



orphanet

2015 Activity Report

2015 Activity Report

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Abbreviation list

BNDMR: French Rare Diseases Data Repository

CEQAS : Cytogenetic European Quality Assessment Service

CHMP : the Committee for Medicinal Products for Human use

CNIL : Commission nationale de l'informatique et des libertés : the French dataprotection authority

CNSA: French National Solidarity Fund for Autonomy

COMP : the Committee for Orphan Medicinal Products

DG Santé : Directorate General Health and Consumers

DIMDI: German Institute of Medical Documentation and Information

ECRIN: European Clinical research Infrastructure Network

EJHG: the European Journal of Human Genetics

EMA: the European Medicines Agency

EMBL - EBI: European Bioinformatics Institute

EMQN: European Molecular genetics Quality Network

EQA: external quality assessment

EUCERD: the European Union Committee of Experts on Rare Diseases

FDA: Food and Drugs administration

HGNC : Human Genome Organisation Gene Nomenclature Committee

HPO : Human Phenotype Ontology
ICD: International Classification of Diseases
ICD-10GM: German ICD-10
ICHPT: International Consortium of Human Phenotype Terminologies
IHTSDO: International Health Terminology Standards Development Organisation
INSERM: the 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: the 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

1.1. Objective

Orphanet endeavours to provide the community at large with a comprehensive set of information and data on rare diseases and orphan drugs in order to contribute to the improvement of the diagnosis, care and treatment of patients with rare diseases.

1.2. Activities

[Orphanet](#) is currently a comprehensive repertory of information and data on RD, notably in terms of referenced documents. It is also the only project that establishes a link between diseases, the existing textual information concerning RD and the appropriate services for patients, researchers, healthcare professionals and decisions makers. Moreover, Orphanet's database content is robust and expert validated, updated continuously, and quality controlled. 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 site provides access to:

- A [comprehensive inventory of rare diseases classified according to a polyhierarchical classification system](#). Each disease is indexed with ICD-10, Online Mendelian Inheritance in Man (OMIM), Medical Subject Headings (MeSH), Unified Medical Language System (UMLS), Medical Dictionary for Regulatory Activities (MedRA), and associated genes, within its 'identity card' that also includes the relevant prevalence category, age of onset category, and mode of inheritance.
- An encyclopaedia covering more than 6,800 rare diseases or group of diseases, with summary texts written by scientific writers and reviewed by world-renowned experts. Summary texts are produced in English and are then translated into French, German, Italian, Portuguese, Spanish, Dutch, Polish, Slovak, Greek and Finnish. For certain selected diseases, emergency guidelines and articles for the general public are produced in French and then translated.
- An [inventory of high quality articles published by other journals or learned societies](#). More than 1000 articles have been published, 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 directory of expert resources, validated by national experts in the 35 member countries and providing information on: [specialised expert centres and centres of expertise](#), [medical laboratories](#), [research projects](#), [clinical trials](#), [registries](#), [networks](#), [technological platforms](#) and [patient organisations](#).

A range of other services:

- A [support-to-diagnosis tool](#) (search by signs and symptoms).
- [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.
- Thematic studies and reports on overarching subjects: the "[Orphanet Report Series](#)" (ORS), published as PDF documents.

1.3. Highlights of 2015

Orphanet international positioning

- **INSERM, US14 - Orphanet now coordinates RD-ACTION** (www.rd-action.eu), the new Joint Action on RD co-funded by the 3rd EU Health Programme.
- The evolution of the Orphanet database of rare diseases into a European, sustainable model has been set as the **main objective of the WP4 of the RD-ACTION**. Participation in this action ensures also that Orphanet's data contributes to the implementation of rare disease policies across Europe and that Orphacodes are used to enable rare disease patients to be identified in health information systems.
- **Orphanet and the Orphanet Rare Disease Ontology (ORDO) have been awarded the "IRDiRC Recommended" label**. This quality indicator, introduced by IRDiRC, endorses selected tools, standards and guidelines that are of fundamental importance to rare disease research and development.
- **Orphanet has also become the French Institute of Bioinformatics' 30th platform**, thereby integrating the **French node of Elixir**: a distributed infrastructure for life-science information (Elixir unites Europe's leading life science organisations in managing and safeguarding the massive amounts of data being generated every day by publicly funded research).
- **New composition of the International Advisory Board** in charge of peer-reviewing the Orphanet project. [Member list is available online](#).

Improving transparency and traceability

- **In addition to the general SOPs** available online since 2013, that are updated regularly, the procedures used for the **alignments with ICD-10** and those used to carry out the **linearisation of disorders** are available online since 2014. **The list of Orpha signs and symptoms used to annotate the diseases, cross-referenced with other nomenclatures (HPO, PhenoDB, LDDb)**, are also available online at www.orphadata.org since 2014.
- **Sources used for validation** of diseases and of the the gene/disease relationship are now available for downloads in the datasets on www.orphadata.org.
- **New board: Genetic Advisory Board** in charge of advising Orphanet on topics related to the gene database and the genetic tests and laboratories database. [Member list is available online](#).

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 directories of expert resources: **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

- **Most of the Orphanet Report Series have been updated**: List of Rare Diseases, Prevalence of Rare Diseases, Lists of Orphan Drugs, Registries, List of Research Infrastructures useful to Rare Diseases in Europe, Orphanet Activity Reports, and Satisfaction Surveys.
- **New format of the epidemiological ORS**: in order to include the new epidemiological data collected such as incidence, prevalence at birth, and numbers of cases/families, in addition to

prevalence data. The methodologies of these reports have also been updated in agreement with new datasets.

- **The Orphanet Activity report 2014 was translated into Italian and Spanish.**
- **The Orphadata user guide was updated.**
- **The Orphanet Journal of Rare Diseases app is now available on Google Play and iOS.**

Orphanet website information

- **The Classification search tab has been improved to help health professionals to implement ORPHA codes when coding patients:** you can now search by ORPHA code using this tab. In the search results, the ORPHA code has been added after each disease name.
- **An improved disease search results page that is clearer, easier and more coherent:** when searching for a disease by OMIM, ICD10 or Orpha number, the search engine displays one result per disease, even if the type string matches with one or several synonyms or keywords for the same disease, (synonyms and keywords are still shown but after the name of the disease, rather than as separate results).
- **Improvements to the gene pages:** genes can be indexed with **several of the external references** of HGNC, UniProtKB, Genatlas, OMIM, Ensembl, Reactome and IUPHAR. In the identity card of the gene, information on **“Previous symbols and names”** has been added in addition to the one for the **“Synonym(s)”**. An **evolution of the gene search engine** has also been implemented, so that it is possible to search both in 'Previous symbols and names' in addition to synonyms and symbols.

Codification of RD using ORPHA codes

- New collaboration between the **IHTSDO and Orphanet** to improve visibility of rare diseases in SNOMED CT.
- The implementation of ORPHA codes in national health information systems is ongoing. In addition to the progression of this implementation in **Germany and France**, pilot experiences are being conducted in **Hungary, Latvia and Norway**. ORPHA codes are currently being used in centres of expertise in **the Netherlands and Slovenia**. The use of ORPHA codes as a complement to already existing coding systems is being explored in most EU Member States, as recommended by the European Commission Expert Group on Rare Diseases.

Users satisfaction

- **Users are satisfied with the utility of the services provided by Orphanet:** in the 2015 satisfaction survey, 76% of respondents stated that the services they used were very useful or useful.
- **A 49% increase in downloads of the Orphanet report Series, compared to 2014**
- **A 20% increase in downloads of Disability factsheets, compared to 2014**
- **A 19% increase in Orphadata downloads, compared to 2014**

2. Orphanet consortium

2.1. The RD-ACTION Joint Action

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).

Because of this assessment, the evolution of the Orphanet database of rare diseases into a more European, sustainable model has been set as the main objective of the WP4 of the RD-ACTION, the new Joint Action on RD co-funded by the 3rd EU Health Programme and launched on the 17th of September, 2015 in Luxembourg. This instrument combines funding from the European Commission and each of the participating Member States, as well as from Switzerland, Canada and Australia, as collaborating stakeholders.

Following the two previous Joint Actions - Orphanet Joint Action and EUCERD Joint Action - RD-ACTION represents renewed support of the European Commission (EC) to rare diseases, through its Directorate General for Health (DG SANTE). This work will last three years (until June 2018) and follows the logic of coherence and continuity vis-à-vis the previous actions, but aims to go further in terms of concrete implementation and consolidation of policies. This action is coordinated by Orphanet (INSERM, US14), bringing together 63 European and non-European participants.

RD-ACTION has three main objectives:

- contribute to the implementation, by member states, of the recommendations of the EC Panel in relation to policies on these diseases,
- support the development of Orphanet and make it sustainable, and finally
- help Member States to introduce the ORPHA codes in their health care systems to make rare diseases visible.

RD-ACTION was designed in the spirit of integration and coherence so that the data produced by Orphanet can contribute in the necessary analysis of policy recommendations and political action that will then guide the production, operation and dissemination of this data. Participants will ensure effective communication between each of the member states and the EC Panel, in order to concretely support the implementation of their recommendations. Most of the Orphanet country coordinators contribute to the work of RD-ACTION's work packages, therefore participating to the RD codification and policy implementation.

2.2. Orphanet 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, guiding the project 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.

External boards:

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

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

In the framework of the RD-Action Joint Action 2015-2018 most of the Orphanet activities are co-funded by the EC. As a result, the Orphanet Management board also refers to the General Assembly of the RD-Action project (please refer to www.rd-action.eu for additional information).

2.3. Expansion of the consortium

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 into 35 neighbouring countries to the East and to the South. In 2011, Orphanet went further west to include Canada. The consortium expanded towards Australasia, with Western Australia joining in 2012. In 2014, Georgia and Tunisia joined the consortium followed by Argentina (the first south-American country), in 2015.

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

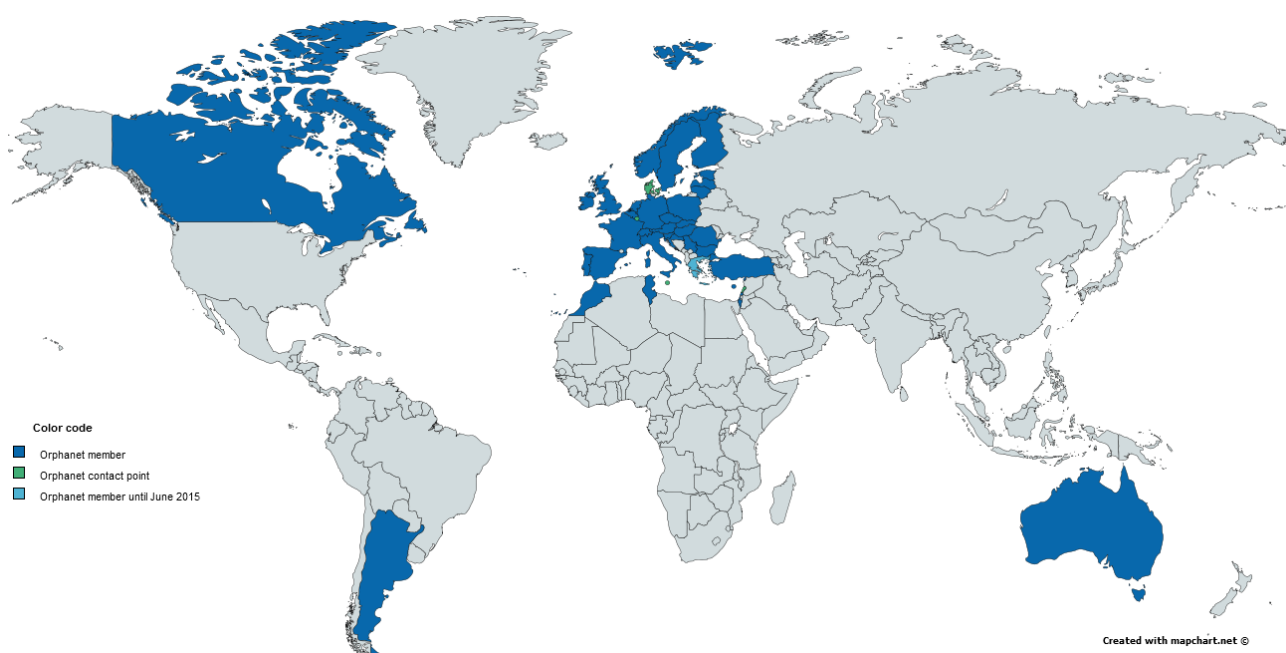


Figure 1 Orphanet members and contact points

2.4. Orphanet members and scope of their activity

2.4.1. COORDINATING TEAM

The coordination of the consortium is managed by the coordinating team, located in Service Unit 14 of INSERM (the French National Institute of Health and Medical Research). INSERM has been the coordinator of the Orphanet consortium since 2001.

The coordinating team is responsible for the coordination of consortium activities, the hardware and software aspects of the project, the database of rare diseases and the production of the encyclopaedia, as well as the training of all members of the consortium and the quality control of the directory of resources in the participating countries.

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. MEMBERS

The establishment of a directory of resources can only be achieved by the consolidation of data collected at the country level. The identification of expert resources 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 clinical trials, medical laboratories, expert centres, research projects, registries, platforms, networks and patient organisations.

Translations of the Orphanet content in the national language are also managed by the national teams, provided that they have a sufficient budget. Currently Belgium, France, Germany, Italy, Spain and Portugal are undertaking the translation of the entire website's content into their national language, while the Polish, Finnish, Slovak teams are translating the summary texts encyclopaedia.

Management of the national website/entry point to the Orphanet portal is also carried out by every national team in their national language.

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

3. Orphanet: Products and Services

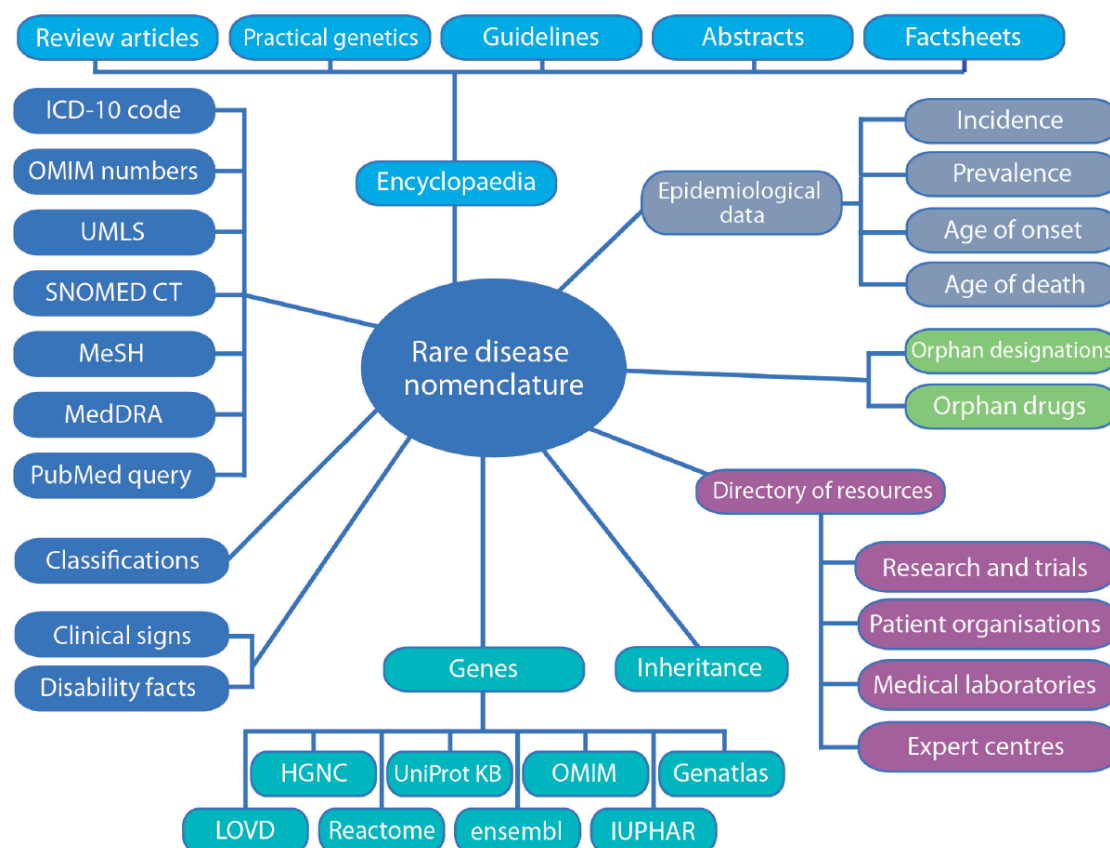


Figure 2 Orphanet relational database

Orphanet is an evolutive relational knowledge database with added value, as the scientific content produced in-house is expert-validated (list of expert reviewers having contributed to the scientific content [here](#)) and integrated with other available resources, as shown in the diagram presented in Figure 2 and described hereafter.

