	General public articles
306	Emergency guidelines
586	Anesthesia guidelines

2,181 diseases interfaced with a **Pubmed query**

17,644 **external links** for 4,255 diseases

Figure 7 The disease database content as of January 2024 *(*Total of all available languages)*

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 provided 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 were produced as stand-alone texts, independent of the General public encyclopaedia. Due to lack of dedicated funding, the production of new Disability Factsheets has been interrupted nowadays.

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 at the end of 2023 and they are also available in the Orpha Guides app. They have been downloaded approximately 308,237times in 2023 (Figure 8). This increased by around 45% as compared with the previous year. Translations into Spanish of these texts started in June 2016, with 54 translated at the end of 2021.

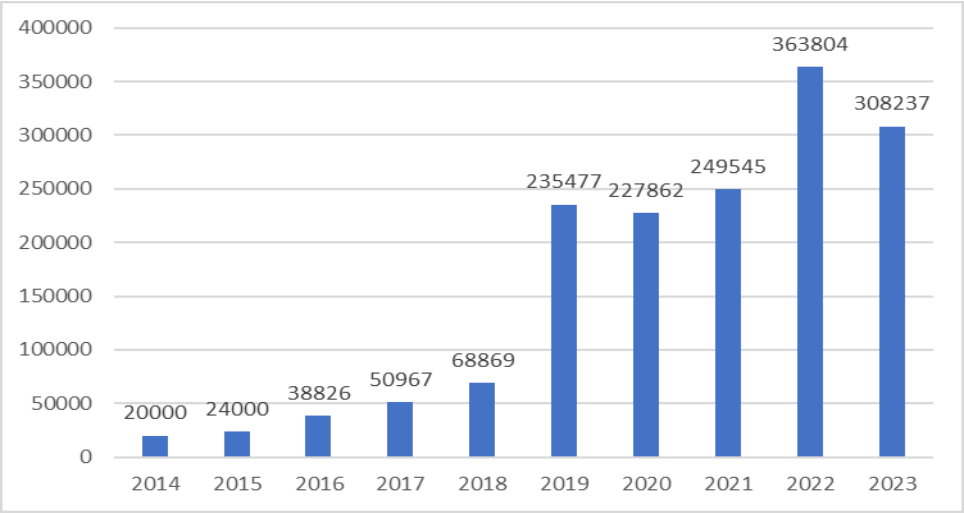


Figure 8 Evolution of number of downloads per year of Disability factsheets since 2014

3.2.4. 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 11 distinct externally produced texts accessible from the Orphanet website:

Review articles
499 review articles were available at the end of 2023.

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 884 articles from GeneReviews (as of beginning 2024).

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[5]. The Orphanet website gives access to 1,045 clinical practice guidelines as of beginning 2024.

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*). 190 guidance documents are available via the website as of beginning 2024.

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. 2,130 articles were available on the website as of beginning 2024. 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* up to 2016. 37 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.

Diagnostic criteria

Information on diagnostic criteria is presented in concise documents intended to avoid misdiagnosis and to facilitate early therapeutic management.

Disability factsheets

A collaboration has allowed Orphanet to link to disability factsheets in Danish, produced by Sjaeldenborger, the Danish Rare Diseases alliance. Two such factsheets were available as of beginning 2024.

Keys to diagnosis

A collaboration with the French Rare Disease Networks is in place provide links between the diseases concerned and individual 'Keys to diagnosis' factsheets (Clés du diagnostic). These factsheets are focused on a clinical sign prevalent in common diseases, but also present in a number of rare diseases: by raising awareness of the link between these signs and rare diseases it is hoped that primary care physicians will be able to detect a potential rare disease earlier and thus reduce the diagnostic odyssey. By 2024 7 of these factsheets were available covering 42 diseases.

[5] *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

Patient Reported/Centred Outcome Measures

Thanks to a collaboration with MAPI Research Trust, Orphanet provides links to Patient Reported/Centred Outcome Measures (PROMs/PCOMs) in the PROQOLID™ database.

Linking these two databases, and providing standardised, curated data, will enable the community to identify PROMs/PCOMs for rare diseases and is the first step towards validated Quality of Life instruments based on functional outcomes.

	Article for general public
Arabic	34
Bengali	24
Bulgarian	3
Chinese	39
Croatian	27
Czech	29
Danish	27
Dutch	70
English	246
Estonian	6
Finnish	13
French	303
Georgian	24
German	187
Greek	35
Hebrew	25
Hungarian	26
Italian	52
Japanese	4
Kirghiz	1
Korean	4
Latvian	26
Lithuanian	2
Norwegian	26
Persian	1
Polish	42
Portuguese	46
Romanian	33
Russian	148
Serbian	26
Slovak	25
Slovenian	26
Spanish	132
Swedish	327
Thai	24

Turkish	31
Ukrainian	27
Urdu	1
Vietnamese	2
TOTAL	2124

Table 5a Total number of Orphanet external content for the general public by language (June 2024)

	Review article	Emergency guidelines	Clinical practice guidelines	Anesthesia guidelines	Guidance for genetic testing	Clinical genetics review	Disability factsheet	Diagnostic criteria	Diagnostic Keys	Patient-Centered Outcome
Arabic	0	0	1	0	0	0	0	0	0	0
Chinese	0	0	3	0	0	0	0	0	0	0
Czech	0	0	0	194	0	0	0	0	0	0
Dutch	0	0	3	0	0	0	0	0	0	0
English	424	45	476	217	152	885	0	20	0	125
Finnish	0	0	0	1	0	0	0	0	0	0
French	31	162	339	3	36	0	81	0	7	0
German	31	24	203	36	2	0	0	2	0	0
Hungarian	0	0	1	0	0	0	0	0	0	0
Italian	0	44	1	15	0	0	0	0	0	0
Polish	0	16	0	0	0	0	0	0	0	0
Portugese	1	17	2	30	0	0	0	0	0	0
Russian	0	0	2	0	0	0	0	0	0	0
Spanish	16	54	55	91	0	0	36	0	0	0

Table 5b Total number of Orphanet external content for professionals by language (June 2024)

3.4. 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
- Variant databases
- Biobanks
- 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 network. 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 29 countries in which Orphanet members collected data in 2023 are the following:
Austria, Belgium, Bulgaria, Czech Republic, Estonia, Finland, France, Georgia, Germany, Ireland, Israel, Italy, Kazakhstan, Latvia, Lithuania, Luxembourg, the Netherlands, Norway, North Macedonia, Poland, Portugal, Romania, Serbia, Slovenia, Spain, Sweden, Switzerland, Turkey, and Japan.

Data collection outside the Orphanet network:
Patient organisations in countries outside the Orphanet network can be registered in the database at their demand 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 (172 patient associations are registered in this way). 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 variant 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): 66 patient registries are included in Orphanet following this procedure.

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

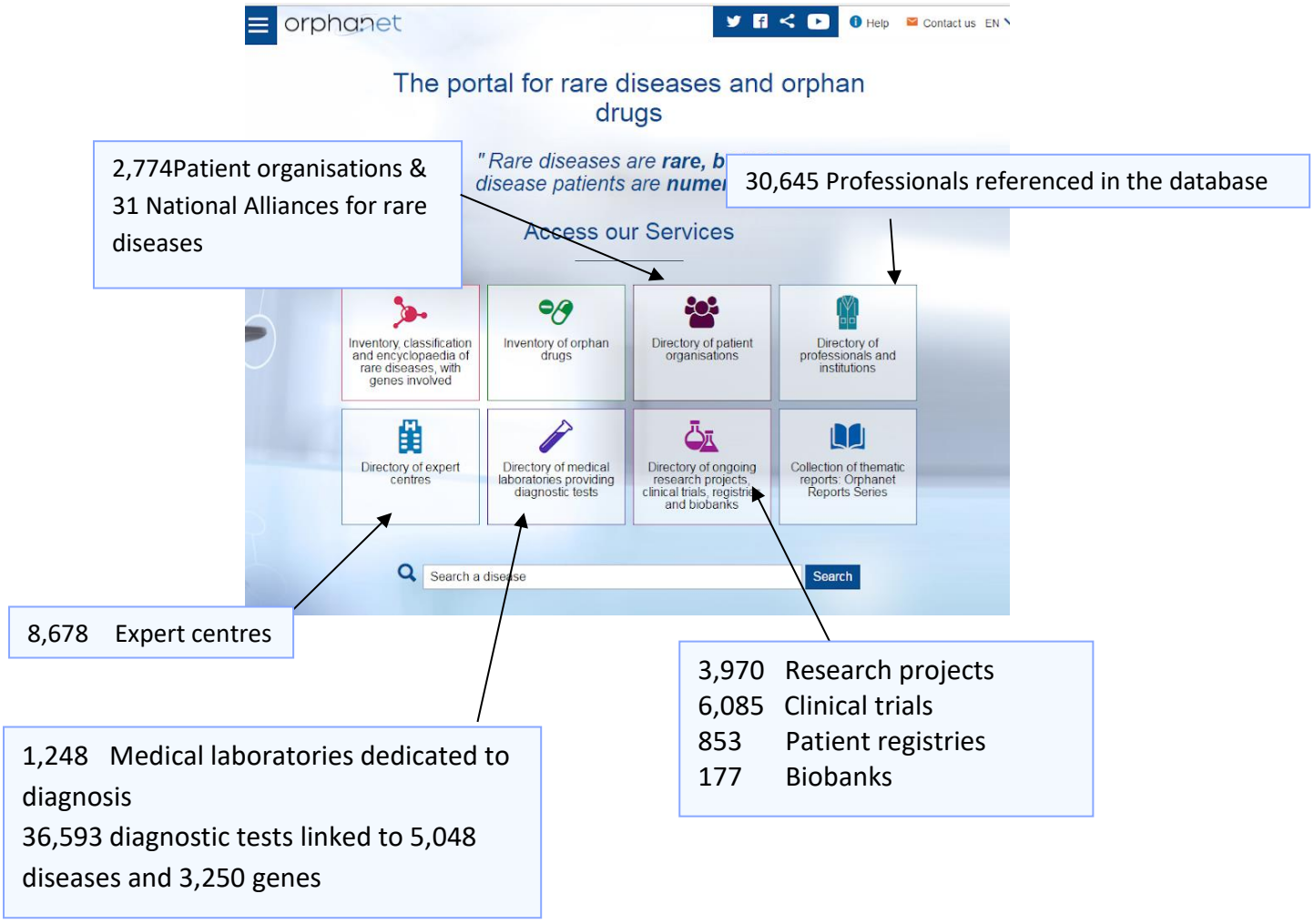


Figure 9 Directory of expert services (January 2024)

3.4.4. 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, Genomics Quality Assessment (GenQA) 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. To date 695 laboratories are registered as practicing EQA in the Orphanet database and 497 are accredited.