Entries in the Orphanet disease database correspond to rare diseases (defined in Europe as having a prevalence of no more than 1/2,000), rare forms of common diseases, and diseases for which prevalence figures are unknown but are potentially rare. Some diseases that are non-rare in Europe but that are rare in other countries, like the USA, can be considered for inclusion if their addition is necessary in order to represent expert resources in these countries.

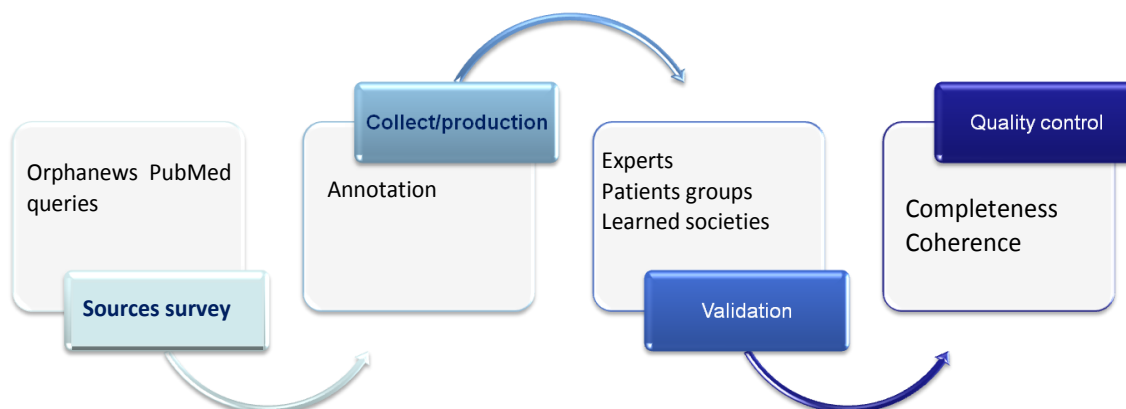


Figure 3 Orphanet data production methodology

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, and is the basis for the production of various texts (encyclopaedia, guidelines, etc.). All texts and data (annotations on epidemiological data, clinical signs, 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 consortium are responsible for the collection, validation and submission of data on expert resources. 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 are developed regularly to resolve the issue of information dispersion and to address specific needs of the different stakeholders.

3.1. 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 (Figure 3). Indeed, the typeface is magnified and information is organised in easy-to-spot blocks that allow users to more readily navigate the site. The disease search function is in the centre of the homepage, while the tabs for Orphanet's other principal resources are organised into a table of contents. The popular Orphanet Report Series, which addresses relevant rare disease and orphan drug topics, is highlighted in a specific area. Finally, OrphaNews, the newsletter of the rare disease community and a dissemination tool for RD-ACTION, is easily identified near the top right corner of the homepage.

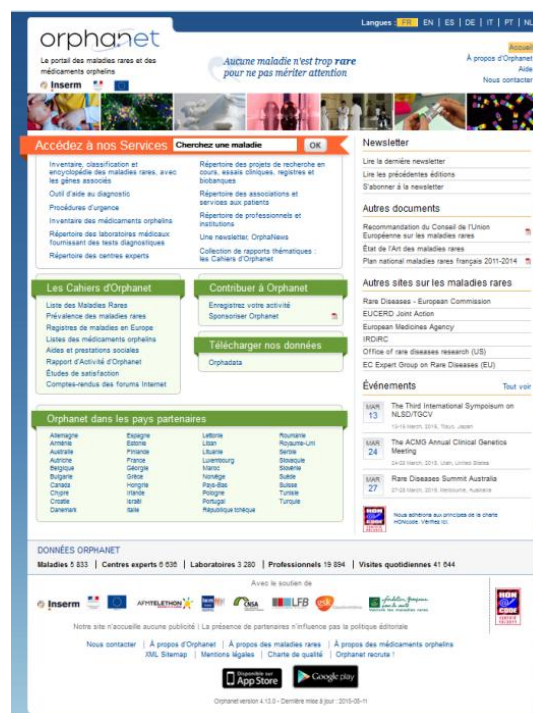


Figure 4 The Orphanet portal homepage in 2015

To help users navigate the website, a list of our principal services is proposed on the “[Help](#)” page. Services are categorised to accommodate different user profiles.

3.1.1. INDEXATION BY SEARCH ENGINES

According to Google, the prominence of the www.orpha.net site can be assessed by the number of results obtained by using the site name as a query, for which there are 3,530,000 responses. Users mainly access the www.orpha.net site through search engines, namely organic searches (51% of visits according to Google Analytics), and Google alone accounts for almost 49% of queries (Figure 5). 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. Other sites generating traffic to Orphanet represent 3% of visits. The remaining visits are made via direct access (bookmarks, 46%).

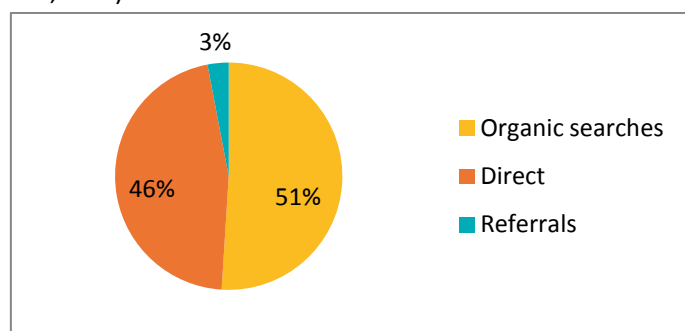


Figure 5 Distribution of the traffic sources
(Source: Google Analytics, 1st of January 2015 to 31st of December 2015)

The wealth of information available on our site attracts a substantial number of visits due to a sizable corpus of keywords (rather than just certain predominant keywords). The keyword primarily used to

access our site is simply “Orphanet”. The indexation of our site is of the “long tail” type: more than 300,000 different keywords generate traffic to the site.

Google Analytics allows users to trace visits made from mobile devices (Smartphone, tablets): these visits represented 20% of all visits during 2015, a figure that remains stable when compared to other years (20% in 2014, and 23% in 2013).

3.1.2. THE WEBSITE’S AUDIENCE

In 2015, around 30 million pages were viewed, thus on average around 82,000 pages were viewed per day (Figure 6). This figure has decreased in comparison to 2014 (90,000 pages viewed per day). This can perhaps be explained by the new policy on informing users about visit counts (please see below).

The Google Analytics tool does not include direct access to PDF documents. However, PDF documents are an important entry point and generate a consistent volume of visits: each month, around 1,910,000 PDF documents are consulted on the Orphanet website. This represents a figure of around 14,260,000 downloads in 2015, which is 20% higher than in 2014 (around 11,824,000 downloads).

The users come from 217 countries. The top ten countries are: France, Italy, Germany, Spain, United States, Belgium, United Kingdom, Switzerland, Brazil and Mexico.

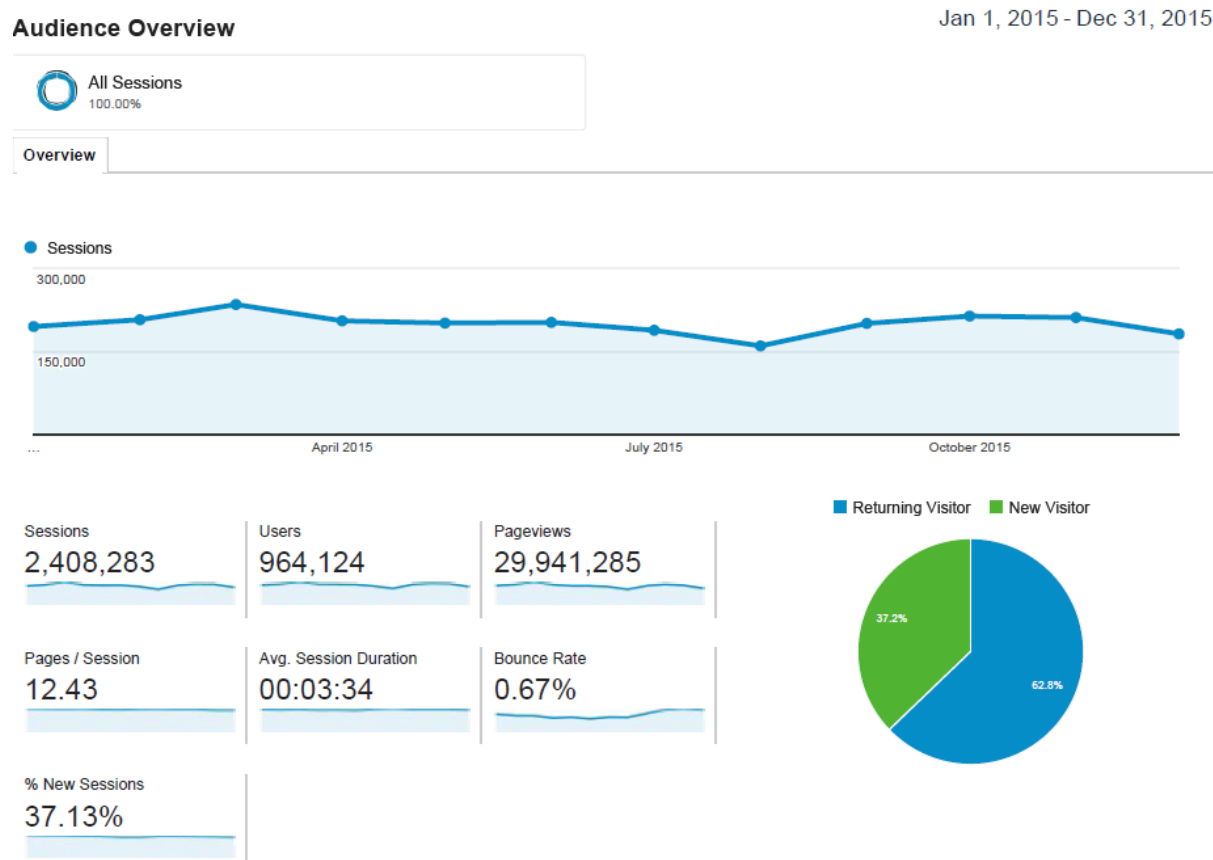


Figure 6 Orphanet website consultations in 2015
(Source: Google Analytics, 1st January 2015 to 31st December 2015)

The tool that is used to track our audience is Google Analytics. It allows 3 parameters to be monitored: sessions, users and page views (thus allowing us to calculate a substantial ratio of page views / visitors). It should be noted that the current way in which users and sessions are counted is liable to change. For example, in 2014, the CNIL (Commission nationale de l'informatique et des libertés: the French data protection authority) recommended that websites inform users of the measurement tools used on the website, such as Google Analytics. During the summer of 2014 we developed a pop-up that requires users to accept this measurement. In case of refusal or inaction (no change of page for example), the user and the session are not properly recognized by the tool. The decrease in the number of sessions and users in 2015 is explained by the fact that users refused to be counted or stayed on the page for only a very short time and thus were not counted. This has no influence on the duration of visits but can explain the decrease in total number of sessions in 2015 compared to 2014.

On the other hand, the pages viewed per visit have doubled in 2015 compared to 2014: this reflects an effective increase in the use of the site. Globally since 2011, the number of pages seen per session has increased by a multiple of 6 (Figure 7).

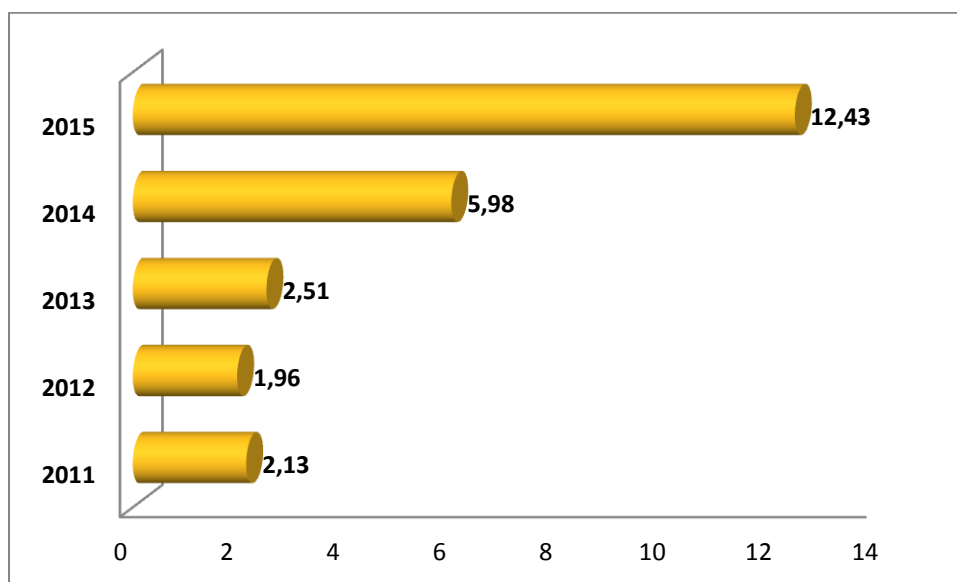


Figure 7 Numbers of pages seen/session since 2011

3.1.3. ORPHANET NATIONAL WEBSITES

In order for Orphanet to become an instrument in national plans or strategies for rare diseases, the international portal in seven languages has evolved towards customised websites by each country in their national language(s).

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 2015, 38 national websites are online. Some of these national websites are published completely in their national language while for other countries, the layout of the national webpage is in English and the mandatory texts (General Information) are in their respective national language.

3.2. The Orphanet servers

The production servers are located to one of the largest civil data centre in France, the CINES (Centre Informatique National de l'Enseignement Supérieur). To ensure structural security, the development servers are located in another INSERM building close to the CINES and linked to it by a fiber optic connection. This allows an excellent connectivity between production servers, development servers and backup environments. The architecture of the servers is represented in Figure 8.

Many production environments are in place: back office, pre-production, preservation and development environments. This makes the Activity Recovery Plan (PRA) of the Orphanet website highly efficient. Back-office tools used by the coordinating team in France, and other teams internationally, are accessed through VPN (Virtual Private Network) servers. No major problems were encountered in 2015 and the www.orpha.net website was highly available despite an increasing amount of visitors, which now reaches over 3 million pages viewed per month. We have made several updates for security reasons (PHP and servers OS).

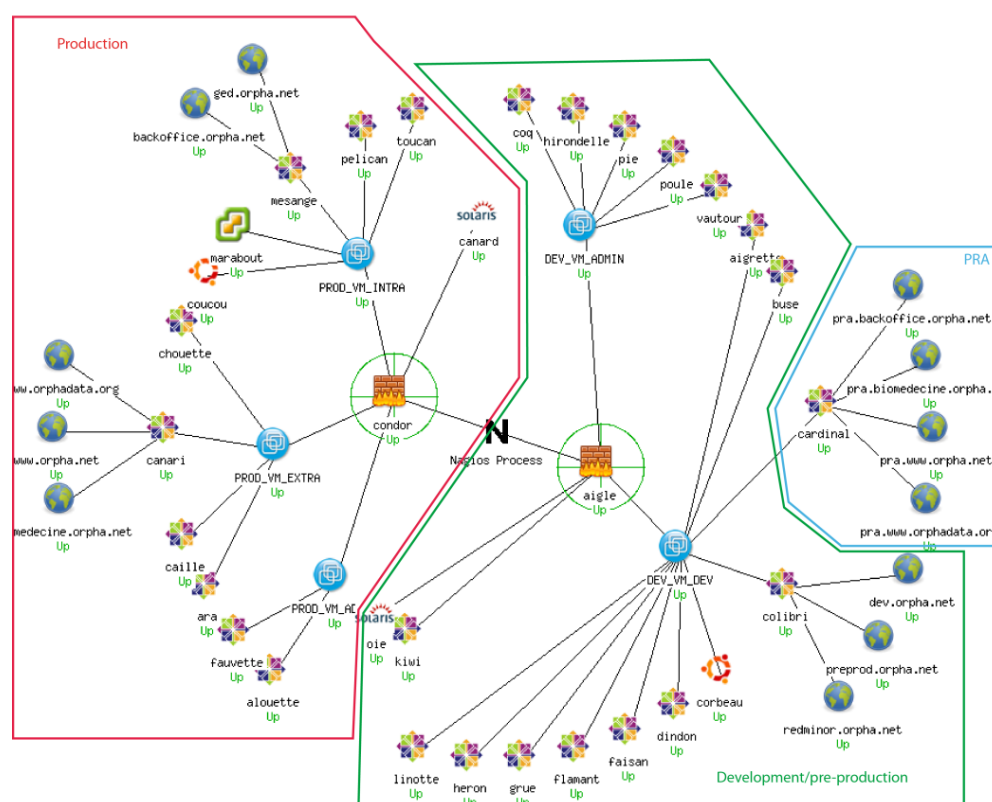


Figure 8 The Orphanet IT architecture in 2015

3.3. Orphanet inventory of rare diseases

Orphanet provides a comprehensive inventory of rare diseases classified according to a polyhierarchical classification system of rare diseases. As new scientific knowledge issues arise, the Orphanet RD inventory and classification system is maintained with regular additions/updates of diseases by the use of two non-exclusive sources: documented sources and/or expert advice (Figure 9), The disease database contains 9,799 phenomes* and their synonyms (including 6368 disorders**) as of 2015. 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 etiological criteria, when diagnostically or therapeutically relevant. The Orphanet classification provides the scope and level of granularity needed by health professionals with different specialties and can be viewed directly on the www.orpha.net website and/or extracted from Orphadata in [XML format](#).

* 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

** diseases, malformation syndromes, morphological anomalies, biological anomalies , clinical syndromes, particular clinical situation in a disease or syndrome

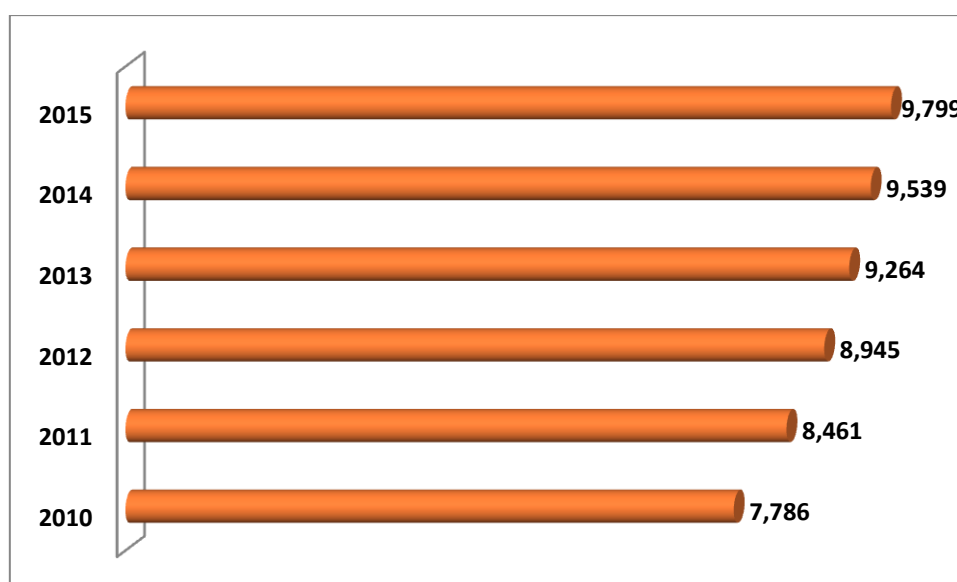


Figure 9 Evolution of the inventory of RD since 2010 (number of phenomes)

Within this classification entries are diseases, syndromes, anomalies, malformations, particular clinical situations, groups of diseases and disease sub-types. Since 2014, each clinical entity is assigned precisely one of these categories, allowing more accurate information on their typology and exact number. Other precisions include updates on diseases now recognised as part of another

disease. Orphanet redirects users towards the disease that is now accepted according to recent literature.

Rare diseases are aligned with ICD-10 codes (see Table 1). This process follows a set of rules, depending on whether rare diseases are mentioned or not in the tabular list or in the index of ICD-10. Rules for attribution of an ICD-10 code for diseases that are not listed in the ICD are established. More details on the process can be found in Orphanet's [ICD-10 coding rules for RD procedure](#). The ICD-10 alignment is manually curated.

Annotations with clinical signs are performed using an in-house thesaurus of phenotypic terms and are carried out with the aim of supplementing the Orphanet assistance-to-diagnosis tool. For each phenotypic term associated with a rare disease, the frequency of its occurrence (very frequent, frequent and occasional) is annotated. The search facility to retrieve diagnoses through signs and symptoms is available for 2,681 RD as of 31 December 2015. Further annotations to HPO are being carried out and will be available in 2016.

Diseases are mapped to one or more OMIM numbers (please refer to table 2). Exact mappings between the Orpha nomenclature and other terminologies (UMLS, MeSH and MedDRA) are available online (see Table 3). Mappings to SNOMED-CT are produced in collaboration with IHTSDO and are available upon request to IHTSDO. Mappings are carried out in a semi-automatic way and are manually curated. Updates follow every UMLS release.

All mappings 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.

Codes	Aligned Orphanumbers
ICD-10	6,716

Table 1 Number of disorders, group of disorders or subtypes aligned to ICD-10 codes as of 31 December 2015

Terminologies/resources	Mapped diseases
UMLS	2,898
MeSH	1,809
SNOMED CT	2,646
MedDRA	1,173
OMIM	4,248

Table 2 Number of mapped diseases per terminology as of 31 December 2015

Information on epidemiological data is available. Disease inheritance patterns and age of onset categories have been refined for more accurate information (table 3). Prevalence, annual incidence,

prevalence at birth and lifetime prevalence data are now available for download on www.orphadata.org, in addition to the prevalence intervals already available (table 4). Minimum, maximum and mean figures for each item are documented according to geographic zones, when information is available. 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 4,800 diseases and constitutes a unique and global source of information which we hope is useful to all users concerned, namely the policymakers, the research community and the orphan drug industry involved in orphan drug development.

Natural history data	Number of diseases
Average age of onset	4710
Mode of inheritance	4851

Table 3 Number of disease per natural history data as of 31 December 2015

Epidemiological data	Number of diseases
Point prevalence	4801
Prevalence at birth	456
Lifetime prevalence	44
Annual incidence	427

Table 4 Number of diseases per epidemiological data as of 31 December 2015

3.3.1. ADDITIONAL FUNCTIONALITIES IN 2015

Improved visibility of Orpha number: the ORPHA number is now indicated after each disease name in the classification page. Moreover, you can now search by ORPHA number in this tab. This should help health professionals to implement ORPHA codes when coding patients (figure 10).

SEARCH A DISEASE

hypersomnia (*) mandatory field

☒ Disease name ☐ Orpha number

OK

OTHER SEARCH OPTION(S)

> Search a group of diseases

[return to list of classifications](#)

:: Orphanet classification of rare neurological diseases

▸ Rare neurologic disease ORPHA98006

└ Sleep disorder ORPHA68354

└ Idiopathic hypersomnia ORPHA33208

└ Idiopathic hypersomnia with long sleep time ORPHA228315

└ Idiopathic hypersomnia without long sleep time ORPHA228318

[return to list of classifications](#)

Figure 10 Improved visibility of the Orpha number in the Classification page

An improved, clearer and easier search results page: when searching for a disease by OMIM, ICD10 or Orpha number, the search engine displays one result per disease, even if the typed string matches with one or several synonyms or keywords for the same disease. As expected, the synonyms and

keywords are still shown, but they now appear after the name of the disease. This evolution improves the clarity of the results as a same disease will no longer appear several times (figure 11).

The screenshot displays the 'SIMPLE SEARCH' interface. A search box contains the text 'hypersomnia' with a red asterisk and the text '(*) mandatory field' below it. To the right of the search box is a radio button menu with five options: 'Disease name' (selected), 'Gene name or symbol', 'OMIM', 'ICD-10', and 'Orpha number'. An 'OK' button is to the right of the menu. Below the search box, the results are displayed under the heading ': : 3 Result(s)'. The results are listed in a table-like format with three rows:

ORPHA33208	Idiopathic hypersomnia
Synonym(s) : Primary hypersomnia	
ORPHA228315	Idiopathic hypersomnia with long sleep time
ORPHA228318	Idiopathic hypersomnia without long sleep time

Figure 11 Improved and easier search results page

A new field called “**source for validation**” in the internal editing tool allows the scientific team to insert the sources of validation of diseases; this evolution was carried out in the framework of the **traceability effort** that Orphanet is adopting. This information is available for download on www.orphadata.org.

3.4. Orphanet Rare Diseases Ontology

The Orphanet Rare Disease ontology (ORDO) is available on three websites [Bioportal](#), [Orphadata](#) and the [EBI Ontologies Lookup Service](#) .

ORDO was jointly developed in 2013 by Orphanet and the European Bioinformatics Institute (EMBL-EBI) to provide a structured vocabulary for rare diseases, capturing relationships between diseases, genes and other relevant features which will form a useful resource for the computational analysis of rare diseases. It is derived from the Orphanet database. It integrates nosology (classification of rare diseases), relationships (gene-disease relations, epidemiological data) and connections with other terminologies (MeSH, UMLS, MedDRA), databases (OMIM, Universal Protein Resource Knowledgebase (UniProtKB), Human Genome Organisation Gene Nomenclature Committee (HGNC), ensembl, Reactome, IUPHAR, Genatlas) or classifications (ICD-10). 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 regularly updated and follows the OBO guidelines on deprecation of terms. It constitutes the official ontology of rare diseases. ORDO Version 2.0 was launched at the end of 2014 to include new content from Orphanet including complete epidemiological data, mappings and genetic annotations, as indicated below. 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.

In 2015, ORDO was downloaded 8,435 times.

3.5. 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: indexation 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). Moreover, genes are now cross-referenced with Ensembl (an EMBL-EBI database that maintains automatic annotations for selected eukaryotic genomes), Reactome (an EMBL-EBI open-source, open access, manually curated and peer-reviewed pathway database) and IUPHAR (International Union of Basic and Clinical Pharmacology) databases. The relationship between a gene and a disease is manually qualified according to the role that the gene plays in the pathogenesis of a disease: causative, modifiers (both from germline or somatic mutations), 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 available. 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.

Since 2014, genetic entries have been expanded to provide 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.

3.5.1. ADDITIONAL FUNCTIONALITIES IN 2015

Genes can be linked to **several external references** for HGNC, UniProtKB, Genatlas, OMIM, Ensembl, Reactome and IUPHAR. Previously, genes could only be linked once with each of the references. All of these references are visible in the identity card of the gene.

In the identity card of the gene a line for the “**Previous symbols and names**” has been added in addition to the one for the “Synonym(s)” (figure 12).

:: FOXP3 - forkhead box P3

ORPHA121913	
Synonym(s) :	AIID, DIETER, JM2, PIDX, SCURFIN, XPID
Previous symbols and names:	IPEX, immune dysregulation, polyendocrinopathy, enteropathy, X-linked
Type:	gene with protein product
Chromosomal location:	Xp11.23
OMIM:	300292 [↗]
HGNC:	6106 [↗]
UniProtKB:	Q9BZS1 [↗]
Genatlas:	FOXP3 [↗]
Ensembl:	ENSG00000049768 [↗]
IUPHAR-DB:	-
Reactome:	-

Diseases list

▶ Disease-causing germline mutation(s) in [Immune dysregulation-polyendocrinopathy-enteropathy-X-linked syndrome](#) ✓

✓ Assessed

Additional information

Health care resources for this gene

> Diagnostic tests (20)

Research activities on this gene

> Research projects (2)
> Registries/biobanks (1)
> Clinical trials (0)
> Networks (0)

Figure 12 Previous symbols and names line included in the gene identity card

In parallel, an **evolution of the search engine** for the genes has been achieved in order to allow retrieval of a gene also by his 'Previous symbols and names' in addition to synonyms and symbols.

A new field called “**source for validation**” has been added to the internal curation tool. This allows the scientific team to insert the source of validation for the gene/disease relationship and thus increase the traceability and transparency of the decision made. This information is available for download on www.orphadata.org.

3.6. 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.

3.6.1. HEALTH PROFESSIONALS ENCYCLOPAEDIA

- **Summary information**

Textual information on a disease can be presented in the form of an abstract, definition, short definition or as an automatically generated text.

Orphanet texts (apart from the automatically generated) are unique and written in English by a member of the Paris-based editorial team. Abstracts and definitions are then reviewed by an invited world-renowned expert. Abstracts and definitions 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.

As of December 2015, summary information for 4,061 rare diseases is available online.

They are translated into the six other languages of the website (French, Italian, Spanish, German, Portuguese and Dutch). In addition, as of 31 December 2015, 336 abstracts are now available in Finnish, 503 in Polish, 103 in Slovak and 436 in Greek. For the additional 2740 entries 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).

- **Practical genetics articles**

These articles are co-produced by Orphanet and the *European Journal of Human Genetics* (EJHG), the official journal of the *European Society of Human genetics*. Freely-accessible articles are published in the *EJHG* (Nature Publishing Group) and are accessible via Orphanet.

- **Orphanet Emergency Guidelines**

These guidelines are intended for pre-hospital emergency health care 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: 72 emergency guidelines in French are now available online. They are being translated into the following six languages: English, German, Italian, Portuguese, Spanish and Polish. Currently, 21 emergency guidelines are available in English, 43 in Italian, 26 in German, 23 in Spanish, 19 in Portuguese, and 18 in Polish.

Epidemiology:

4,801 diseases annotated with point prevalence data

Natural history:

4,851 diseases annotated with mode of inheritance

4,637 diseases annotated with age of onset

Mappings:

6,798 diseases mapped to ICD-10

4,312 diseases mapped to OMIM

2,960 diseases mapped to UMLS

1,227 diseases mapped to MedRA

1,809 diseases mapped to MeSH

:: Tuberous sclerosis complex

ORPHA805		ICD-10:	Q85.1
Synonym(s):	Bourneville syndrome Tuberous sclerosis	OMIM:	191100 [↗] 613254 [↗]
Prevalence:	1-5 / 10 000	UMLS:	C0041341
Inheritance:	Autosomal dominant	MeSH:	D014402
Age of onset:	All ages	MedDRA:	10045138

SUMMARY

Tuberous sclerosis complex (TSC) is a neurocutaneous disorder characterized by multisystem hamartomas and associated with neuropsychiatric features.

Additional Information

Further information on this disease

- > Classification(s) (8)
- > Gene(s) (2)

The Orphanet encyclopaedia contains the following summary texts:

4,061 in English

3,344 in French

3,356 in Italian

3,234 in German

2,954 in Spanish

1,233 in Portuguese

670 in Dutch

503 in Polish

436 in Greek

336 in Finnish

261 in Russian

116 in Slovak

1/11,300 in Europe.

hamartomas, most commonly skin, brain, kidney, lung and heart, appearing at different ages. macules (ash leaf) present within the first years of life; angiofibromas that appear at pulvular lesions; ungual fibromas; cephalic and lumbar (shagreen patch) fibrous ring in childhood to early adolescence. Brain is involved in almost all cases of TSC, with lesions, such as cortical/subcortical tubers, radial migration lines, subependymal nodules, dysplasia (growth risk higher in the first 3 decades). Early-onset epilepsy (infantile spasm in 85% of patients). Neuropsychiatric features (intellectual disability, attention-deficit disorders (ADHD; see this term), self-injury, anxiety and obsessive compulsive disorder). Angiomyolipomas (AML) develop during childhood with a higher risk of growth during by pain, hematuria/retroperitoneal hemorrhage, abdominal masses, hypertension and (LAM; see this term), multifocal micronodular pneumocyte hyperplasia (MMPH) and manifest with dyspnea, pneumothorax, or chylothorax. Cardiac rhabdomyomas may become symptomatic (outflow tract obstruction or by interfering with valvular function). Additional features include dental enamel pitting, intraoral fibromas and skeletal

and TSC2 (16p13.3) which encode proteins that indirectly inhibit mTOR. In excess, mTOR leading to disrupted synaptic plasticity. Expressivity is variable and is due to mosaicism

cortical dysplasias; subependymal nodules; SEGAs; hypomelanotic macules (≥2 or ≥3) or fibrous cephalic plaque; multiple retinal hamartomas; ungual fibromas (≥2); intraoral fibromas; confetti skin lesions; nonrenal hamartoma; myoclonus. A definite diagnosis is defined as presence of ≥2 major features or 1 major feature in the presence of 1 major or ≥2 minor features. TSC can be diagnosed

to hypomelanosis (see these terms), cardiac myxoma, isolated brain tumors, pulmonary

lesions may be detected by fetal MRI. Prenatal genetic screening may be possible

genetic counseling is recommended. Two thirds of affected individuals have

and includes the use of vigabatrin (GABA transaminase inhibitor), effective in infantile spasms and early onset seizures; everolimus (mTOR pathway inhibitor) may be used to treat SEGAs not suitable for surgery in adults and children, and for treatment of AML in adults.