3.4.5. ADDITIONAL FUNCTIONALITIES IN 2023

In 2023 the Orphanet orphan drug database has been updated to include information on appraisal and reimbursement in different countries around the world. The new "Appraisal/reimbursement" section of the drug pages, found under Additional information, now contains links to the French national health authority's "Historique des avis" when available. This provides an overview of the assessments which have been conducted in France. For general information on processes in other countries, there is also a link to the Impact-HTA project's Country Vignettes page.

3.5. 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 January 2024):

For Europe:

- 1,996 Orphan Designations linked to 1,532 substances and covering 672 diseases

- 598 Marketing Authorizations (of which 185 already had an Orphan Designation and 414 without Orphan Designation), covering 398 diseases

For the USA:

- 1,778 Orphan Designations linked to 1,487 substances and covering 625 diseases

- 788 Marketing Authorizations (of which 774 already had an Orphan Designation and 15 without Orphan Designation), covering 492 diseases.

3.6. 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 2023 ORS were downloaded at total of 125,317times (Table 6).

	English	French	German	Spanish	Italian	Dutch	Polish	Portuguese	Czech
List of rare diseases in alphabetical order	4171	4101	970	4584	11035	148	17994	467	598
Prevalence of rare diseases by alphabetical list	20163	1579	7159	1321	778	343	NA	449	NA
Prevalence of rare diseases by decreasing prevalence or cases	4858	3684	2661	2360	1078	351	NA	1101	NA
List of Orphan Drugs in Europe	9118	1651	1978	476	338	NA	NA	220	NA
Vivre avec une maladie rare en France	NA	24795	NA	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 2023 by language

3.7. Orphanet's IT infrastructure

The main 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 fibreoptic connection. This allows an excellent connectivity between production servers, development servers and backup environments. The architecture of the servers is represented in Figure 10.

During 2023 the www.orpha.net website was unavailable during August 20th, partially August 21 and October 30th, 99.17% uptime. Moreover, the website had several "slow down" periods mainly in November and December.

The main issues were DOS (Denial of Service) due to a massive automated crawl and fraudulent access attempts. Plus, we experienced new type of automated crawl coming from "AI" operators which overloaded the system. Due to that, we have decided to block the main "AI" bots, also for PI reasons.

The audience totalled 16 million users and 35 million viewed pages in 2023.

In order to secure and improve the website usage, we launched during 2023 a complete overhaul of the IT platform, updating it with faster and upgrated technologies (PHP8 standard framework SYMFONY, Elastic Search stack) and a new hosting facility. This will be in production yearly 2024 (expected delivery time: February 2024). Having a separate and fully dedicated infrastructure solution to deliver the www.orpha.net website will greatly increase both security and stability. Plus, without direct dependencies to the legacy database, the new website configuration will ease the main changes needed at the level of this legacy DB.

Nevertheless, the legacy infrastructure hosted by the Inserm Department of Informatics (Inserm DSI), still needs to be maintained, as it manages the main database. During December 2023 we experienced a DB failure (due to a side effect during a project deployment) which was leading to reload a backup and reimport the one-week changes without losses. The relative instability of the current legacy infrastructure managed by Inserm DSI needs to be solved. We will reallocate resources to boost the project dedicated to the new database and the interfaces needed to manage our datasets.

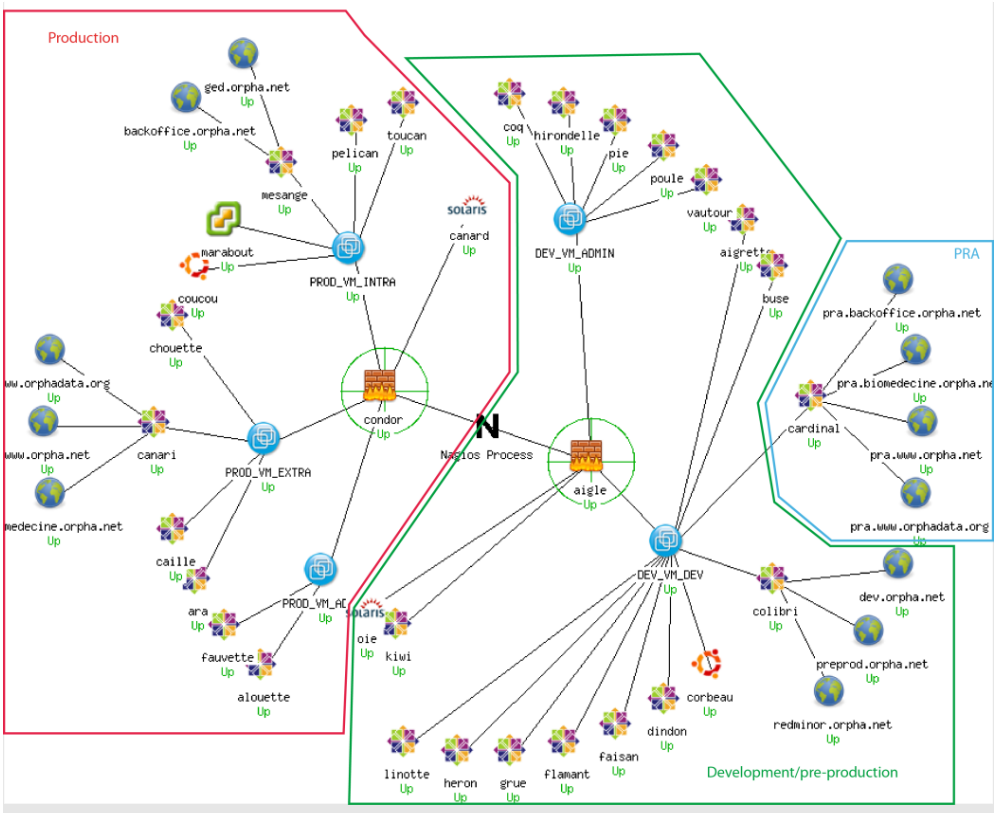


Figure 10 Orphanet's IT architecture in 2023

3.8. 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 by contacting the Orphanet national teams: 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.

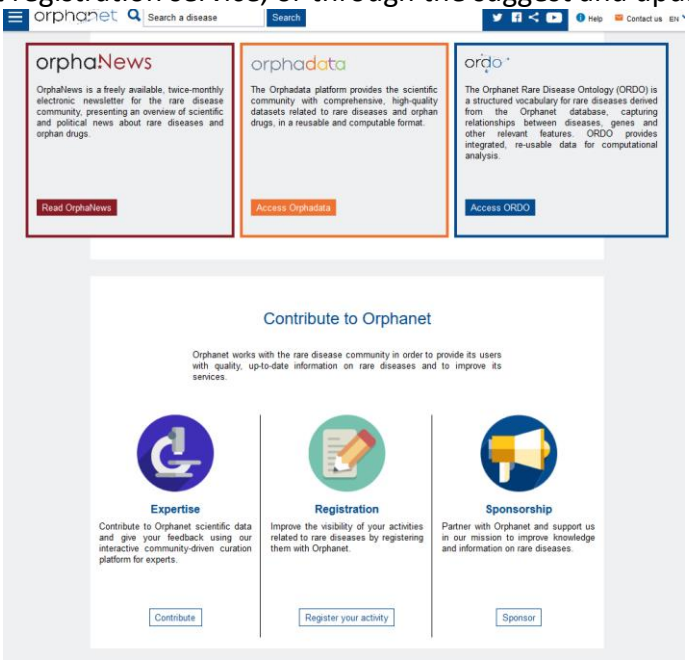


Figure 12 Access to Orphanet services and services for interaction with the curation team

3.8.4. INDEXATION BY SEARCH ENGINES

According to Google webmaster tools, the prominence of the www.orpha.net site can be assessed by the number of indexed pages, for which there are 1,410,000 responses (plus 19M “pages” crawled but not indexed by Google).

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 90.5% 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 6.3% of visits come from users directly visiting Orphanet, without passing by a search engine, and the rest come from other sites' referral or social media referrals, for example.