TSC is a chronic, life-long condition. As patients transition into adulthood seizures may persist; renal and/or pulmonary issues may become more important, and may pose risks of significant morbidity and occasionally mortality; and psychological and behavioral concerns may appear, persist, or become more significant.

Expert reviewer(s)

Pr Paolo CURATOLO

Last update: October 2015

[Suggest an update](#)



Detailed information	
Summary information	Slovak [↗] (2005,pdf)
Emergency guidelines	Deutsch [↗] (2007,pdf) English [↗] (2007,pdf) Português [↗] (2007,pdf) Polish [↗] (2007,pdf) Français [↗] (2007,pdf) Italiano [↗] (2007,pdf) Español [↗] (2007,pdf)
Clinical practice guidelines	English [↗] (2013)
Diagnostic criteria	Français [↗] (2013,pdf) English [↗] (2012,pdf)
Practical genetics	English [↗] (2006,pdf)
Guidance for genetic testing	English [↗] (2013,pdf)
Article for general public	Français [↗] (2015,pdf) Svenska [↗] (2015)
Clinical genetics review	English [↗] (2015)
Disability factsheet	Français [↗] (2015,pdf)

Genes:

3,506 genes linked to 3377 diseases, including:

3,505 genes interfaced with HGNC

3,500 genes interfaced with OMIM

3,458 genes interfaced with Genatlas

Getting involved/informed

- > Read the newsletter
- > Read QORD [↗]

2,307 diseases interfaced with **Pubmed**

2,681 diseases indexed with **clinical**

5,461 **external links** for 4,931 diseases

Link to external RD literature

518 Review articles

619 Clinical genetics reviews

312 Best practice guidelines

129 Guidance for genetic testing

595 General public articles

29 Emergency guidelines

In-house produced texts: 142 **articles for the general public** in French, 72 **emergency guidelines** in French, translated in German, English, Spanish, Italian, Portuguese, and Polish. 30 **Disability factsheets** in French

Figure 13 The disease database content as of 31 December 2015

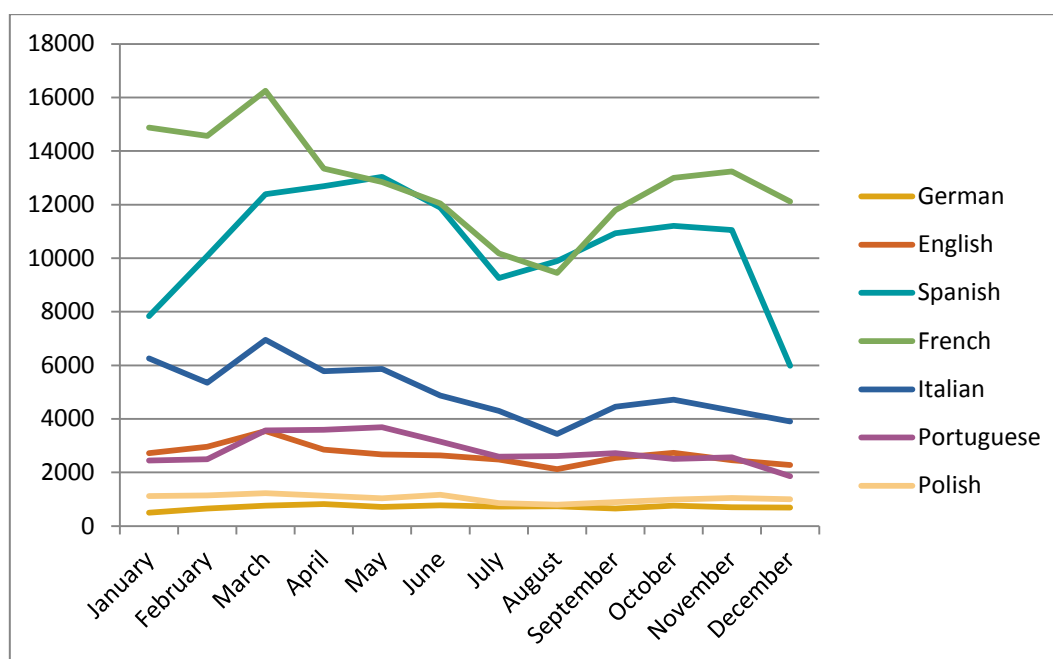


Figure 14 Downloads of the Orphanet emergency guidelines by language in 2015

Emergency guidelines were viewed more than **426,700** times in 2015 (Figure 14), versus approximately 400,000 in 2014 (Polish Emergency guidelines included), representing an increase of 7% in one year (Figure 15). The ratio of the number of consultations for each language to the number of guidelines shows that this collection is a success in several languages such as French, Italian, Spanish, Polish and Portuguese.

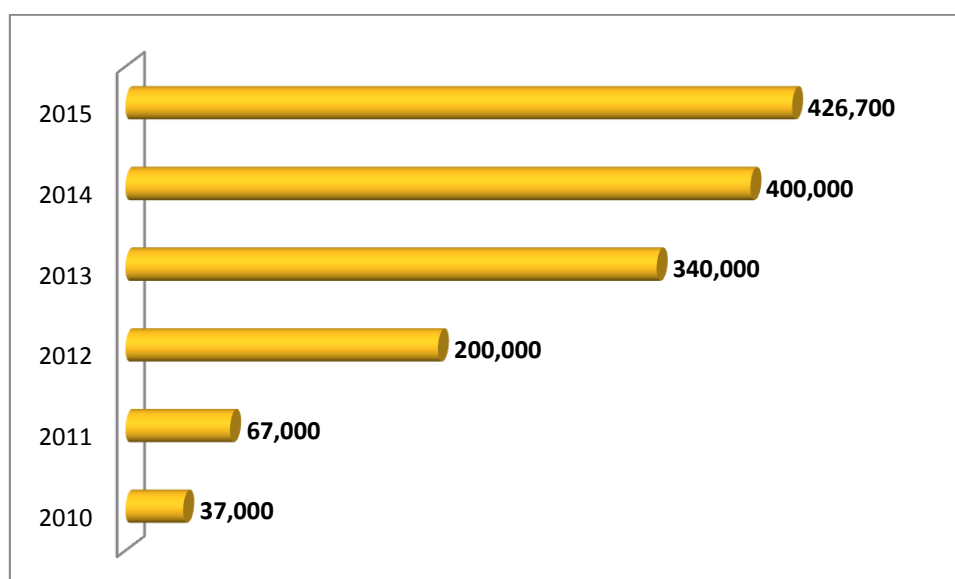


Figure 15: Downloads of the Orphanet emergency guidelines since 2010 in all languages

3.6.2. GENERAL PUBLIC ENCYCLOPAEDIA

The general public encyclopaedia was initially a French project 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.

As of 31 December 2015, 142 in-house French texts are available online. Documents from this encyclopaedia are downloaded approximately 510,000 times per month, which corresponds to more than 6.1 million downloads in 2015 (Figure 16). This represents an increase of 9% compared to the 5.6 million downloads in 2014 (Figure 17).

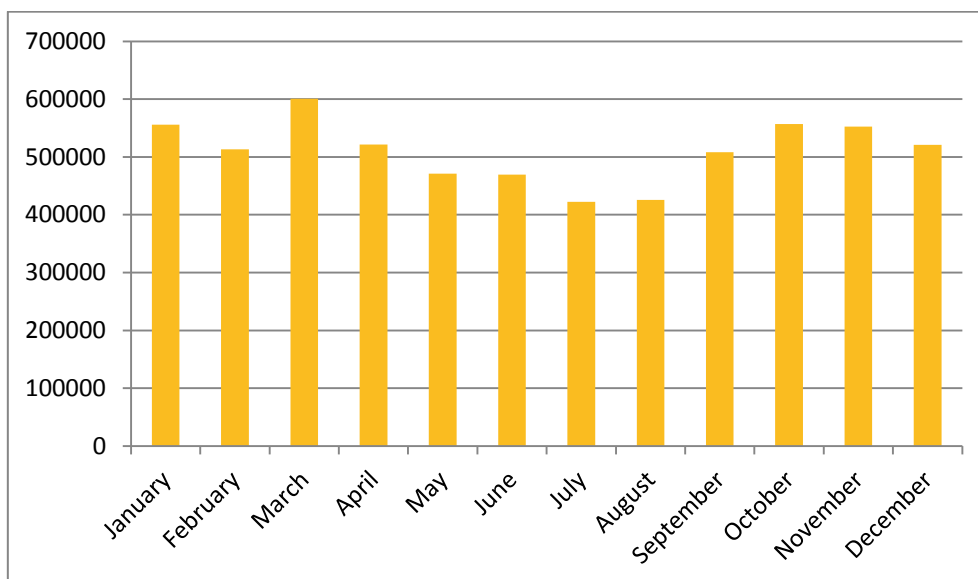


Figure 16 Total number of downloaded French Orphanet general public encyclopaedia texts in 2015

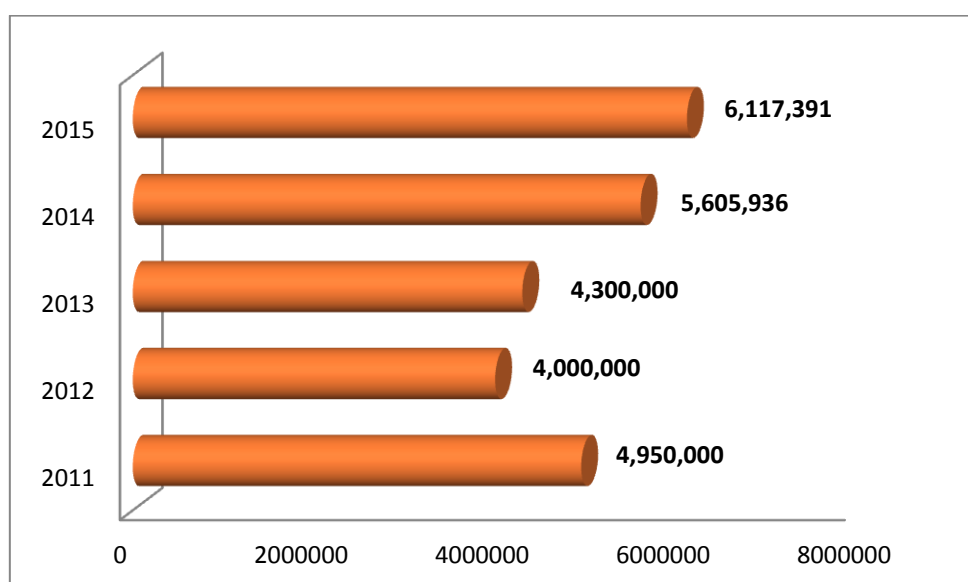


Figure 17 Downloads of the general Public encyclopaedia since 2011

3.5.3 DISABILITIES ENCYCLOPAEDIA

As part of the collaboration between CNSA (French National Solidarity Fund for Autonomy) and INSERM, Orphanet provides since 2013 a collection of texts named “**disability factsheets**” in the Orphanet Encyclopaedia of Disability devoted to the disabilities associated with each rare disease.

This collection is addressed to the professionals in the field of disability as well as to the patients and their families. These texts have been elaborated in order to better understand and to assess the needs of people with disabilities associated with a rare disease and to promote guidance and appropriate support in the national health care system as well as in the care and social support system.

Each text contains a description of the disease (adapted from the corresponding summary text from the Orphanet encyclopaedia for professionals) and a focus on disability-related measures and consequences in everyday life (taken from the corresponding text of the Orphanet general public encyclopedia). In 2015 many of these texts were produced as stand-alone texts, independent of the General public encyclopedia. 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 tabs "Encyclopaedia for professionals" and "Encyclopaedia for general public". Thirty of these texts are available online since November 2013. They have been downloaded approximately 24,000 times in 2015 (Figure. 18). This represents an increase of 20% compared to the 20,000 downloads in 2014.

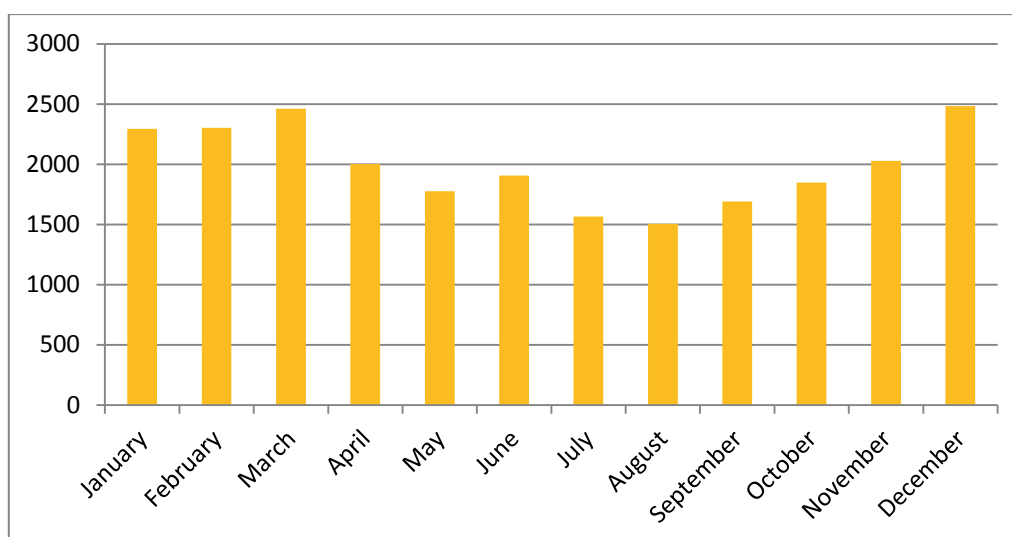


Figure 18 Number of downloads per month of the French Disability factsheets in 2015

3.6.3. DIAGNOSTIC CRITERIA

Information on diagnostic criteria is presented in 33 concise documents intended to avoid serial misdiagnosis and to facilitate early therapeutic management. This information is extracted from peer-reviewed journals and is validated by international experts, with a reference to the original paper given at the top of the page.

3.6.4. LINKS TO EXTERNAL RARE DISEASE LITERATURE

With the purpose of expanding the number of articles available online and to disseminate articles matching Orphanet's quality criteria, the editorial team is also in charge of identifying articles suitable for publication on the website produced by other journals or learned societies. National teams are contacted for evaluation of the document in their national languages. Authorisations from the copyright holder are requested so as to give access to the full text. Numbers of external texts per category are presented in Table 5.

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

- **Review articles**

As of 31 December 2015, 518 review articles (excluding those published in the Orphanet Journal of Rare Diseases) were available on the website.

- **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.

As of 31 December 2015, the clinical genetic review collection comprised 619 articles from GeneReviews.

- **Best 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 agency's 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. As of 31 December 2015, 312 best practice guidelines were available on the website. These guidelines were downloaded more than 1, 300, 000 times in 2015 (Figure 19).

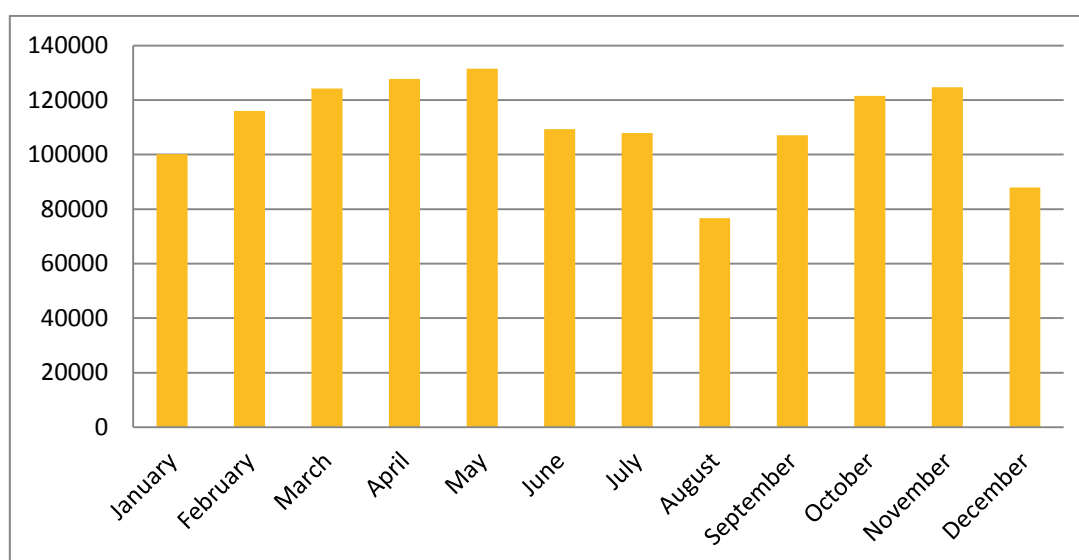


Figure 19 Downloads per month of External Best practice guidelines in 2015

New collaboration in 2015: the AWMF (Association of the Scientific Medical Societies in Germany) cooperates with Orphanet Germany by supplying the web links of their clinical practice guidelines to the Orphanet encyclopaedia.