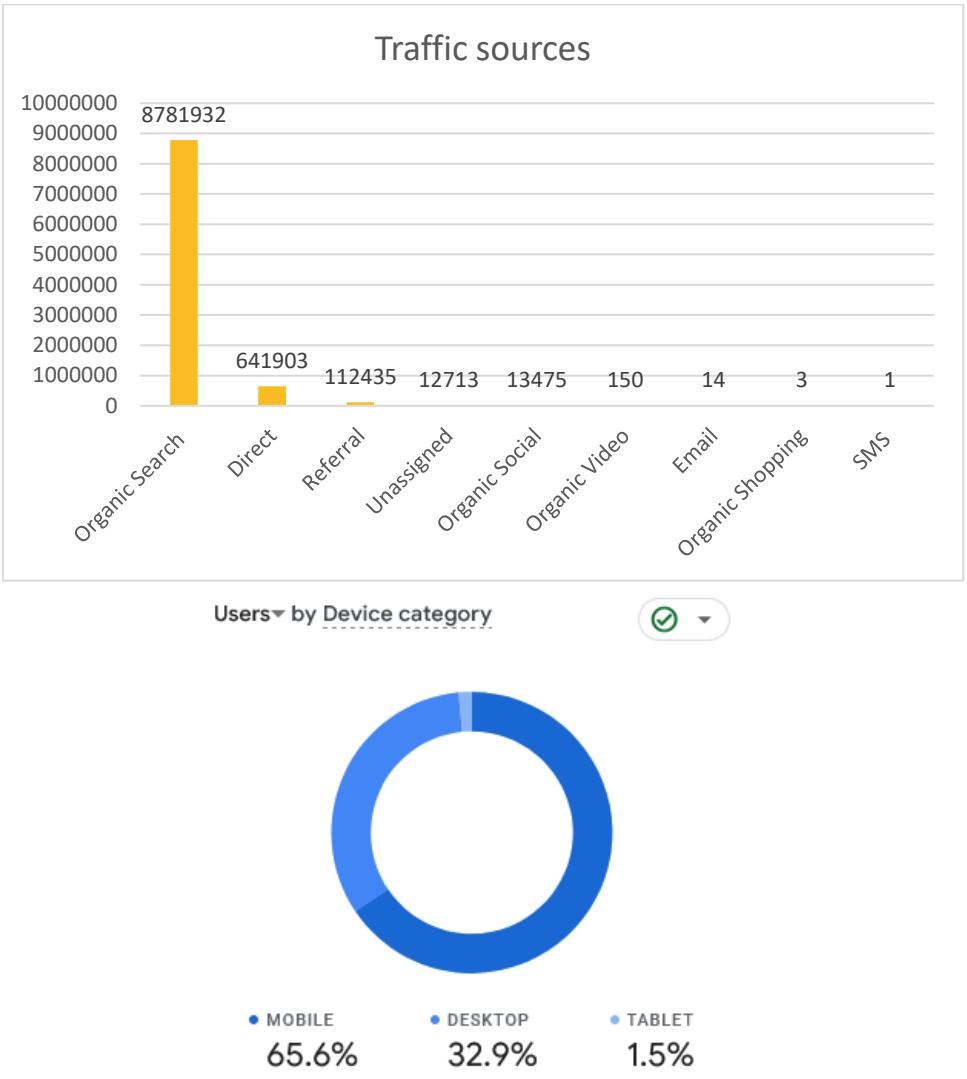


Figure 13 Distribution of the traffic sources and users by device category
(Source: Google Analytics, 23 May 2023 to 31 December 2023)

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.

Google Analytics allows users to trace visits made from mobile devices (Smartphone, tablets): these visits represented 65.6% of all visits during 2023, an increase of 3% when compared to 2022). The newest version of Orphanet has a responsive design and so provide a much better adaptation to any mobile device.

3.8.5. THE WEBSITE'S AUDIENCE[6]

ORPHANET IN NUMBERS

- 16 million users
- 34 million pages viewed
- 2.9 million PDFs downloaded
- Visits from 236 countries

In 2023, around 16 million users consulted the Orphanet website with around 34 million pages viewed, thus on overage around 93'000 pages were viewed per day.

The Google Analytics module does not include direct access to PDF documents. However, PDF documents are an important entry point and generate a consistent volume of visits: 2.9 million PDFs were downloaded from the site in 2023.

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

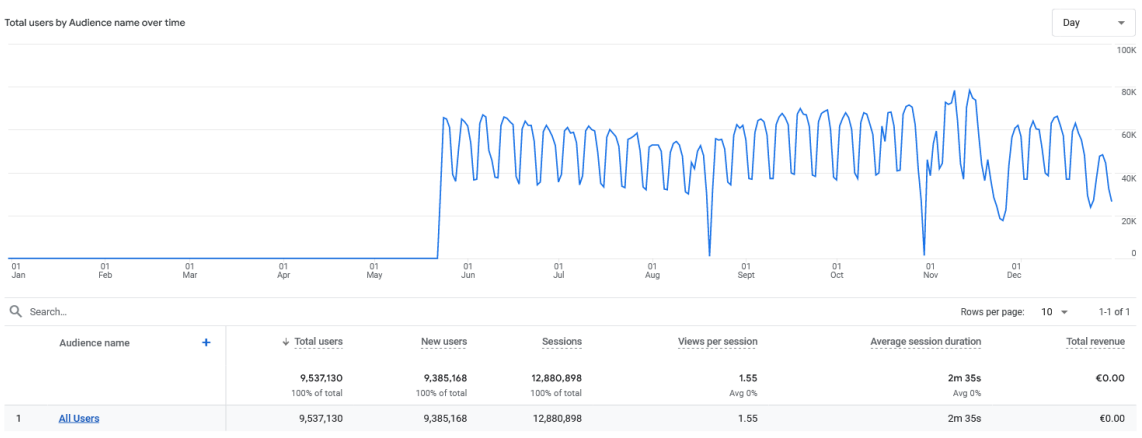


Figure 14 Orphanet website consultations in 2023
(Source: Google Analytics 4, June 2023 to December 2023)

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). From June 2023 Google Analytics 4 is now used to track the use of the Orphanet website with significant changes to how numbers of users are counted. We have decided to extrapolate results for January to May 2023 from the June-December 2023 Google

[6] The Google Analytics module changed from June 2023. To calculate the statistics for the total year 2023 we have extrapolated the figures presented in this section from the reference set of Google Analytics 4 results for June-December 2023.

Analytics 4 results for the statistics of the whole of the year 2023. 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.

The number of sessions rose compared to 2022, from 20 to 22 million Figure 15), and there was a small increase in the number of users (16 million compared to 15.3 million in 2022); the number of pages per session decreased from 1.66 to 1.55, the average session duration was 2m35s.

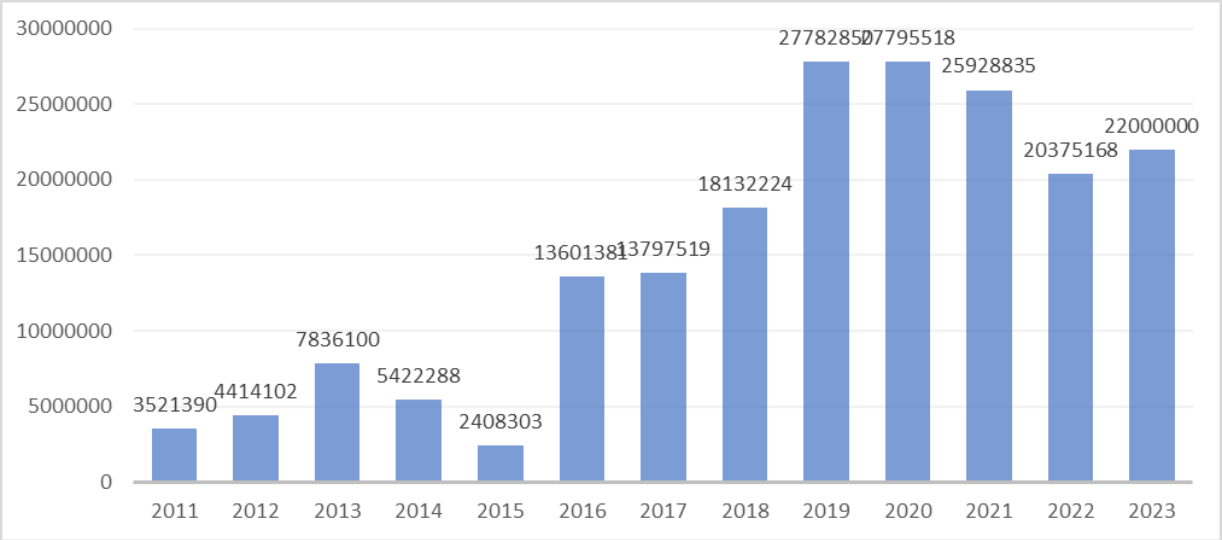


Figure 15 Evolution of number of sessions since 2011 (Source: Google Analytics)[7]

3.8.6. 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 2023, 29 national websites are online. Some of these national websites are published completely in their national language while for other countries, the layout of

[7] Please note that Google Analytics setup major changes during 2023 with the new version GA4. Comparisons with previous years will may not be totally relevant. Consider also that the next version of www.orpha.net will be more align with GDPR and cookie management which may lead to having less data directly (a larger proportion of users will not allow tracking by Google).

the national webpage is in English and the mandatory texts (General Information) are in their respective national language.

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

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

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

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 (118’357 HPO-Disorder associations and 132,786 HOOM classes of which HPO-Disorder Associations as of September 2023) 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 2023, ORDO files were downloaded 6413 times from Orphadata and 11,567 times from Bioportal. In 2023, HOOM files were downloaded 3692 times from Orphadata and 344 from Bioportal.

3.10. 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 Science, the open-access section of the platform was designated as an ELIXIR Core Data Resource at the start of 2019 and as a Global Core Biodata Resource at the end of 2022.

In 2022 the Orphadata website was reworked to provide better visibility to the different datasets, resources and tools, and to provide better navigability to end-users. The APIs made available by Orphadata, including the ORPHAcode API, were also made more visible. A distinct area for our CC BY 4.0/open data entitled 'Orphadata Science' was also integrated into the new site. Orphadata also moved from its original www.orphadata.org to www.orphadata.com after this face-lift.

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 nine languages: English, French, German, Italian, Portuguese, Spanish, Dutch, Polish and Czech. Part of the datasets, those in the Orphadata Science section, 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, ICD-11 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).**
• **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)**

• **Orphanet nomenclature files for coding (Nomenclature pack)**

Table 7 Products freely accessible via Orphadata Science (ELIXIR Core Data Resource & Global Core Biodata Resource)

• 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 eight 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. Only non-nominative/non-personal data are accessible, in accordance with personal data protection laws.

The datasets were updated one a month until the end of 2022, and twice a year from 2023 (n.b. the Orphanet nomenclature pack is updated once a year in July). The date of the last release is indicated.

Since 2019 Orphanet provides the "Nomenclature pack", also : 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.

The pack also includes:

- A Linearisation dataset, that includes all rare diseases present in the Orphanet nomenclature (ORPHAcode and preferred term in English), each with the preferential medical specialty as attributed by Orphanet.
- A "Master file", initially developed in the framework of the EU RD-Action joint action, which contains the minimal information needed for satisfactory data sharing and statistical analysis at the EU level: all active ORPHAcodes present at the Disorder level only (i.e. excluding Groups and Subtypes), with their respective preferred term, synonyms, and aligned ICD-10 & ICD-11 codes. This file, which is available in Excel format and in English only, provides a simplified visualisation of the Nomenclature file content, and easier access for users who are not in capacity of exploiting XML files and need a simple tool to help them code rare diseases manually.
- An Orphanet Nomenclature differential file, that enlists all clinical entities that have been created, inactivated (deprecated, obsolete, and non-rare entities), or modified (preferred term, synonyms, definition, aggregation level, etc.) since the previous release.

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, methodology of linearisation, procedures for the epidemiological data collection in Orphanet, and procedures for the inventory of genes related to rare disease.

The XML models for Orphadata products, and UML schema for ORDO are published on Orphadata. 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 (the Orphanet Rare Disease Ontology) and HOOM (HPO-ORDO Ontological Module), and thus facilitate the use and reuse of the data and tools available via the platform.