- **Guidance for genetic testing**

This collection comprises summary recommendations intended to disseminate the best practices in genetic testing. They include Gene Cards (published in the EJHG). As of 31 December 2015, 129 recommendations were available on the website.

- **Articles for the general public**

Publication 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. 634 articles are available on the website as of 31 December 2015.

New collaboration in 2015: the **Swedish Information Centre for Rare Diseases**, which is responsible for producing and updating information provided in the rare disease (RD) database of the Swedish National Board of Health and Welfare. The latter is a government agency under the Ministry of Health and Social Affairs, with a very wide range of activities and many different duties within the fields of social services, health and medical services, environmental health, communicable disease prevention and epidemiology. Currently, the RD database includes descriptions of over 300 diagnoses in Swedish, of which 170 have been translated into English. New articles are continually added, and they are revised on a regular basis. All texts undergo a quality assurance process before being released, which includes a review by RD medical experts and patient representatives.

- **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. Currently 23 external emergency guidelines are available in English and 8 in other languages.

- **Disability factsheets**

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

	Article for general public	Review article	Best practice guidelines	Guidance for genetic testing	Clinical genetics review
Croatian	2	0	0	0	0
Czech	2	0	0	0	0
Danish	0	0	0	0	0
English	178	399**	109	128	619
Finnish	12	0	0	0	0
French	39*	53	97	1	0
German	34	30	84	0	0
Greek	4	0	0	0	0
Hungarian	0	0	1	0	0
Italian	24	33	1	0	0

	Article for general public	Review article	Best practice guidelines	Guidance for genetic testing	Clinical genetics review
Polish	2	0	0	0	0
Portuguese	6	1	1	0	0
Romanian	4	0	0	0	0
Russian	4	0	1	0	0
Slovak	0	0	0	0	0
Spanish	17	2	17	0	0
Swedish	301	0	0	0	0

***including 213 Orphanet Journal of Rare Diseases reviews*

** not including the in-house produced articles*

Table 5 Total number of Orphanet external content in 2015: type of text per language

3.7. Orphanet directory of expert resources

Orphanet provides a directory of:

- Centres of expertise/genetic counselling clinics
- Medical laboratories
- Patient organisations
- Clinical trials
- Patient registries
- Mutation registries
- Biobanks
- Ongoing research projects
- Platforms
- Networks

Data is collected either from official national sources, or proactively from non-official sources by information scientists in each country. 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. 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 resources they are involved in.

The 36 countries in which Orphanet members collect data are the following:

Argentina, Armenia, Austria, Belgium, Bulgaria, Canada, Croatia, Cyprus, Czech Republic, Estonia, Finland, France, Germany, Greece*, Hungary, Ireland, Israel, Italy, Latvia, Lithuania, Morocco, the Netherlands, Norway, Poland, Portugal, Romania, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland, Tunisia, Turkey, the United Kingdom and Western Australia.

Data collection, updates received through the online registration tool annual updates are managed either by the teams at country level, when they have sufficient funding for a dedicated professional, or by the coordinating team on behalf of the Orphanet national team. In 2015, all countries managed both data collection and updates at the country level with the exception of Argentina, Bulgaria, Norway, and Turkey. Also, updates received by the online registration tools for data regarding Denmark, Georgia, Lebanon and Luxembourg were managed at the coordinating team on behalf of the Orphanet contact points.

* since the beginning of the new RD-ACTION Joint Action, no team in Greece was designated to participate by the Ministry of Health and data collection has stopped.

Data Collection outside the Orphanet consortium:

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

Research related resources (research projects, clinical trials, patient registries, biobanks and mutation databases) funded by funding agencies in countries outside of the Orphanet consortium are collected by the coordinating team if the funding agency is [a member of the IRDiRC consortium](#). The database cannot yet be regarded as comprehensive. If no research project is listed for a disease, a group of diseases or a gene, it may be that there is no ongoing research activity, or that we have not yet collected the information, but it is also possible that the researcher has refused to be listed. A disclaimer is available explaining this limitation to the users.

Patient registries, biobanks, mutation databases and platforms can also be registered if they fulfill inclusion criteria (Please refer to the technical procedures for an exhaustive list of inclusion criteria).

The directory of expert resources in the Orphanet consortium contains the following data:

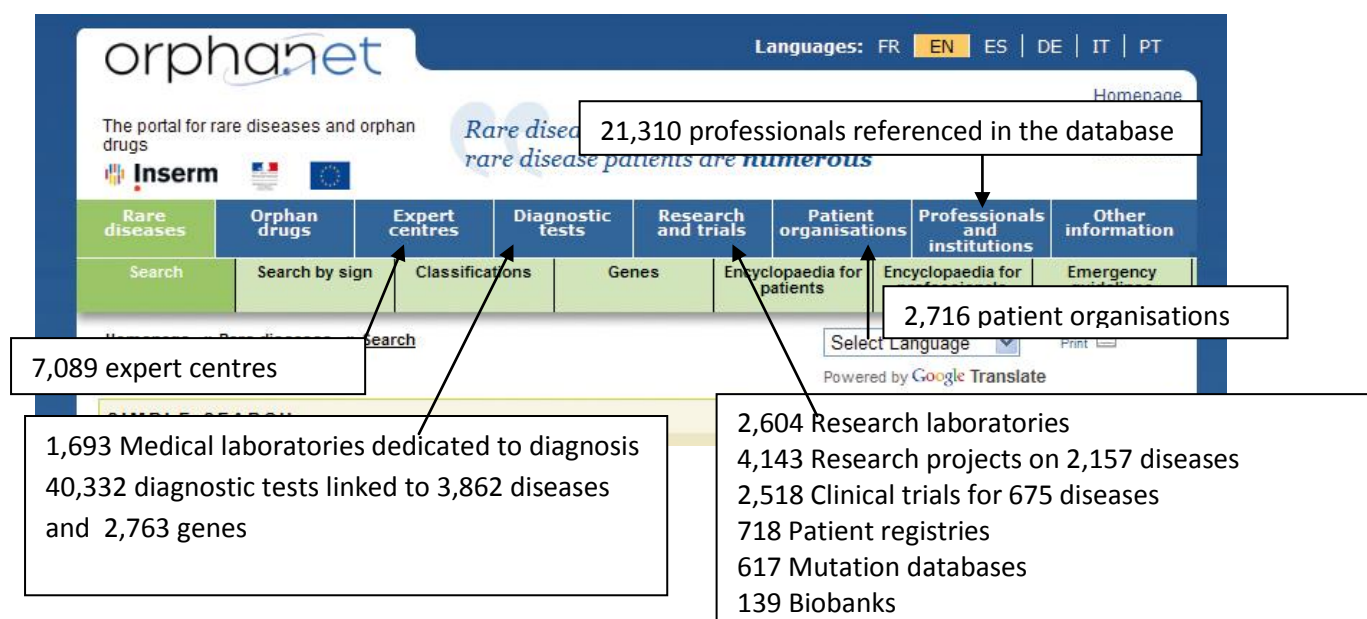


Figure 20 2015 Directory of expert resources

3.7.1. ADDITIONAL FUNCTIONALITIES IN 2015

With the evolution of the research projects registration, two new elements are collected: **the start and end date of a research project**. These new fields allow for a better tracking of a registered research project's duration and, consequently, enhance the accuracy of our data.

Moreover, in order to **better characterise the aims of research projects registered in the Orphanet database**, 7 new categories have been created: Natural history study, Biotechnology innovation, Induced pluripotent stem cells (iPS) creation / study, Ontology / bioinformatics study, Outcome measures development, Drug repurposing, and Small molecule screening. The category "Public health study" was renamed "Public health study (excluding health economics)", to better reflect its use. All information on research projects and their category is available on request on www.orphadata.org.

The list of selectable countries in the personal profile form of the online registration tool has been updated in order to present a **more relevant choice of countries**.

Each type of expert resource (except the expert centres) and their networks are now displayed in the same tab, allowing for networks of expert resources and the expert resources themselves to be found at the same place. The counting of the activities in the right hand side menu of the website has been changed accordingly.

An evolution **in the search tool of expert centres inventory** allows for users to know how many expert centres there are of each type (medical management, genetic counselling or both but also adult vs. paediatric clinic or both).

3.7.2. DATA QUALITY VALIDATION OF MEDICAL LABORATORIES

Medical laboratories listed in Orphanet are those offering tests for the diagnosis of a rare disease or a group of rare diseases, and those performing genetic testing whatever the prevalence of the disease. Information on quality management for medical laboratories and diagnostic tests is provided in Orphanet. Medical laboratories can be accredited and this involves a procedure by which an authoritative body gives formal recognition that a body or person is competent to carry out a specific task (ISO 9000, 2000 Quality management systems – fundamentals and vocabulary). Moreover, medical laboratories can undergo an external quality assessment (EQA) whereby a set of reagents and techniques are assessed by an external source and the results of the testing laboratory are compared with those of an approved reference laboratory (WHO). This allows a laboratory to compare its performance for an individual test or technique against those of other laboratories.

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

3.8. Orphanet directory of orphan drugs

The list of orphan drugs includes all those substances that have been granted an orphan designation for a disease considered as rare in Europe, whether they were further developed to become drugs with marketing authorisation (MA) or not. The Orphanet database also includes drugs without an orphan designation as long as they have been granted a 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 included in the database because they have been tested in a clinical trial performed on a rare disease, but they do not have a regulatory status.

Drugs with a regulatory status in Europe are collected from reports issued by the two Committees of the EMA: the COMP (Committee for Orphan Medicinal Products) and the CHMP (Committee for Medicinal Products for Human use). Orphanet has started collecting information on Orphan Drugs from Food and Drug Administration in the USA(FDA), but this inventory is not comprehensive yet.

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:

For Europe:

- **1241** Orphan Designations linked to **970** substances and covering **469** diseases
- **199** Marketing Authorizations (of which **85** already had an Orphan Designation and **113** without Orphan Designation), covering **204** diseases

For the USA:

- **529** Orphan Designations linked to **418** substances and covering **305** diseases
- **86** Marketing Authorizations (of which **84** already had an Orphan Designation and **2** without Orphan Designation), covering **98** diseases

3.9. 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.

On this website, the whole Orphanet dataset has been directly accessible in a reusable format since June 2011. Orphadata was developed within the context of the Rare Diseases Portal project and the Orphanet Europe Joint Action contract funded by DG Santé. The dataset is a partial extraction of the data stored in Orphanet and is updated monthly.

Freely accessible in six languages since 2011 (English, French, German, Italian, Portuguese and Spanish) and a seventh language has been added in 2015: Dutch. The Orphadata dataset encompasses:

<ul style="list-style-type: none"> • An inventory of rare diseases, cross-referenced with OMIM, ICD-10, MeSH, MedDRA, UMLS, 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.
<ul style="list-style-type: none"> • A classification of rare diseases established by Orphanet, based on the literature and expert classifications.
<ul style="list-style-type: none"> • Epidemiological data related to rare diseases based on the literature.
<ul style="list-style-type: none"> • A list of signs and symptoms associated with each disease, with their frequency class within the disease noted.
<ul style="list-style-type: none"> • The thesaurus of Orphanet signs and symptoms used to annotate the diseases, cross-referenced with other terminologies (HPO, PhenoDB, LDDb).
<ul style="list-style-type: none"> • Linearisation of RD : for analytical purposes, each disorder is attributed to a preferred classification (linearisation) by linking it to the head of classification entity.
<ul style="list-style-type: none"> • Orphanet Rare Diseases Ontology (ORDO)

Table 6 Products freely accessible on Orphadata

<ul style="list-style-type: none"> • An inventory of Orphan Drugs at all stages of development, from EMA orphan designation to market authorization, cross-linked with diseases.
<ul style="list-style-type: none"> • Summary information on each rare disease in six languages (English, French, German, Italian, Spanish, Portuguese)
<ul style="list-style-type: none"> • URLs of other websites providing information on specific rare diseases
<ul style="list-style-type: none"> • 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 organizations in the field of rare diseases, in each of the countries in the Orphanet network.

Table 7 Products accessible on Orphadata after signature of a Data Transfer Agreement

Orphadata provides a guide for users that defines and describes the elements of the dataset and gives access to the [methodology of alignment of ICD10 coding rules for rare diseases](#) and the [methodology of linearisation](#).

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

In 2015, **Orphadata products were downloaded more than 200,800 times**, with an average of 16,700 times per month. This represents an increase of 19% compared to 2014 (Figure 21).

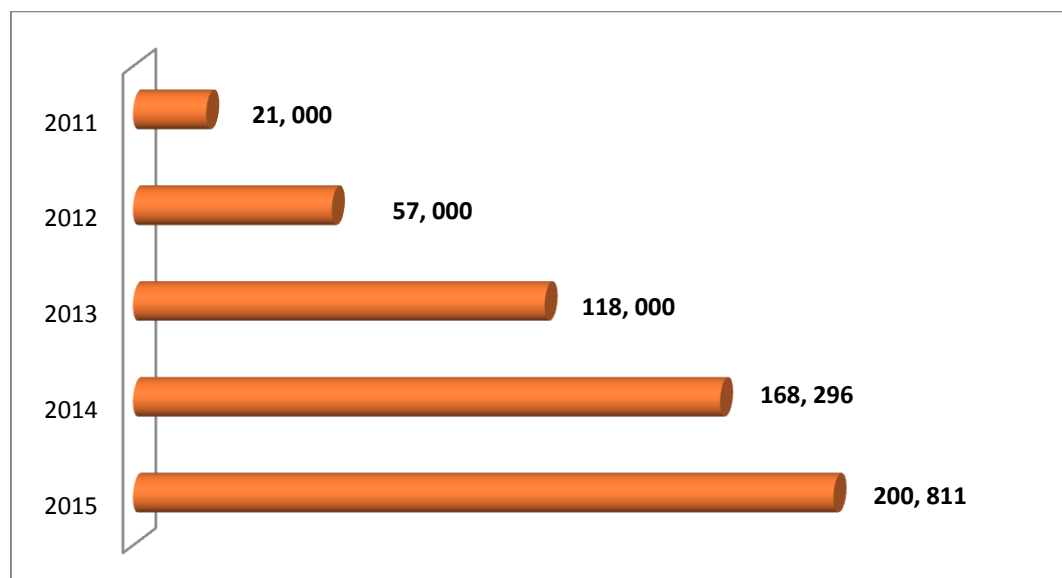


Figure 21 Number of downloads from the Orphadata website since mid 2011

The most requested Orphadata product is the inventory of diseases with clinical signs (figure 22 and Figure 23).