In 2023, **Orphadata products (free and on request) were downloaded more than 147,020 times**. This represents an increase of around 65% compared with 2022 (Figure 17); This decrease can be explained by a stabilisation in the number of downloads of the classifications and nomenclature pack products (which were massively downloaded in 2021).

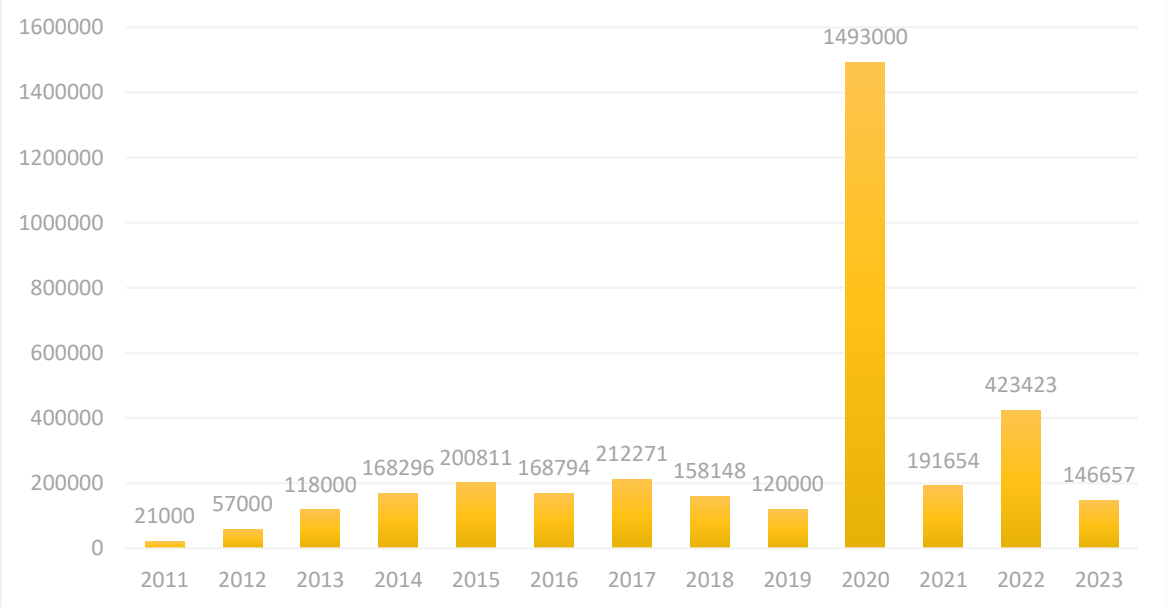


Figure 17 Number of downloads from the Orphadata website since mid-2011. It should be noted that in 2020 there was a massive download of the classifications datasets that constituted an anomaly that has not since been reproduced.

The most requested Orphadata product in 2023 were the classifications.

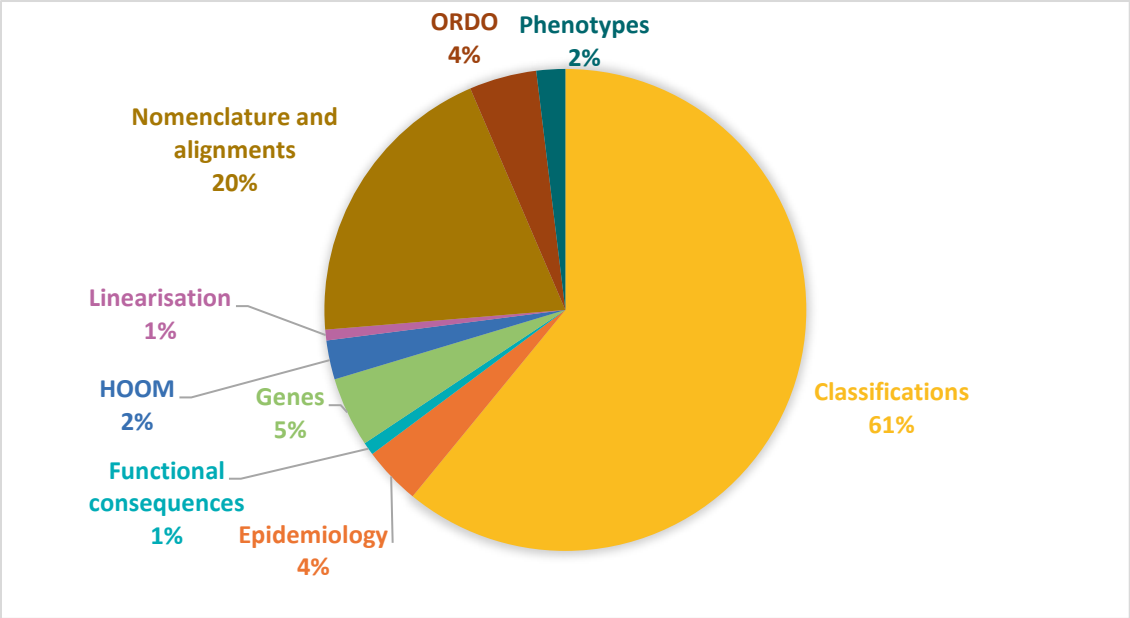


Figure 18 Distribution of the downloads of Orphadata freely available datasets (Orphadata Science) in 2023 [total 141,751 downloads]

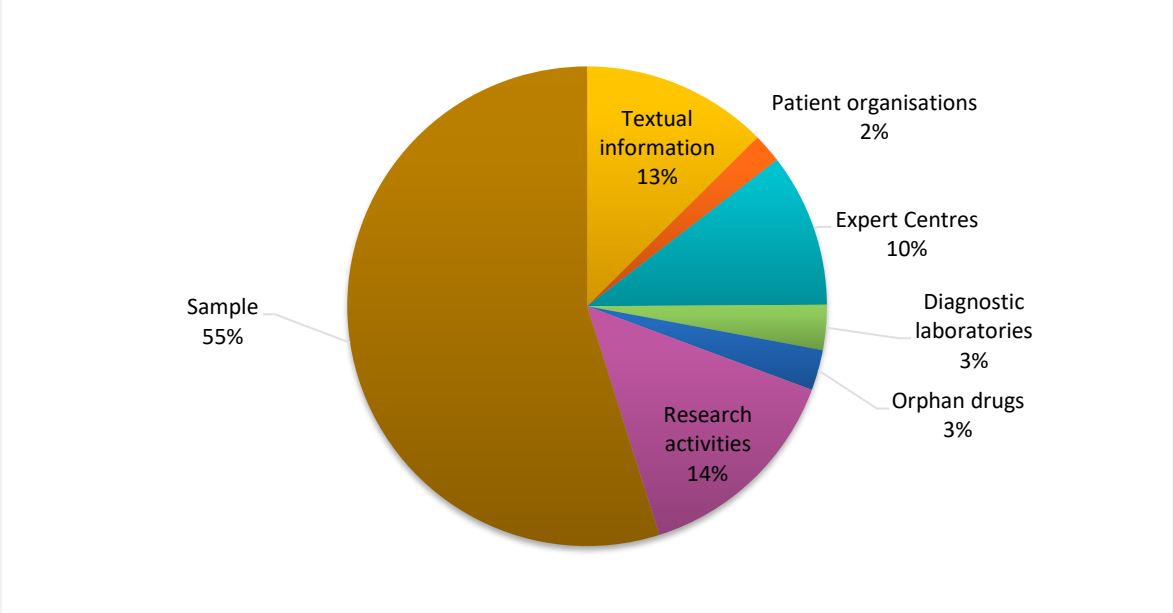


Figure 19 Distribution of the downloads of Orphadata Datasets accessible on demand in 2023 [total of 5,269 downloads]

3.10.4. ADDITIONAL FUNCTIONALITIES IN 2023

In 2023, alignments with ICD-11 were added to the Orphadata Science datasets and to the Orphanet nomenclature pack.

3.11. 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 was supported by the European Commission's DG SANTE (PP-1-2-2018-Rare 2030) until the start of 2021, and is realised with the support of Fondation IPSEN, under the aegis of Fondation de France, from September 2021 to the end of 2023. OrphaNews France is supported by the French Muscular Dystrophy Association (AFM-Téléthon), while OrphaNews Italy is supported by Sanofi.

In 2023 both the email and web presentations of the newsletter were updated for a more modern feel and smoother user experience which aligns with Orphanet's "Know the Rare for Better Care" visual identity. A survey of subscribers was carried out to gauge feedback on the new format in 2023: 79% agreed that the new site was easier to navigate, 83% agreed that the new format was easier to read and more attractive, and 78% reported that they could find articles that interested them more easily.

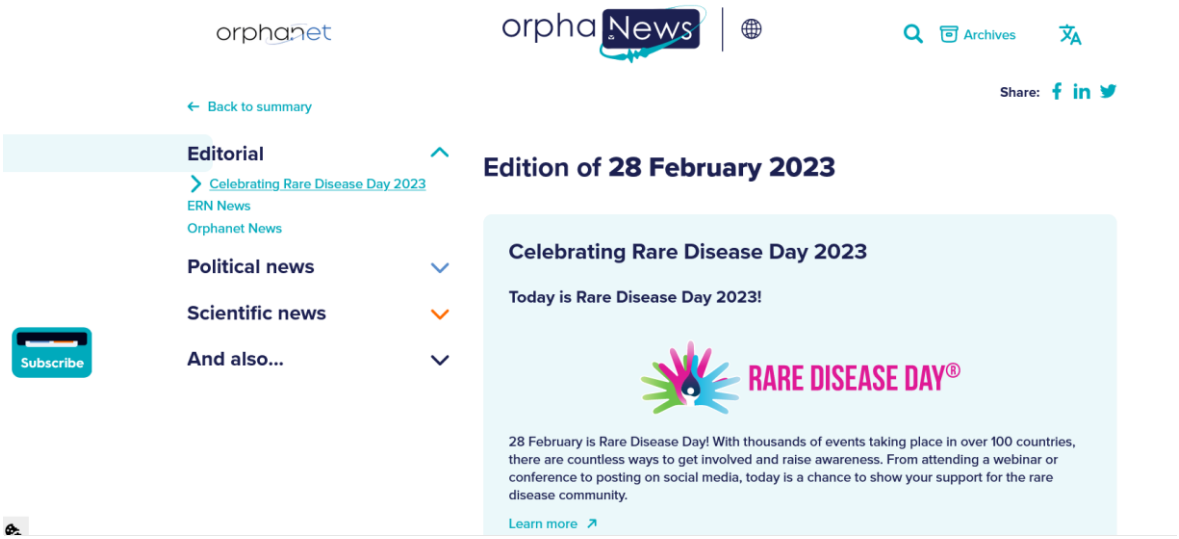


Figure 20 OrphaNews' new look

At the end of 2023 OrphaNews in English had 11 942subscribers. OrphaNews in French had 6,947 subscribers and OrphaNews in Italian had 5,350 subscribers.