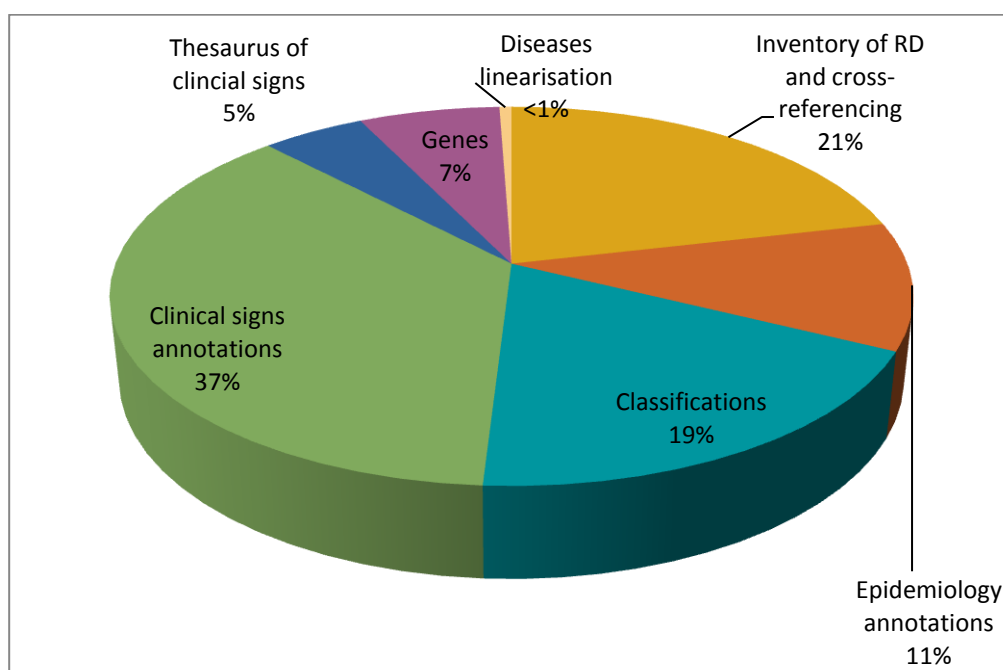


Figure 22 Distribution of the downloads of Orphadata freely available datasets in 2015
[total of 200,383 downloads]

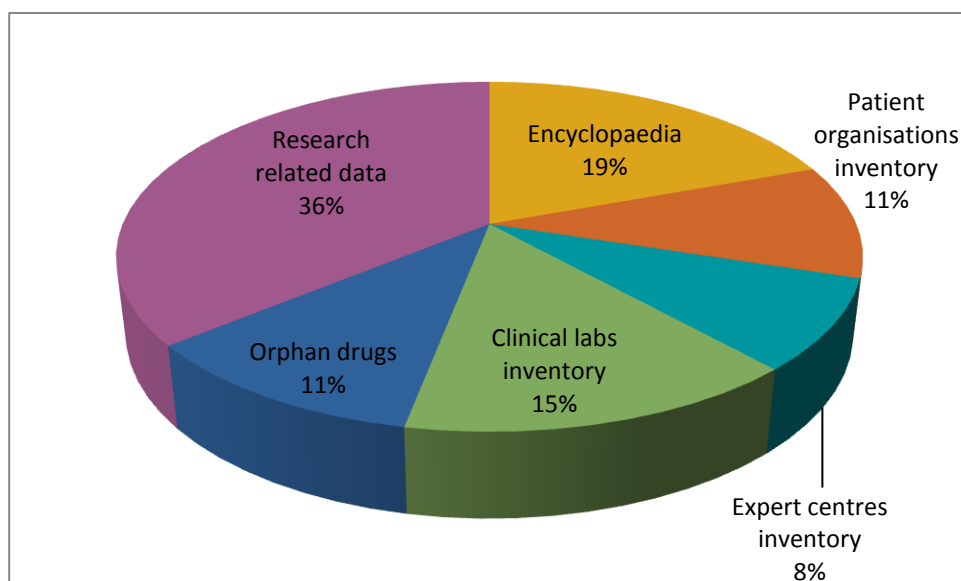


Figure 23 Distribution of the downloads of Orphadata Datasets accessible on demand [total of 428 downloads]

3.9.1. ADDITIONAL FUNCTIONALITIES IN 2015

The homepage of www.orphadata.org was made more user-friendly in order to allow for the products to be accessed more easily.

Welcome to Orphadata

The mission of Orphadata is to provide the scientific community with a comprehensive, high-quality and freely-accessible dataset related to rare diseases and orphan drugs, in a reusable format. For more information on Xml format files, see the [user's guide](#).

See ["How the data are produced"](#)

Freely-accessible dataset



The dataset is a partial extraction of the data stored in Orphanet, which is also accessible at www.orpha.net for consultation purposes only. This freely-accessible dataset is available in seven languages (English, French, German, Italian, Portuguese, Spanish and Dutch).

Datasets available on request

These datasets are available for free on signature of a Data Transfer Agreement for Academia ([consult the catalogue](#)).

These datasets are available for a fee on signature of a Data Transfer Agreement for Industry ([consult the catalogue](#)).



Figure 24 New Orphadata homepage products presentation

3.10. Orphanet Report Series

Orphanet Reports (ORS) are a series of texts 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 other page of Orphanet's website.

New versions of these publications are advertised in OrphaNews.

The ORS are heavily downloaded: in 2015, more than 3,350,000 ORS were downloaded (Table 8).

This represents an increase of 49% compared to 2014 (approximately 2,250,000 downloads) (figure 22).

2015 Downloads	English	French	German	Italian	Portuguese	Spanish	Dutch	Total
List of Rare Diseases	258, 237	1, 078, 363	903, 12	151, 514	38,102	199,452	645	1,816,625
Prevalence of RD by alphabetical list	131,677	28,170	9,498	15,794	11,950	25,368	N.A	222,457
List of orphan drugs in Europe	141,316	34,231	8,467	20,614	4,626	21,952	37	231,243
Prevalence of RD by decreasing prevalence or cases	42,734	548,510	6,193	12,307	22,466	43,737	N.A	675,947
Activity report 2014	21,756	N.A	N.A	2,979	N.A	882	N.A	25,617
Registries	55,946	N.A	N.A	N.A	N.A	N.A	N.A	55,946
ICD10 coding rules	2,821	N.A	N.A	N.A	N.A	N.A	N.A	2,821
Linearisation rules	1,547	N.A	N.A	N.A	N.A	N.A	N.A	1,547
Research Infrastructures for RD in Europe	21,550	N.A	N.A	N.A	N.A	N.A	N.A	21,550

Table 8 Number of downloads of selected Orphanet Report Series in 2015 by language

N.A. = ORS not available in this language

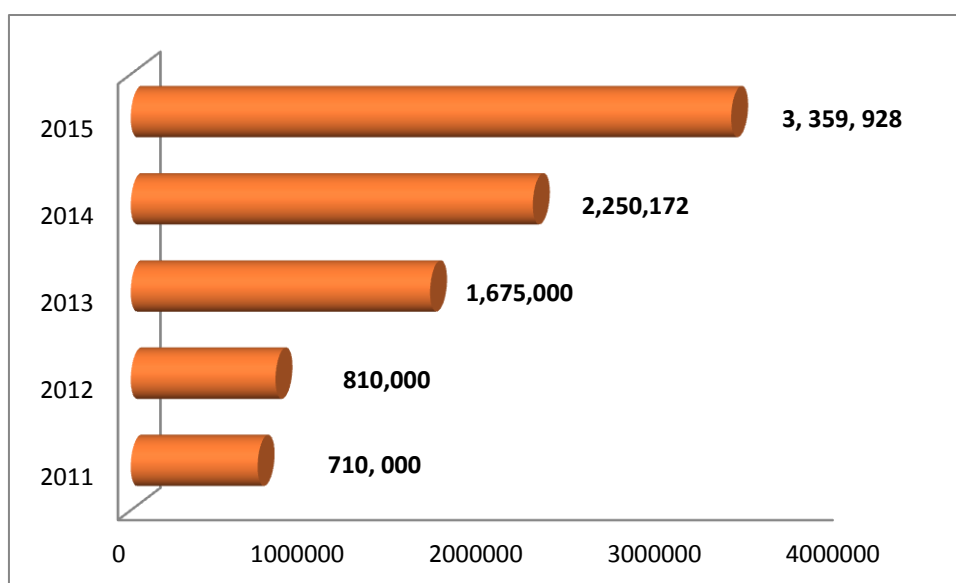


Figure 25 Number of downloads of the Orphanet Report Series in all languages since 2010

3.11. The Orphanews Newsletter

A literature review is performed twice a month in order to update the database and to collect news to report in [OrphaNews](#), a bi-monthly electronic newsletter, to which the subscription is free. [OrphaNews](#) presents an overview of scientific and political news about rare diseases and orphan drugs. It is now supported by the European Commission's DG SANTE RD-ACTION Joint Action N° 677024 and it is the dissemination tool of this Joint Action. [OrphaNews](#) France is supported by the French Muscular Dystrophy Association ([AFM](#)), while [OrphaNews](#) Italy is supported by Genzyme.



Figure 26 OrphaNews homepage

[OrphaNews](#) in English has more than 16,100 subscribers. [OrphaNews](#) in French has more than 9,850 subscribers and [OrphaNews](#) in Italian has more than 6,150 subscribers.

3.11.1. ADDITIONAL FUNCTIONALITIES IN 2015

Orphanews Italia app is a free mobile application developed with the support of Sanofi Genzyme. It allows users to consult directly on their smartphones new and old issues of the OrphaNews Italia newsletter, to save their favourite issues in a specific section and to share the most interesting articles on social medias. It is available on Play Store and Apple's App Store.

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 Thompson Scientific after only two years of being in publication. Its current impact factor is 3.36. In 2015, 484 publications were submitted to the journal. Of these, 161 were accepted for publication.

3.12.1. ADDITIONAL FUNCTIONALITIES IN 2015

The Orphanet Journal of Rare Diseases app is available on Google Play and iOS: the most recent developments for rare diseases and orphan drugs can be accessed using the app produced by the Orphanet Journal of Rare Diseases. This free app provides valuable features including:

- Save and share articles
- Advanced search
- Document details - including abstracts

The app is available for download on Android or iPhone.

4. Users

2015 Orphanet user satisfaction survey

An online survey was carried out for 3 weeks in January 2016. The satisfaction of the portal users was assessed by asking them to respond to a short online questionnaire. 3,795 users replied to the survey.

The following results present the responses collected in all languages (Dutch, English, French, German, Italian, Portuguese and Spanish). More results from this survey are available in the Orphanet Report Series dedicated to the [2015 survey](#).

Question 1: In what capacity are you consulting the Orphanet website TODAY?

This question aimed to determine the profile of Orphanet's users. Seven categories were proposed (i.e. health professional, patients/entourage, researcher, industry, health care manager/policy maker, and students) and a free text field was included for other types of users to enter their profession. Only one response was possible. For this analysis, the users who answered "other" in question 1 were not reattributed to another category as the questionnaire was modified this year to help users find the category corresponding to their social-professional situation more easily and reduce the need for reattribution.

Figure 27, shows the distribution of respondents amongst these categories:

The largest category of respondents is the health professional category (45%). The second largest category of respondents is patients and their entourage (including patient organisations, alliances

and support groups) with 26% of responses. Many students (17%) also use Orphanet. The 'other' category included respondents working in unrelated socio-professional categories and those generally interested in rare diseases but who did not state their professional category.

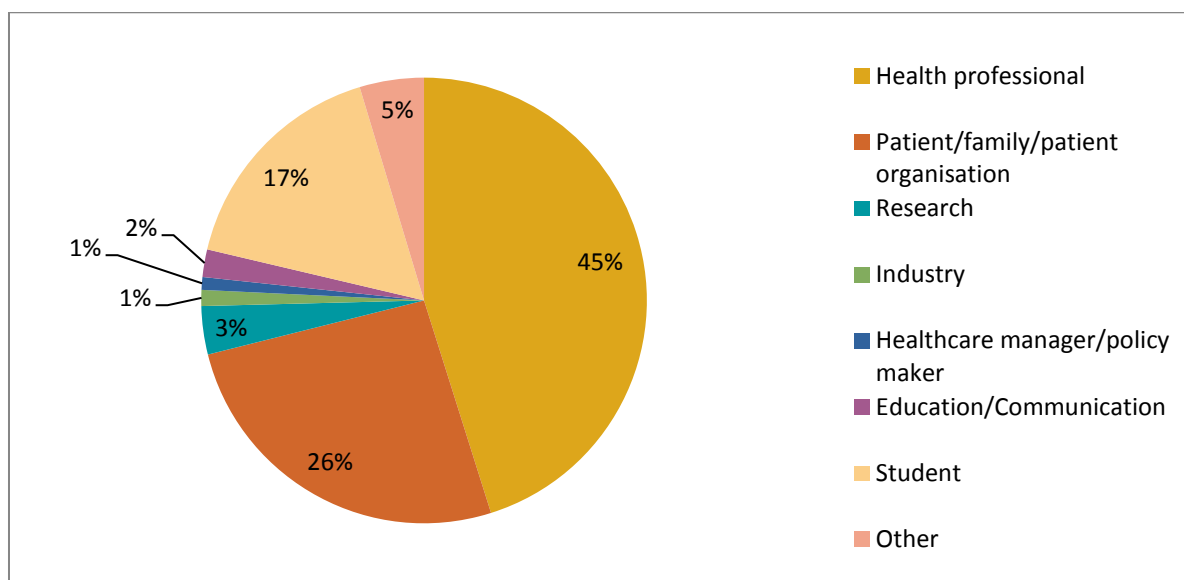


Figure 27 Types of Orphanet users (percentage of total respondents) n = 3795

Question 2: How often do you visit Orphanet?

Only one response was possible. Around 50 % of those answering the survey are regular users, whereas 26% were visiting Orphanet for the first time (Figure 28).

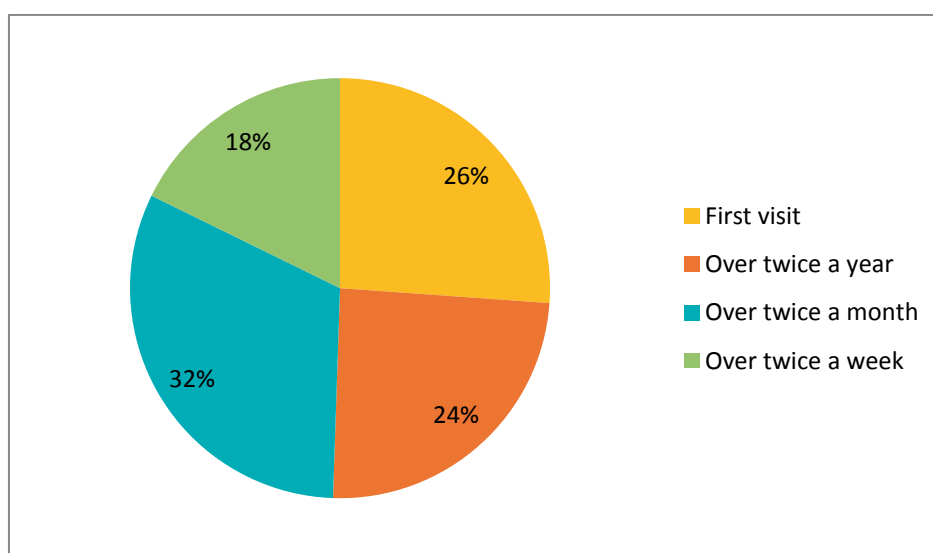


Figure 28 Visiting frequency of respondents

Question 3: What sort of information are you looking for during THIS CONNECTION to Orphanet?

This question aims to determine which kind of information visitors sought on Orphanet. More than one choice was possible.

The principle reason for visiting the site across all categories of users is information on a specific disease (Figure 29).

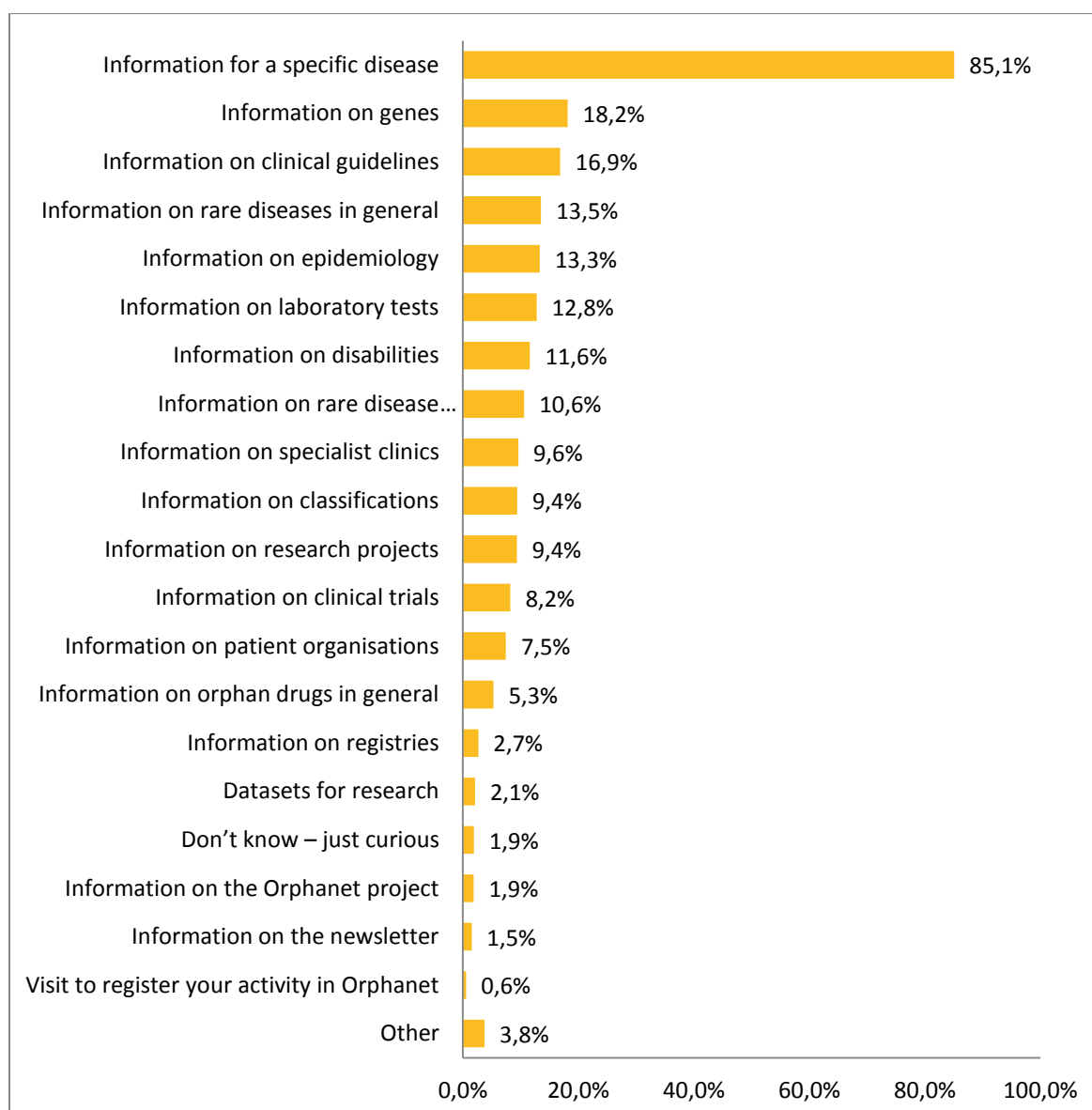


Figure 29 Information sought by respondents during their connection to Orphanet (percentage of total number of respondents)

The results show a clear trend: most of the respondents were looking for information for a specific disease (85%). Our visitors also look for information on genes (18%), clinical guidelines (17%), rare diseases in general (14%), and epidemiology (13%). A smaller percentage of respondents were seeking information concerning an expert resource in particular: laboratory tests (13%), specialist clinics (10%), research projects (9%), clinical trials (8%), and patient organisations (8%). 11% of users were looking for information related to the nomenclature and coding of rare diseases.