In order to help professionals and people living with rare diseases find expert recommendations and services concerning COVID-19 and rare diseases, Orphanet published a list of resources available in different languages from March 2020 in a special edition of OrphaNews. This list includes resources curated by the European Reference

Networks and EURORDIS and is updated regularly, most recently integrating recommendations concerning vaccination.

In response to the humanitarian crisis resulting from the war in Ukraine, we have compiled and made available via a special edition of OrphaNews, a list of resources for people living with rare diseases affected by conflict/displacement. These are updated as necessary.

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 *3*.9. Articles have been downloaded over 3,764,904times as of end 2023. 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.

Figure 21: Orphanet Journal of Rare Diseases Homepage

Users: 2024 Edition of the annual Orphanet satisfaction survey

The 2024 satisfaction survey to ascertain users' experience over the previous year was conducted in one phase launched in June 2024 via a pop-up window appearing on the first page users landed on. The survey was translated in 8 out of 9 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 was closed after 6 weeks of display on the website. This survey was composed of 13 questions split into 3 sections : Knowledge of and reasons for using the Orphanet website ; Your opinion on Orphanet's products/services and its website ; More information about you.

An Orphanet Report Series providing an analysis of the results is available.

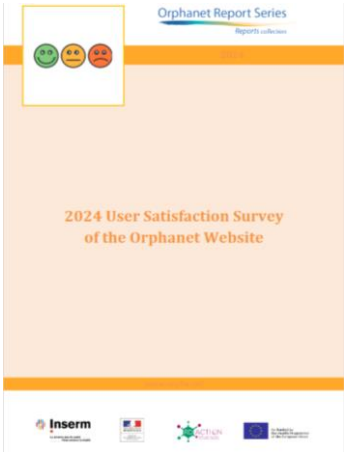


Figure 22 Orphanet Report Series: 2024 User Satisfaction Survey

4. 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. A table resuming the inclusion of Orphanet activities in national plans and strategies for RD is available here.

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 is according to the German Action Plan on Rare Diseases, 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 Centers, to coordinate the identification and registration of Dutch centers 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, advised by medical experts and patient organizations, evaluates potential centers 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 center is ensured within the institute. Since this year the

application of candidate centers should follow as much as possible the thematic structure of the European Reference Networks (ERNs) to facilitate a smooth collaboration between the centers of expertise and ERNs. Centers from both University Medical Centers and non-university major "top-clinical" hospitals are invited to apply for designation. More information regarding the application and evaluation process is published on the NFU website (in Dutch; https://www.nfu.nl/themas/zorg-op-de-juiste-plek/zeldzame-aandoeningen/vws-erkenning-ecza-jaarlijkse-aanvraagronde). Between the start of the project, in 2015, and 2020, 3 rounds of evaluation took place. From this year on evaluation rounds will take place in a yearly cycle. Currently (results from the evaluation round of 2021 aren't included yet) ~340 medical centers are designated by the Ministry as official Dutch centers of expertise for rare diseases. These centers can be found on the Orphanet website or by using the 'Expertisezoeker' (https://www.expertisezoeker.nl/) developed by the Erfocentrum.

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

5.2.1. 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 and maintains the Orphanet nomenclature of rare diseases, a unique and multilingual standardised system aimed at providing a specific terminology for rare diseases. It is composed of a unique and stable ORPHAcode for each entry of the inventory which 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 had already expressed their interest in using ORPHAcodes (as a complement to existing coding systems) was provided via a dedicated work package (WP5) of the Joint Action for rare diseases RD-ACTION from 2015 to 2018 (www.rd-action.eu). This work package has notably

produced essential information resources, guidelines and recommendations on ORPHAcoding.

Following the recognition of the Steering Group on Promotion and Prevention (SGPP) of ORPHAcodes as best practice (https://webgate.ec.europa.eu/dyna/bp-portal/transferred) RD-CODE (www.rd-code.eu/), co-funded by the Third Health Programme, ran from 2019 to 2021.
The objective of this project was to support 4 Member States in improving gathering information on rare diseases by demonstrating real-world ORPHAcodes implementation in different settings, to guide other countries in the future. The project delivered tools, support services, information resources, guidelines and recommendations according to real-world use of ORPHAcodes . These are indispensable tools to guarantee the appropriate use of the coding resources allowing comparability across countries and settings. Also, a new ORPHAcode to capture remaining **undiagnosed patients** after full investigation was made available to ensure the visibility of this important group of patients. Finally, a study "ORPHAcodes use for the coding of rare diseases: comparison of the accuracy and cross country comparability" (Mazzuccato et al. 2023) was published in 2023.

The experience from the RD-CODE project , showed that the real-life implementation in health information systems is challenging due to the heterogeneity of coding systems, practices, and tools and that local support in local language for coders and technical teams is necessary to achieve proper implementation in compliance with good practice guidelines for coding so as to increase data quality and comparability. And OD4RD and then OD4RD2 project were launched to guarantee the appropriate use of the coding resources allowing comparability across countries and settings (as described in the paragraphs above). In the framework of OD4RD2 a state of play report was conducted and published mi-2023 which documents use of ORPHAcodes in Member States. In two participating countries ORPHAcodes are used to produce data or statistics for RD in all hospitals. In most cases ORPHAcodes are used in registries, either national registries (10) and/or regional registries (3). In most countries ORPHAcodes are used in centers of expertise for RD, either nationally (5) or regionally (7). In three countries ORPHAcodes are not yet used for that purpose, but two of them are preparing for implementation. Among the five countries that participated in 2022 that did not use ORPHAcodes at the time of last year's survey, only one is not yet using ORPHAcodes, but is preparing to launch a national registry using ORPHAcodes in 2023.

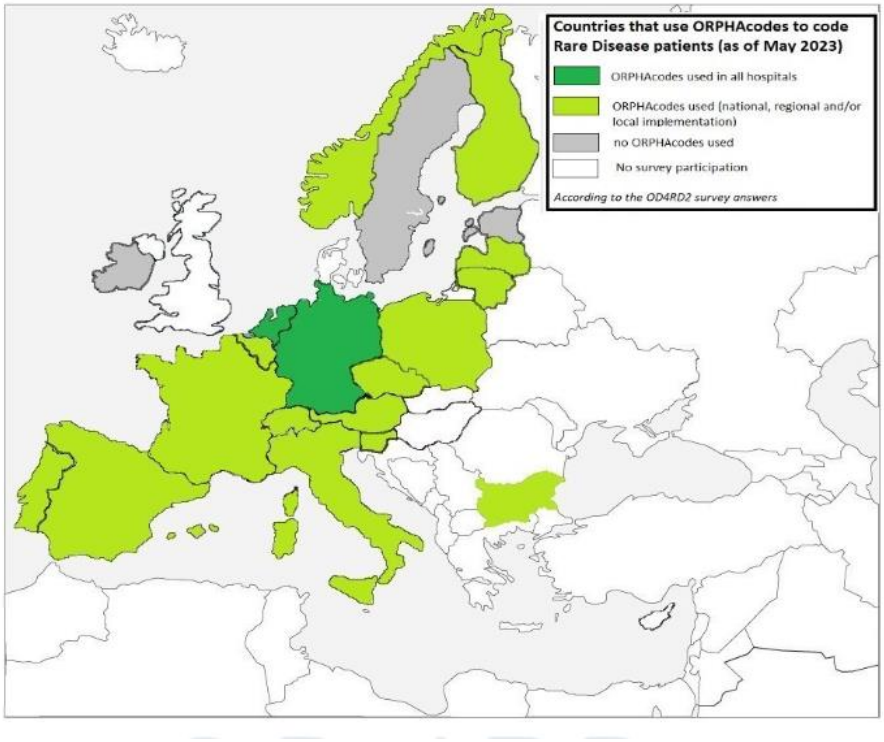


Figure 23: Use of ORPHAcodes in countries participating in the OD4RD2 survey (2023)

Czechia

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 was to better identify patients in the healthcare system so as to improve knowledge of their healthcare pathways. Within the French third National Plan for Rare Diseases and 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 played a major role. A governmental memo was released in January 2018, 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 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. In addition, Orphanet provides yearly training sessions to the French networks of expertise in order to increase the harmonisation of coding practices. ORPHA codes are being implemented in electronic health records progressively, as is the rare diseases minimum dataset. The introduction of ORPHAcodes allows the BNDMR to be used in studies regarding, amongst

others, the diagnostic delay, the mortality as well as health-economic studies that would not have been possible without this codification.

Germany
After conclusion of the 6-year project on coding of rare diseases which intended to integrate the Orphanet classification of diseases by adding ORPHAcodes and by expanding the inventory of rare diseases within the ICD-10-GM a better alignment of German disease terms within both database systems lead to more congruence between both systems. As of April 2023, the use of the resulting Alpha-ID-SE file will be mandatory for all German hospitals with regard to the coding of rare diseases.

The Netherlands
To prepare for the implementation of ORPHAcodes in the Dutch hospital information systems a working group of DHD (Dutch Hospital Data), Nictiz and Orphanet Netherlands checked the alpha mapping file in which SNOMED concepts are linked to specific ORPHAcodes. Several suggestions for modifications and new mappings were sent to both SNOMED International and the coordinating Orphanet team.

Italy
In 2017, ORPHA codes were integrated into the health and research information systems of eight Italian regions. The new national plan regarding the policies on rare diseases (LEGGE 10 novembre 2021, n. 175 Disposizioni per la cura delle malattie rare e per il sostegno della ricerca e della produzione dei farmaci orfani) has been released in November 2021. The article 4 states that the updated list of rare diseases/groups of rare diseases to be covered by the Essential Levels of Care, must refer to the ORPHA codes and to the Orphanet classification system. The ORPHAcode is implemented and currently used by 10 Italian Regions/Regional Registries for rare diseases.

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.

The Ministry of Health of Portugal was recommended by the Assembly of the Republic to implement a personal card for people with rare disease in order to give them a special status in the health system. In the end of 2013, a card of people with rare diseases was issued. This card is being distributed, since 2014, to patients and it includes relevant information such as, the name and the "ORPHA code" of the disease; the name and contact of the Reference Centre and it has on its back-side specific health recommendations (totally addressed for each patient) to be provided in case of emergency.

5.2.2. 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, 65.8% of rare disorders in Orphanet are represented in the ICD-11 (Joint Linearisation for Mortality and Morbidity Statistics and/or Foundation). A mapping file between ICD11 and ORPHA codes is released together with the Orphanet Nomenclature Pack for coding since 2023. Orphanet contributes to the enrichment of ICD-11 with rare disease terms, as part of the French WHO collaborating center since 2021, and through direct reinforced collaborationA 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. 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/).

5.2.3. 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 first alignment file was made available in October 2021, and it isued in October each year since, distributed alongside SNOMED CT by SNOMED International to its licensed members in a machine-readable format, and by Orphanet via Orphadata in a human-readable format.

5.2.4. 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. Alignments were revised and updated in 2023.

5.3. Catalogue of services

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

5.4.1. Current

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 South-Korea or South-Africa, amongst others. Thanks to European Commission co-funding (under Support-IRDiRC project and the European Joint co-fund Programme for Rare Diseases, EJP RD), Orphanet has coordinated the development of a rare disease research analysis platform made available to IRDiRC and Orphanet members allowing for easily landscape the research situation and to contribute building a RD research strategy in the IRDiRC realm.

Orphanet also provides regular data analysis for the following indicators on the IRDiRC website on a yearly basis: number of new RD, number of genes linked to RD, 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 secretariat 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.

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.

COLLABORATION WITH THE FRENCH INSTITUTE OF BIOINFORMATICS – ELIXIR FRANCE

Orphanet is a French Institute of Bioinformatics' contributing 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, 20 platforms are full members, 7 contributing platforms, and 8 associated teams. 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.

After having participated in an ELIXIR pilot use case on rare diseases in the context of the EXCELERATE project and having been included in the ELIXIR Biosharing platformat 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

pursues its work to develop and maintain quality standards for its scientific data and will move forward to adopt FAIR data principles.

Collaboration with NIH

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, maintained through regular calls, improves 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). In 2022 an agreement was signed with the National Library of Medicine to allow the integration of the Orphanet nomenclature of rare diseases into UMLS, a key achievement in positioning ORPHAcodes as an interoperability vector for health and research at a global level.

Gene Curation Coalition

Orphanet is one of the founding members of the Gene Curation Coalition (GenCC), a coalition composed of several groups and resources providing information on validity of gene-disease relationships. GenCC has created a database bringing together this data: curated gene-disease relationships are submitted by GenCC member organisations, including Orphanet. By providing harmonised definitions for different levels of gene–disease validity based on existing resources, GeneCC aims resolve curation conflicts, thus permitting better consistency in genetic testing and variant interpretation.

MAPI Research Trust

Orphanet co-leads WP3 of the European Project ERICA, which has the general aim of facilitating the Europe-wide implementation of standardised Patient-Centred Outcome Measures (PCOMs) and Patient Reported Outcome Measures (PROMs) for rare diseases while ensuring the involvement of the patient community in their development and validation process. Orphanet contributes to this work with the Disabilities annotations and collaboration with MAPI Research Trust (MRT) in order to assess what PCOMs and PROMs are already available and what are the gaps, and which could be exploited for more than one disease. Outside the scope of this project, Orphanet and MRT collaborates establishing direct links between the Orphanet's individual RD pages to the PROQOLID database And vice-versa, in order to give visibility through Orphanet to RD-specific PCOMs and PROMs (see Links to external Rare Disease literature for more information and statistics).

GLOBAL BIODATA COALITION

On 15 December 2022, the Global Biodata Coalition announced its first list of Global Core Biodata Resources (GCBRs). Amongst the 37 resources whose long-term funding and sustainability is deemed to be critical to life science and biomedical research worldwide figures Orphadata Science, which includes Orphanet's scientific knowledge base, nomenclature (ORPHAcodes) and ontologies.

This status comes 4 years after Orphadata Science received ELIXIR Core Data Resource in 2019, and makes Orphadata Science one of the 12 European resources to have been designated at international level by the Coalition.

The selected resources are deemed to be essential to the management curation and access of research data, and are either deposition databases, or knowledge bases such as Orphanet, that draw together data and add value through expert curation and annotation. The Coalition, through a rigourous two-step application process and the implication of over 50 independent, expert reviewers, frames these open resources such as "keystone species in an ecosystem.... whose failure would have a critical impact on the global research endeavour".

The Coalition's partner funders will now work actively with the selected resources in order to determine the funding models that would assure the long-term sustainability of these resources so that they can develop and continue to serve the global research community.

5.4.2. Past

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

From 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".

6. Funding

Orphanet's budget was approximately 4.45 million Euros in 2023, originating from 10 different contracts for the core activity funding and from various other contracts in some of the participating countries (Figure 24).

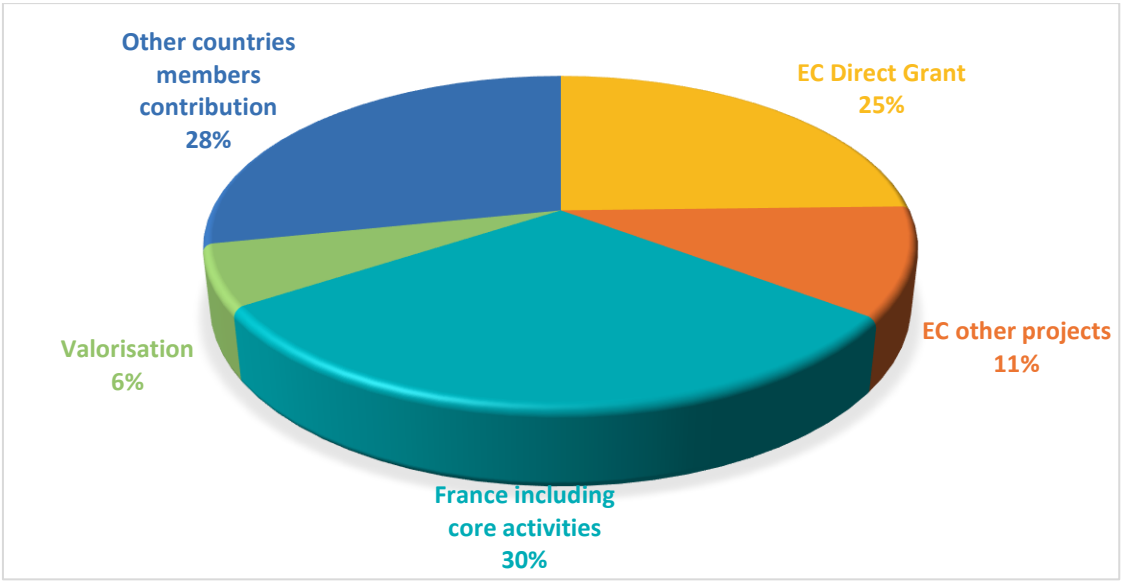


Figure 24 Orphanet's global budget 2023

6.1 Orphanet's core activity funding

Orphanet's core activities include the infrastructure, the coordination activities (management, management tools, quality control, rare disease nomenclature in English, classifications, scientific annotations and production of the encyclopaedia, as well as the Quality Management System -QMS-) and communication, partnerships and valorisation activities. It excludes the collection of data on expert resources in the participating countries as well as translation activities.

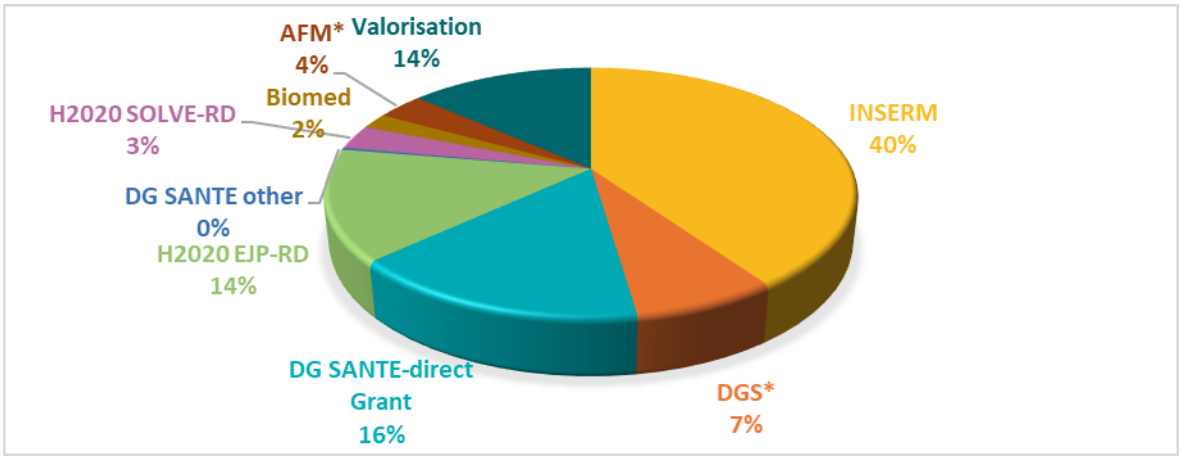


Figure 25 Orphanet core activities funding 2023.

This budget (approx 1.98 million Euros) excludes the costs of infrastructure (office space) which are essentially covered by INSERM (Figure 25).