Question 4: How useful would you rank the following Orphanet services for your own use?

The usefulness of Orphanet products was evaluated through this question. This question was asked to all respondents, except those consulting Orphanet for the first time as the aim was to

assess the usefulness of available tools and services for users' needs, based on their experience, and to also assess their knowledge on the existence of the range of services available. Only one response was possible for each product for the 2528 respondents. For the first time a new scale was used for respondents to rate the services according to their utility, in regards to the respondents' own use: ++, +, -, --. Two other options were given: 'I do not use this service', and 'I did not know Orphanet offered this service'. The results (Figure 30), show that Orphanet products are highly appreciated but not sufficiently well known. In order to assess the usefulness of Orphanet products for the needs for each respondent, an analysis of the results for this question was carried out. A product was deemed to be of use for a user if they answered '++' or '+' in the scale proposed to assess the usefulness of Orphanet's services. The percentage of these replies was calculated from the total number of replies to this question for this product, with the 'I don't use this service' and 'I didn't know Orphanet offered this service' answers subtracted from the total results beforehand so as to more faithfully represent the utility of the products, according to those who are aware of these services and using them (i.e. total replies = answers concerning the scale of utility '++', '+', '-', '--'). The most useful Orphanet services, according to our users, are the texts on diseases (95%) and the list of diseases and classifications (96%). The data concerning the epidemiology of rare diseases is also highly appreciated (92%), as are the clinical guidelines made available via Orphanet (88%), the Orphanet Report Series - List of Rare Diseases (86%), and the cross-referencing of terminologies (86%). 80% of respondents highly appreciated the search by sign facility and 79% were satisfied with the utility of the emergency guidelines.

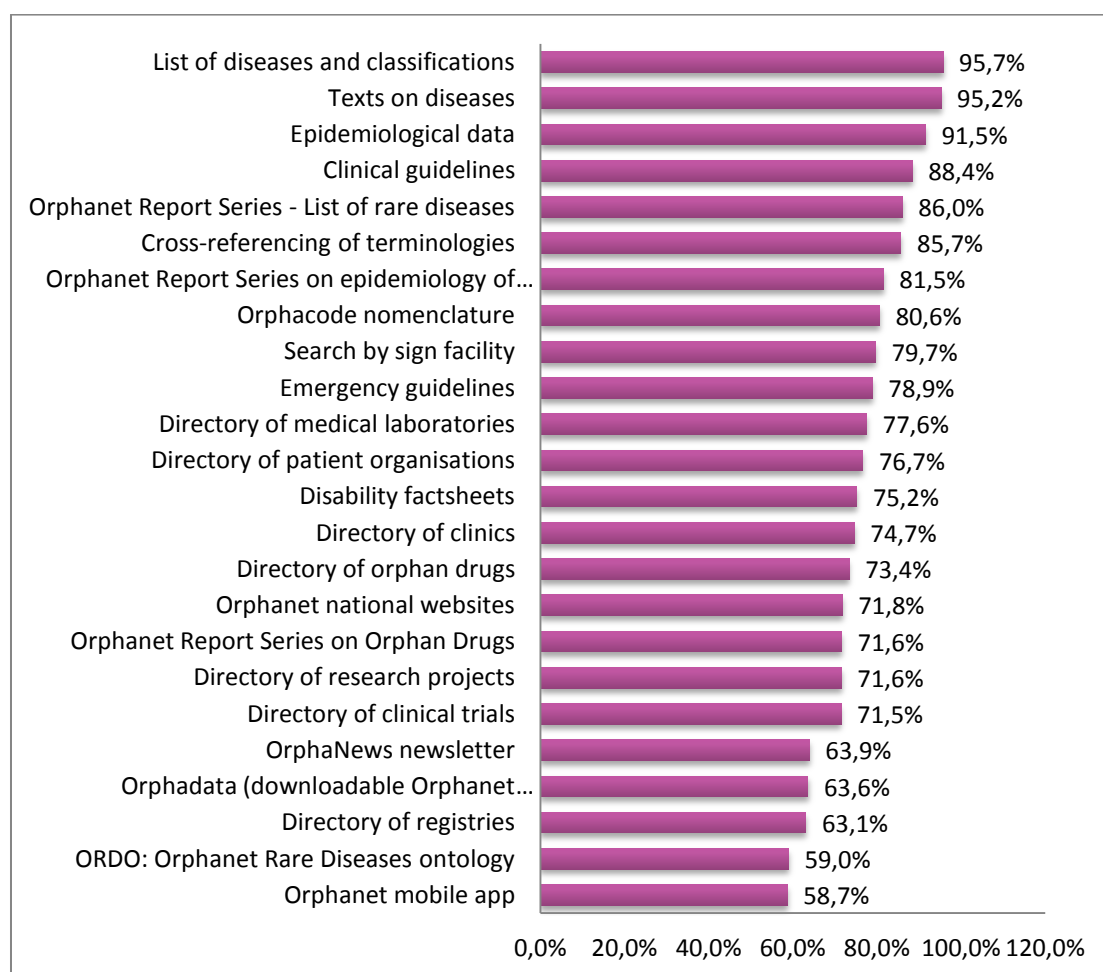


Figure 30 The most useful services offered by Orphanet according to respondents (answers ‘++’ or ‘+’ on the scale of usefulness).

An analysis of the answer ‘I didn’t know that Orphanet offered this service’ highlights that our users are not sufficiently informed about our range of products and services (Figure 31).

Orphadata, the website that allows users to download Orphanet datasets for research purposes, is fairly well appreciated but is one of the least well known services (36% of respondents). This service was launched in 2011, and is research orientated, which may explain why it is not known or used by most of the Orphanet website’s users. Similarly, ORDO, the Orphanet Rare Disease Ontology, launched in 2013, is not known by 34% of the website’s users: as for Orphadata, the targeted audience for this service is researchers, and in particular those in the bioinformatics sphere, which may explain why it is relatively unknown to those responding to the survey.

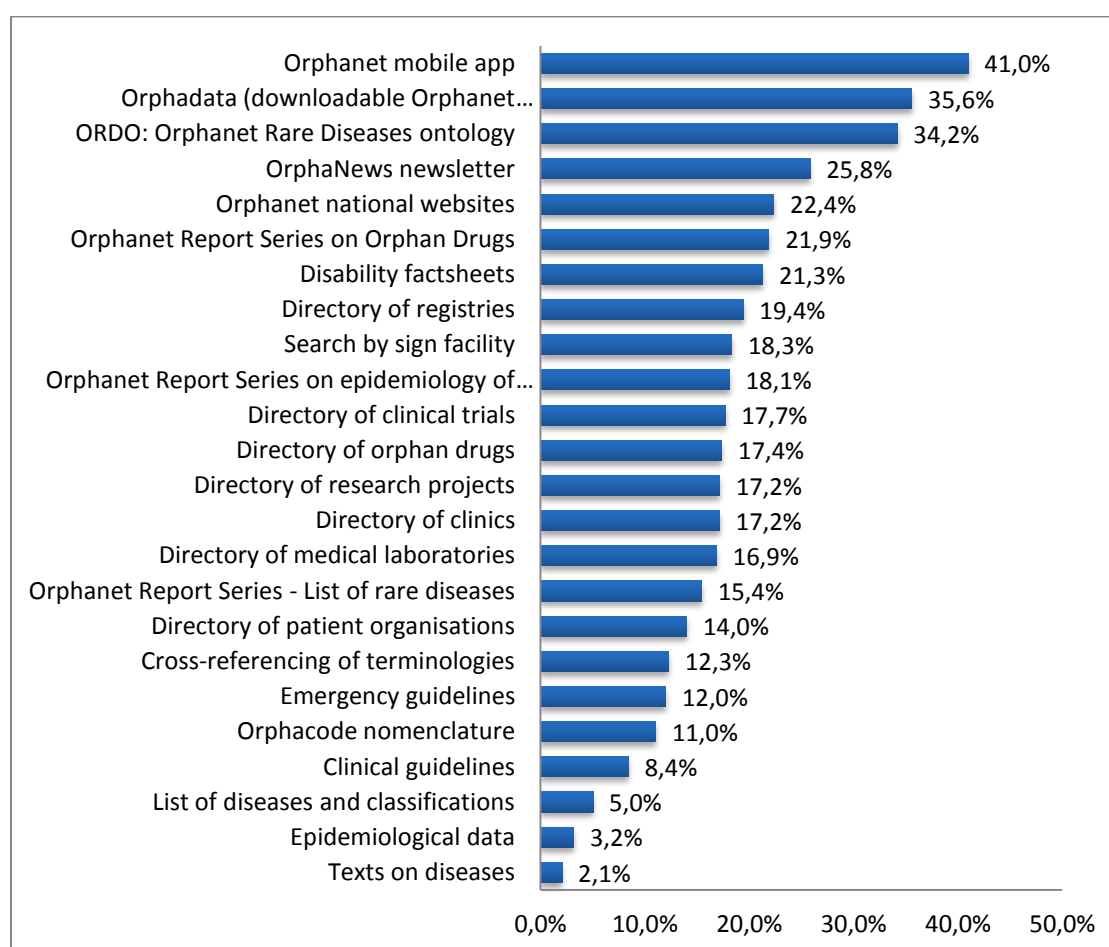


Figure 31 Least well known Orphanet products (respondents answering ‘I didn’t know this service existed’)

The OrphaNews newsletter is another service which is less well known to users with 26% of users citing it as unknown to them. 22% of users are also unaware of the existence of Orphanet’s national websites, introduced in 2011, and the Orphanet Report Series on Orphan Drugs (22%).

The most well known products remain the texts on diseases, with only 2% being unaware of their existence. Only 3% of respondents did not know about the epidemiological data made available

by Orphanet, and only 5% of respondents did not know about the existence of the list of diseases and classification.

This analysis will help the Orphanet team structure outreach activities in the future, especially for newer services such as the Ontology and Orphadata.

5. Network: Orphanet's national and international collaborations

5.1. 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. It includes over 5,000 rare diseases. The beta version is available [here](#) for public consultation.

5.2. Collaboration with Health Authorities

5.2.1. NATIONAL PLANS

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

Orphanet is mentioned either as the reference portal for rare diseases or main source of information on rare diseases in the recommendations and proposed measures of the majority of national plans or strategies adopted to date.

Germany

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

The Netherlands

The Minister of Health, Welfare and Sport in the Netherlands appointed the NFU, the Netherlands Federation of University Medical Centres, to coordinate the identification and documentation of Dutch centres of expertise for rare diseases together with Orphanet Netherlands and the VSOP (umbrella organisation of parent and patient organisations for genetic, congenital and rare disorders). The potential centres of excellence have been evaluated based on the EUCERD criteria established at the European level that include the presence of guidelines, protocols, standards and indicators of care, and equally evaluate scientific research, the relationship with patient organization(s) and how the continuity of the centre is ensured within the institute. The NFU published the procedure on the NFU website (in Dutch; www.nfu.nl/patientenzorg/complexezorg/procedure-expertisecentra). In the first round, 288 potential centres from the University Medical Centres were evaluated, in the second round 125 potential centres from both University Medical Centres and non-university major "top-clinical" hospitals were assessed. The minister assigned from both rounds centres of expertise as official Dutch centres of expertise. These 302 centres are listed on the Orphanet website by the Dutch information scientist. The list can also be found on the Erfocentrum website www.erfelijkheid.nl.

5.2.2. ADOPTION OF THE ORPHANET NOMENCLATURE IN HEALTH INFORMATION SYSTEMS

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

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

A number of countries have already taken some concrete steps in implementing ORPHA codes in their healthcare systems and national Orphanet teams are playing a key role in the following countries:

France

In 2012, it was decreed that the French hospital system database would use ORPHA codes to code all hospitalised patients. The aim is to better identify patients in the healthcare system so as to improve knowledge of their healthcare pathways. The ORPHA code has been added in a dedicated part of the coding system, in addition to the ICD-10 derived code. Also because of the development of electronic health records in France, the French Ministry of Health has set up an advice committee for the codification of RD in which Orphanet plays a major role. A series of measures were set up in order to help use the ORPHA codes in their records, which is mandatory.

This will help in collecting data that is to be included in the French Rare Diseases Data Repository [BNDMR](#), which will be deployed at the end of 2016. Coding with the ORPHA codes shall be extended to other sectors of the health system in the future.

Germany

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

The Netherlands

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

5.2.3. EXPERT RESOURCES DOCUMENTATION

The Belgian Orphanet team is piloting a nationwide survey on behalf of the Ministry of Health to document Belgian expertise for rare diseases.

5.3. Scientific collaborations and partnerships

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.

5.3.1. PARTNERSHIP WITH THE INTERNATIONAL CONSORTIUM OF HUMAN PHENOTYPE TERMINOLOGIES (ICHPT)

A collaboration between Orphanet, HPO (Human Phenotype Ontology) and OMIM was established in order to prepare a proposal for a core set of terms that describe human phenomes. A consortium of partners was set up: the **ICHPT**. There is now an agreement on 2,372 terms which are proposed to be adopted by all existing terminologies. This core terminology was made available on the IRDiRC website in 2015 [here](#), and mappings with other phenotype terminologies in use (HPO, PhenoDB, LDDb, SNOMED CT, Elements of Morphology amongst others) will be

provided in order to ensure inter-operability between databases and patient data worldwide. This project, now overseen by the IRDiRC, was initiated and coordinated by Orphanet.

5.3.2. PARTNERSHIP WITH INTERNATIONAL UNION OF BASIC AND CLINICAL PHARMACOLOGY (IUPHAR)

A partnership was established with **IUPHAR** at the end of 2011 to cross-link Orphanet with the IUPHAR database and the cross-linking is ongoing. This project is being expanded in order to take into account the evolutions of the IUPHAR database. In particular a scientific collaboration has been undertaken in order to explore the relationships between RD, genes and druggable targets.

5.3.3. PARTNERSHIP WITH THE INTERNATIONAL RARE DISEASES RESEARCH CONSORTIUM

The INSERM unit that hosts the Orphanet coordinating team is a partner of an FP7 research support action entitled “**Support IRDiRC**”.

IRDiRC was launched in April 2011 to foster international collaborations in rare disease research. IRDiRC unites 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. Orphanet hosts 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. In addition, Orphanet data is at the disposal of the IRDiRC working groups and their scientific committees and is analysed for them on request.

Orphanet also provides regular data analysis for the following indicators on the IRDiRC website: number of new RD on a monthly basis, number of genes linked to RD, number of RD for which there is a genetic test available and number of medicinal products with an orphan designation and marketing approval for the treatment of RD in the US and/or Europe.

5.3.4. PARTNERSHIP WITH EUROPEAN CLINICAL RESEARCH INFRASTRUCTURE NETWORK

Since 2012, Orphanet is involved in **European Clinical Research Infrastructure Network Integrated Activities (ECRIN-IA)** as the leader of the work package on Rare Diseases. ECRIN (European Clinical research Infrastructure Network) is a network dedicated to fostering clinical research and helps organise multinational clinical trials mainly directed towards academics. In October 2015 a workshop was organised in order to consolidate the collaboration between Orphanet’s national teams and ECRIN national contact points with the aim of fostering the identification of clinical research centres for RD in member states.