6.2.1. EUROPEAN FUNDING

The European Commission funded the inventory of rare diseases, the encyclopaedia, and the collection of data on expert resources 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 Orphanet Europe Joint Action 20102206 (2011-2013) & DG Santé Operating Grant Orphanet 20133305 (2014). From 2015 to 2018 Orphanet coordinates the DG Santé 3HP grant RD-ACTION Joint Action 677024; fom 2028 to 2020 Orphanet coordinates the DG Santé 3HP OrphaNetWork Direct Grant (831390); from 2019 to 2021 the DG Santé 3HP RD-Code project (826607); and the DG Santé EH4H OD4RD 101070531 Project in 2022. In 2015, Orphanet participated in the ECRIN Integrating Activity (ECRIN-IA, 284395), funded by the European Union Framework Program 7. From 2012 to 2018 Orphanet coordinated the Support-IRDiRC Contract. Orphanet coordinated the HIPBI-RD project (Erare Joint calls) [2016-2019] and from 2018, Orphanet participates in the H2020 project Solve-RD 779257 and from 2019 Orphanet participates in the H2020 EPJ-RD project 825575 and the H2020 XeHealth project 951938, from 2021 Orphanet Participates in the H2020 ERICA (964908) and in the EU4H TEHDAS 101035467 (2021-2023) and in the EUH4 EHDS2 101079839 (2023-2024).

Orphanet network is funded by the EU4H Orphanet Direct Grant OD4RD2 101110100 (2023-2025).

6.2.2. OTHER CURRENT FINANCIAL PARTNERSHIPS FOR CORE ACTIVITY FUNDING

Instituts thématiques Inserm Institut national de la santé et de la recherche médical	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 newborn screening and HTA.
FONDATION IPSEN	OrphaNews International and the annotation rare diseases with their functional consequences with the supported in 2023 Fondation IPSEN, under the aegis of Fondation de France.

Table 9 Other current financial partnerships for core activity funding

6.2.3. 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).
REACTOME A CURATED PATHWAY DATABASE	Cross-referencing with Reactome.
e!Ensembl	Cross-referencing with Ensembl.
IUPHAR international union of basic and clinical pharmacology	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.
	Orphanet and RD-Connect shared information on biobanks and patient registries in the frame of EJP RD since 2019. Orphanet provides RD-Connect with the nomenclature and ontology of RD for inclusion in RD-Connect's GPAP platform. Both initiatives collaborate in the frame of the Solve-RD project and in EJP RD.
	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. Orphadata Science 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. The Orphanet nomenclature is integrated into the UMLS (Unified Medical Language System) since 2022.
	Orphadata Science is a Global Core Biodata Resource, designated by the Global Core Biodata Coalition.

Table 10 Current non-financial partnerships for core activities

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 of Research related Expert resources at the national level is also supported by the European Commission (EJP-RD) and in 2023 the established of National Nomenclature Hubs was supported by the OD4RD2 Direct Grant . Globally this budget reaches 2.47 M € of which 1.56 M € of national contributions in 2023. Please refer to Figure 26 for an overview of funding of national activities contributions.

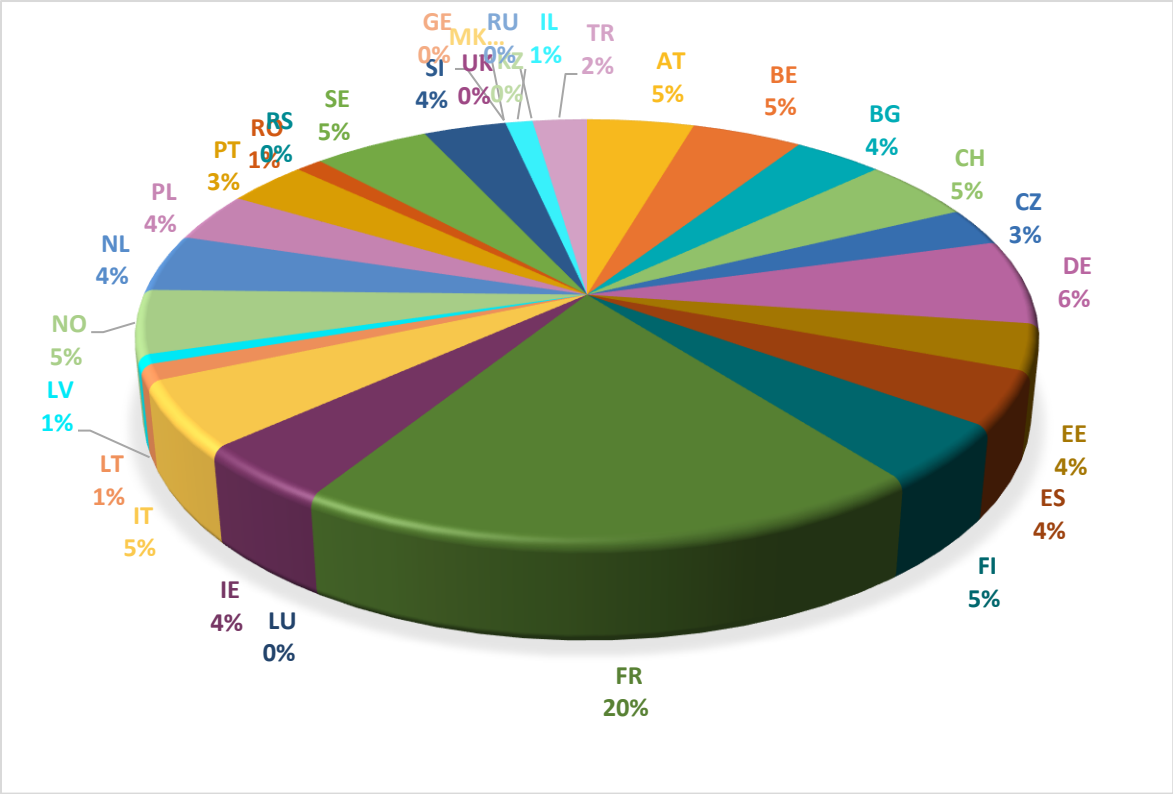


Figure 25 Funding sources for national activities in 2023[8]

6.2.4. 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

8 To calculate this budget: real costs are used for INSERM US14; (DGS and AFM budget are arbitrarily split into 2 for core activities and national activities). For other countries the budget is estimated from the THE position needed for expert resources data collection and the median EU salary of 6K/month.

	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	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.
federal public service HEALTH, FOOD CHAIN SAFETY AND ENVIRONMENT	The Federal Public Service Health, Food Chain Safety and Environment was a beneficiary in RD-ACTION 677024 (financial support from the European Health Program).
INAMI-RIZIV	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	
Bulgarian Association for Promotion of Education and Science BAPES	The Bulgarian Association for Promotion of Education and Science (BAPES) hosts Orphanet Bulgaria's activities.
CROATIA	
Hrvatski savez za rijetke bolesti	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.

	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).
	CZ Orphanet team is collaborating together with the Institute of Health Information and Statistics of the Czech Republic on the RD-Code project.
ESTONIA	
	The University of Tartu was a beneficiary in RD-ACTION 677024.
FINLAND	
	Rinnekoti Foundation was a beneficiary in RD-ACTION 677024.
FRANCE	
	The French Directorate General for Health (DGS) finances the collection of data in France for the expert resources catalogue.
	The “Association Française contre les Myopathies“ finances OrphaNews France.
	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.
GERMANY	

Federal Institute for Drugs and Medical Devices	BfArM (Federal Institute for Drugs and Medical Devices) finances the collection of data in Germany for the expert resources catalogue.
HUNGARY	
ÁNTSZ	Orszagos tisztifoorvosi hivatal - OTH was a beneficiary in RD-ACTION 677024.
	Semmelweiss Egyetem was a beneficiary in RD-ACTION 677024
ITALY	
	The Italian Health Ministry finances Orphanet-Italy activities through current research funding.
Bambino Gesù OSPEDALE PEDIATRICO	The Bambino Gesù Children's Hospital was a beneficiary in RD-ACTION 677024.
SANOFI GENZYME	Genzyme, a Sanofi Company, finances OrphaNews Italia.
IRELAND	
Feidhmeannacht na Seirbhíse Sláinte Health Service Executive	The Health Service Executive provides co-funding for Orphanet Ireland staff.
JAPAN	
AMED	Japan Agency for Medical Research and Development (AMED) provides funding to the Orphanet Japan's core activities.
Boehringer Ingelheim	Nippon Boehringer Ingelheim Co ., Ltd., a pharmaceutical company, provided funding to support national activities 2021.
LATVIA	
Centre for Disease Prevention and Control of the Republic of 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 Dutch Ministry of Health, Welfare and Sport co-funds the work of Dr. Judith Carlier and Prof. Wendy van Zelst-Stams.
	The Amsterdam UMC contributes to the project by allocating time of Prof. Martina Cornel, chair of the Dutch Orphanet Scientific Advisory Board.
	The Radboudumc contributes to the project by allocating time of Dr. Wendy van Zelst-Stams.
NORWAY	
	The Norwegian Directorate of Health hosts part of Orphanet Norway’s activities and contributes to the project by allocating the time of some professionals.
	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.
	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 - Institute for Molecular and Cell Biology hosted Orphanet-Portugal from 2009 to June 2015.

	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.
	DGS - The Directorate-General of Health, at the Portuguese Ministry of Health, was a 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	
	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	
	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

6.2.5. 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	
	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	
INH	The National Institute of Hygiene hosts Orphanet Morocco's activities and contributes to the project by allocating the time of some professionals.
SERBIA	
ИМГГИ IMGGE	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	
PRINCIPE FELIPE CENTRO DE INVESTIGACION	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

6.2.6. 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	

SOSIAALI- JA TERVEYSMINISTERIÖ	The Ministry of Social Affairs and Health of Finland officially supports Orphanet.
DUODECIM TERVEYSPORTTI	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	
maladies rares	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
MALADIES RARES INFO SERVICES	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	
achse Allianz Chronischer Seltener Erkrankungen	The "Allianz Chronischer Seltener Erkrankungen e.V." (ACHSE) works together with Orphanet Germany on information services for patients.
KINDERNETZWERK WIR HELFEN WEITER	The "Kindernetzwerk e.V. - für Kinder, Jugendliche und (junge) Erwachsene mit chronischen Krankheiten und Behinderungen" provides data on associations in Germany.
Federal Ministry of Health	The Federal Ministry of Health (BMG) officially supports Orphanet
NAKOS Nationale Kontakt- und Informationsstelle zur Anregung und Unterstützung von Selbsthilfegruppen	Nationale Kontakt- und Informationsstelle zur Anregung und Unterstützung von Selbsthilfegruppen (NAKOS) officially supports Orphanet.

AWMF	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.
HUNGARY	
Emberi Erőforrások Minisztériuma	The State Secretary of Health within the Ministry of Human Resources officially supports Orphanet.
IRELAND	
An Roinn Sláinte Department of Health	The Department of Health officially supports Orphanet and provides governance of Orphanet Ireland.
NRDO National Rare Diseases Office	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.
HSE Feidhmeannacht na Seirbhíse Sláinte Health Service Executive / Royal College of Physicians of Ireland	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 / medical research charities group / IPPOSI Irish Platform for Patients' Organisations, Science and Industry	'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	
Istituto Superiore di Sanità	The "Istituto Superiore di Sanità" officially supports Orphanet.
Telethon	Telethon collaborates with Orphanet for the collection of data concerning research projects.
UNIAMO Federazione Italiana Malattie Rare Onlus	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.it project by BURLO	Netgene collaborates with Orphanet for the diffusion of information on rare diseases.
Farmindustria	Farmindustria promotes Orphanet publications.

Osservatorio Malattie Rare O.Ma.R.	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	
NFU NEDERLANDSE FEDERATIE VAN UNIVERSITAIR MEDISCHE CENTRA	The NFU (Netherlands Federation of University Medical Centres) coordinates the designation of expert centers for rare diseases. After evaluation of candidate centers according to the EUCERD criteria by external experts the Dutch Ministry of Health is advised on the official designation of individual centers. The Dutch Orphanet team is a partner in this procedure.
erfocentrum	The Erfocentrum provides information to the general public on genetic, mainly rare 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 organizations dedicated to rare diseases and participates in the designation of Dutch expert centers for rare diseases.

	DHD (Dutch Hospital Data), responsible for the Diagnosis thesaurus used in Dutch Hospital information systems collaborates with Orphanet Netherlands to prepare for the implementation of ORPHAcodes in the Diagnosis thesaurus.
	Nictiz, the Dutch competence centre for electronic exchange of health and care information, is responsible for the Dutch SNOMED edition and collaborates with DHD and Orphanet Netherlands in the implementation of ORPHAcodes in the Diagnosis thesaurus.
POLAND	
	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	
	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.
	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.
	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	
	The Ministry of Health of Slovenia officially supports Orphanet.

SPAIN	
	The Spanish Ministry of Health, Consumption and Social Welfare- Office for Health Planning and Quality officially supports Orphanet.
	The Institute of Health Carlos III (ISCIII) provides Orphanet with data on national research projects funded through the Health Strategic Action Calls.
	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	
	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.
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 2023, A5-size flyers to present Orphanet and Orphanet services were updated when necessary:

- Orphanet
- Orphadata (English)
- Orphanet Guides application (French)
- ORPHA codes (English)
- OrphaNews (English &French)
- Newborn Screening Library (English & French)
- Rare Disease Knowledge™ App (English & French)
- Resources for ERNs (English)
- Orphanet tutorials

A short brochure about Orphanet's global positioning and achievements in the previous year was also produced and made available.

In 2022 we launched our video explaining Orphanet's missions and a communications pack for Orphanet teams in the scope of our sustainability objective, centred around the slogan "Orphanet: Know the Rare for Better Care".

In the scope of the EU 3rd Health Programme funded project RD-CODE Orphanet has produced a short video explaining to potential end users what ORPHA codes are and how they can help make rare diseases visible in health information systems. The video also highlights the different resources available to those who wish to implement ORPHA codes. In addition to the English version, the video is now available in Czech, German, French, Italian, Romanian, and Spanish. A guidelines to ORPHAcoding video was also made available.

A video presenting guidelines for coding undiagnosed patients was also made available.

7.2. Invitations to give lectures at conferences in 2023

Orphanet representatives, as specialists in the field of rare diseases, were invited to give lectures and to participate with poster presentations in 52 conferences and events worldwide in 2023. These lectures were mostly focused on presenting the Orphanet

database, the ORPHA nomenclature, Orphadata, 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 2023

In 2023, we held a booth at the following events:

- SIGU Congress 2023, 04-05/06/2023, Rimini, Italy
- European Society of Human Genetics, 10-12/06/2023, Glasgow, UK
- French Rare Disease Alliance Congress, 10/06/22 Paris, France
- American Society of Human Genetics, 02-04/11/2023, Washington DC, USA

7.4. Articles in peer-reviewed journals

Members of the Orphanet network contributed to the following articles:

Mazzucato, M., Pozza, L.V.D., Facchin, P. et al. ORPHAcodes use for the coding of rare diseases: comparison of the accuracy and cross country comparability. Orphanet J Rare Dis 18, 267 (2023). https://doi.org/10.1186/s13023-023-02864-6

Roberts AM, et al. Towards robust clinical genome interpretation: developing a consistent terminology to characterize disease-gene relationships - allelic requirement, inheritance modes and disease mechanisms. medRxiv [Preprint]. 2023 Apr 3:2023.03.30.23287948. doi: 10.1101/2023.03.30.23287948. Update in: Genet Med. 2024 Feb;26(2):101029. doi: 10.1016/j.gim.2023.101029. PMID: 37066232; PMCID: PMC10104222.

Anne-Sophie Denommé-Pichon et Al, A Solve-RD ClinVar-based reanalysis of 1522 index cases from ERN-ITHACA reveals common pitfalls and misinterpretations in exome sequencing, Genetics in Medicine, Volume 25, Issue 4, 2023, 100018, ISSN 1098-3600, https://doi.org/10.1016/j.gim.2023.100018.

Fiore, M., Giraudet, JS., Alessi, MC. *et al.* Emergency management of patients with Glanzmann thrombasthenia: consensus recommendations from the French reference center for inherited platelet disorders. Orphanet J Rare Dis 18, 171 (2023). https://doi.org/10.1186/s13023-023-02787-2

Lennart F. Johansson et al, A unified data infrastructure to support large-scale rare disease research, medRxiv 2023.12.20.23299950; doi: ttps://doi.org/10.1101/2023.12.20.23299950

Orphanet, ORPHA code and Orphanet resources were cited around 365 times in 2023.

7.5. Social media

The Orphanet coordinating team maintains a Facebook page (6,500 followers and 6,000 likes) and a Twitter account (@orphanet : -6,479 followers) as well as the Orphanet Youtube channel. A LinkedIn page is also available.

The Orphanet Italy team also maintains a Facebook page (17'000 followers) and a YouTube channel.

7.6. Events

Orphanet was again invited by EURORDIS to promote the annual Black Pearl Awards, aimed at recognising those who make a difference in the field of rare diseases every day around Rare Disease Day. Orphanet also helped the review of the nominations for the scientific award.

8. The Orphanet team in 2023

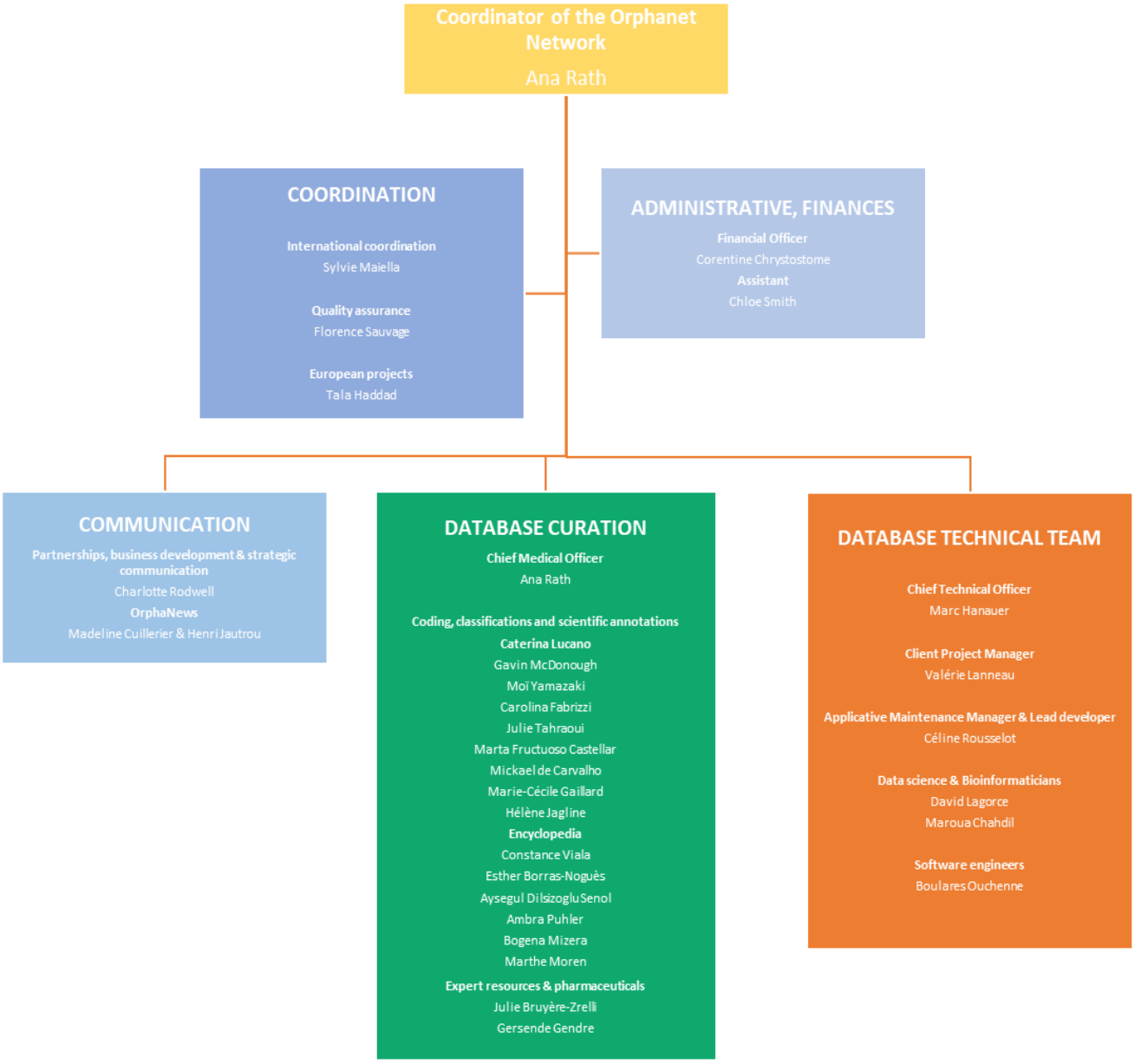


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Figure 26 Organisational chart (December 2023)

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