5.3.5. PARTNERSHIP WITH RARECARENET

Since mid-2013, Orphanet has had a partnership with **RareCareNet**, providing them with information on expert centres and rare cancer patient organisations. RareCareNet in return provides Orphanet with information on the epidemiology of rare cancers, and a common effort is currently performed in order to agree on the classification of rare cancers. This work will continue in the context of the EU Joint Action on Rare Cancers, which has been proposed for funding in 2016.

5.3.6. COLLABORATION WITH IHTSDO

Collaboration with the International **Health Terminology Standards Development Organisation** (IHT-SDO) 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 increase in numbers of RD included in SNOMED-CT will start in 2016 onwards. The alignment file will be available in 2017.

5.3.7. COLLABORATION WITH THE EUROPEAN BIOINFORMATICS INSTITUTE

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

Orphanet and EMBL-EBI have jointly developed the **Orphanet Rare Disease Ontology** (ORDO) and in 2014, a new version of this ontology was launched (ORDO 2.0). ORDO 2.0 was updated in 2015. A new version (ORDO 3.0) is foreseen in 2016, improving both the ontology model and the content.

5.3.8. COLLABORATION WITH THE FRENCH INSTITUTE OF BIOINFORMATICS

Orphanet has become the French Institute of Bioinformatics' 30th platform. The IFB is a national bioinformatics infrastructure bringing together platforms from the main players in research in France: CNRS, INRA, INRIA, CEA and the INSERM, as well as the Curie and Pasteur Institutes and French universities. At the moment, 30 platforms are members, grouped into six regional centres across France. The IFB's primary mission is to provide the basic services and resources in the field of bioinformatics for scientists and engineers working in life sciences. Notably, IFB is the French node of the European research infrastructure ELIXIR. ELIXIR is a distributed infrastructure for life-science information, uniting Europe's leading life science organisations in managing and safeguarding the massive amounts of data being generated every day by publicly funded research. As a platform of the IFB, Orphanet is also part of this European research infrastructure, offering data and a bio-ontology of rare diseases to advance research in this field.

Orphanet will, in particular, participate in the ELIXIR pilot use case on rare diseases in the context of the EXCELERATE project. This project aims to build an ELIXIR registry of data resources and analysis tools that are critical for the development of rare disease research, implement a technical framework for the comparison and standardisation of services useful for rare disease communities, and collaborate with rare-disease communities in organising and running their training courses, workshops and jamborees. One of the principal goals of ELIXIR is to work towards the sustainability of resources and tools such as those offered by Orphanet, which makes this a strategic step in the right direction for Orphanet's future.

5.3.9. COLLABORATION WITH RD-CONNECT

A partnership has been established between Orphanet and RD-Connect. The latter is a European funded project (2012-2018) aimed at creating an integrated platform connecting databases, registries, biobanks and clinical bioinformatics for rare disease research. This partnership will be focused on sharing data on biobanks and registries between Orphanet and RD-Connect in order to enrich both databases. Discussions on the technical implementation of the partnership and how it will affect the data collection on biobanks at the national level are still ongoing.

6. Funding

Orphanet's budget was approximately 2.6 million Euros in 2015, originating from 6 different contracts for the core activity funding and from various other contracts in some of the participating countries (Figure 32).

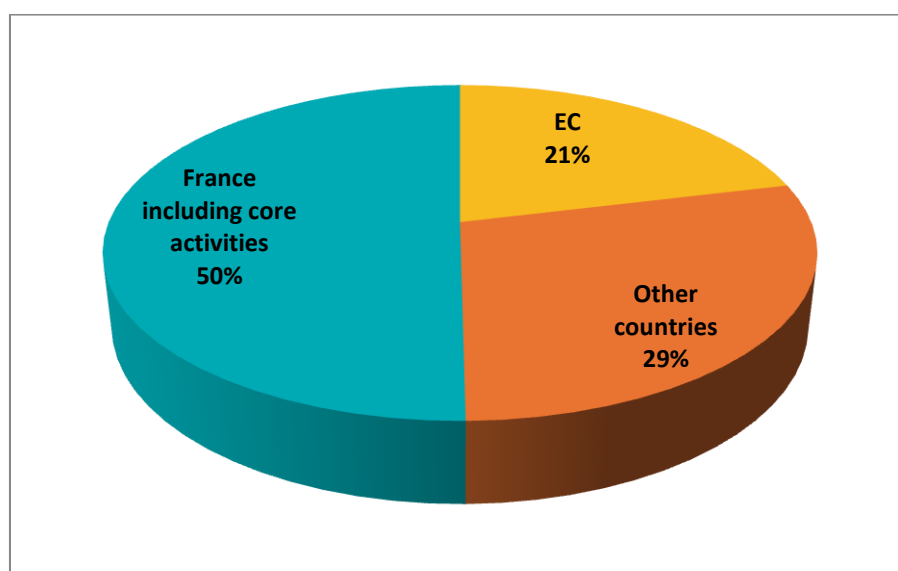


Figure 32 Orphanet's global budget 2015

6.1. Orphanet's core activity funding

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

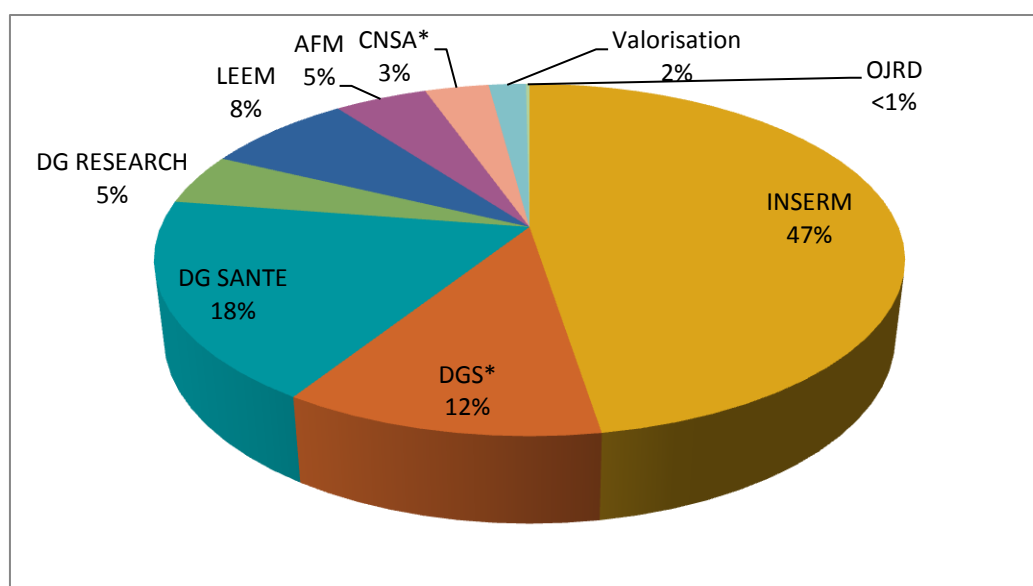


Figure 33 Orphanet core activities funding 2015



This budget (approx 1.3 million Euros) excludes the costs of infrastructure (office space) which are essentially covered by INSERM (Figure 33).

6.1.1. EUROPEAN FUNDING

The European Commission funds 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 grant 20133305-Operating Grant Orphanet). In 2014, the DG Santé grant 20102206 (Orphanet Europe Joint Action) was extended for one year without additional funding. In 2015, Orphanet participated in the ECRIN Integrating Activity (ECRIN-IA, 284395), funded by the European Union Framework Program 7.

Orphanet consortium is funded by the DG Santé grant RD-ACTION Joint Action 677024 (2015-2018).

6.1.2. OTHER CURRENT FINANCIAL PARTNERSHIPS FOR CORE ACTIVITY FUNDING







	<p>The “Institut National de la Santé et de la Recherche Médicale” finances Orphanet’s core activities.</p> <p><i>Inserm Transfert</i> is in charge of supporting Orphanet in licensing its data and in providing advice concerning intellectual property.</p>
	<p>The French Directorate General for Health (DGS) finances Orphanet’s core activities.</p>

 <p>Co-funded by the Health Programme of the European Union</p>	The European Commission finances the database of diseases and the encyclopaedia in English, as well as the coordination, communication and IT of the project through the EU Health Programme.
	The "Caisse nationale de solidarité pour l'autonomie" supports the indexing of rare diseases with the International Classification of Functioning, Disability and Health (ICF) and the Orphanet encyclopaedia of disabilities.
	The "Association Française contre les Myopathies" finances OrphaNews France the scientific literature survey, as well as data collection on clinical trials.
	The "Fondation des Entreprises du Médicament" finances the collection of data on orphan drugs and clinical trials.

Table 9 Other current financial partnerships for core activity funding

6.1.3. 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.

	Collaboration with the World Health Organisation (WHO) in the process of revising the International Classification of Diseases.
	Cross-referencing with Genatlas which collaborates in updating the data on genes involved in rare diseases.
	Cross-referencing with UniProt KB which collaborates in updating the data on genes linked to proteins involved in rare diseases.
	Cross-referencing with HGNC which collaborates in updating the data on genes involved in rare diseases.
	Cross-referencing with OMIM (The Online Mendelian Inheritance in Man). OMIM has added Orphanet to the list of external links provided on its website.
	Cross-referencing with Reactome.









	Cross-referencing with Ensembl.
	Cross-referencing with The International Union of Basic and Clinical Pharmacology DataBase (IUPHAR-DB).
	The LOVD (Leiden Open Variation Database) platform has been updated with links to Orphanet's gene pages.
	EuroGentest financed the creation of a thesaurus of clinical signs to harmonise international phenotype nomenclatures. EuroGentest collaborates with Orphanet in the field of quality management of medical laboratories.
	Orphanet and RD-Connect share information on biobanks and patient registries. Orphanet provides RD-connect with nomenclature of RD.
	Orphanet and EMBL-EBI have developed ORDO and in 2014, a new version of this ontology was launched (ORDO 2.0).
 Delivering 	Collaboration with the International Health Terminology Standards Development Organisation (IHT-SDO) is ongoing in order to include RD lacking in SNOMED-CT, and to provide alignments between ORPHA codes and SNOMED-CT terms

Table 10 Current non financial partnerships for core activity

6.2. Financial and non-financial partnerships for national activities

Orphanet's national activities are also supported by national institutions, specific contracts and/or contributions in kind. In European countries, data collection at the national level is also supported by the European Commission. Globally this budget reaches 1.3 million Euros. Please refer to Figure 34 for an overview of funding of national activities.

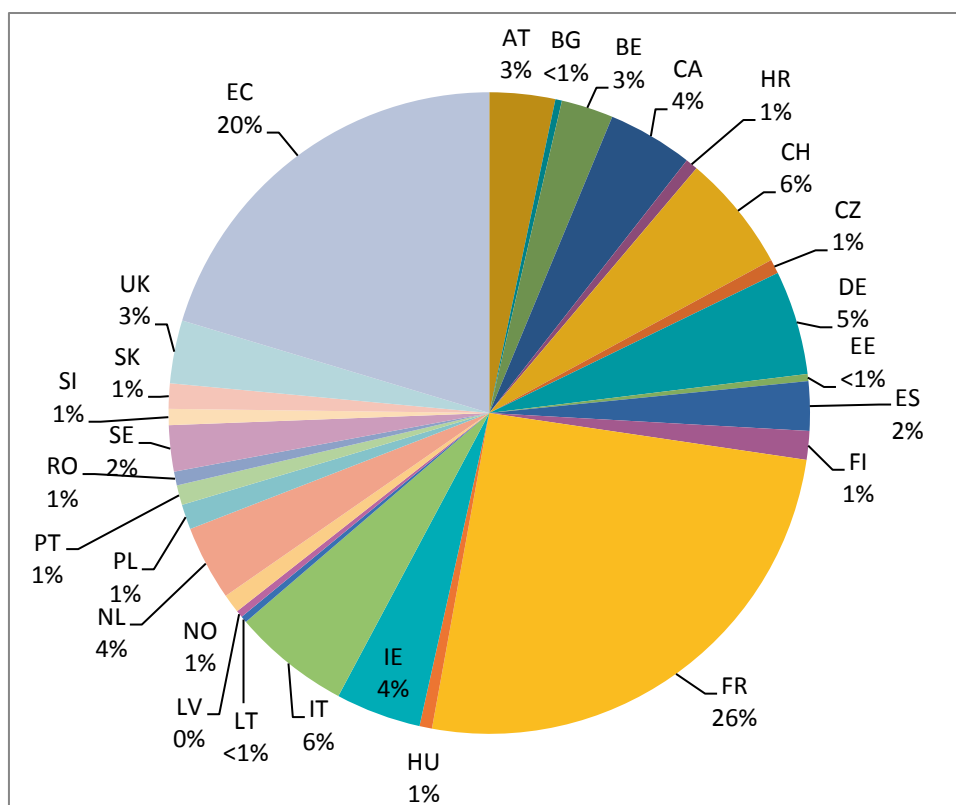










Figure 34 Funding sources for national activities in 2015








6.2.1. 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	
	The Medical University of Vienna is a beneficiary in the RD-ACTION 677024 and hosts Orphanet Austria since 2005. It further provides part-time funding (in kind) for the work of the country coordinator.
	The Austrian Ministry of Health provides funding to the RD-ACTION 677024 since June 2015.
BELGIUM	
	The Federal Public Service Health, Food Chain Safety and Environment is beneficiary in RD-ACTION 677024
	The “Wetenschappelijk Instituut Volksgezondheid – Institut Scientifique de Santé Publique” is a beneficiary in RD-ACTION 677024
	For the period 2014-2016, a convention between the Scientific Institute of Public Health (hosting the Orphanet team) and the National Institute of Health and Disability Insurance (NIHDI) includes financial support for the Orphanet project.

BULGARIA	
	The Bulgarian Association for Promotion of Education and Science (BAPES) is a beneficiary in the RD-ACTION 677024 and hosts Orphanet Bulgaria's activities.
CANADA	
	The Canadian institute of Health Research is the host institution of Orphanet Canada, finances a position for the project manager and provides additional administrative support for the project.
	The Québec "Ministère de la Santé et des Services sociaux" finances a project manager position in Quebec and some administrative support.
	The Department of Medical Genetics of the McGill University Health Centre is the host institution of Orphanet-Quebec and provides the medical coordinator.
	Le "Regroupement québécois des maladies orphelines" provides the project coordinator and administrative support.
CROATIA	
	HSRB-The Croatian Alliance for Rare disease is a beneficiary in RD-ACTION 677024
CZECH REPUBLIC	
	The Charles University Prague - 2nd School of Medicine is beneficiary in RD-ACTION 677024
	The Czech Association of rare diseases finances the activity of the Czech team since April 2012.
	The Czech Medical Genetics society 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. They have a joint partnership for the development of the Czech National Plan for rare diseases following the Czech National Strategy from 2009. The first and second Czech National Plans (2012-2014 and 2015-2017) are 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.
ESTONIA	
	The University of Tartu is a beneficiary in RD-ACTION 677024

FINLAND	
 RINNEKOTI -Säätiö	RinneKoti Foundation is a beneficiary in RD-ACTION 677024
FRANCE	
 <i>Fondation Groupama pour la santé</i> Vaincre les maladies rares	The “Fondation Groupama pour la santé” contributes to the development of the mobile application.
 LFB L'ENGAGEMENT ÉTHIQUE	The “LFB Biomédicaments” helps finance the development and update of emergency guidelines and the French encyclopaedia for the general public.
 agence de la biomédecine	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.
 CNSA Caisse nationale de solidarité pour l'autonomie	The “Caisse nationale de solidarité pour l'autonomie” supports the development of the French encyclopaedia for the general public with information on the functional consequences of rare diseases, as well as the production of fact sheets on rare disabilities not necessarily related to rare diseases.
GERMANY	
 MHH Medizinische Hochschule Hannover	The Medical School of Hanover (MHH) supports data collection, and is a beneficiary in RD-ACTION 677024
HUNGARY	
	Országos tisztifőorvosi hivatal - OTH is a beneficiary in RD-ACTION 677024
	Semmelweis Egyetem is a beneficiary in RD-ACTION 677024
ITALY	
 Ministero della Salute	The Italian Health Ministry finances Orphanet-Italy activities through current research funding.
 Bambino Gesù OSPEDALE PEDIATRICO	The Bambino Gesù Children’s Hospital is a beneficiary in RD-ACTION 677024
 genzyme	Genzyme Italia finances OrphaNews Italia.
IRELAND	
 HE Feilimhearsa na Seirbhíse Sláinte Health Service Executive	The Health Service Executive jointly funds Orphanet Ireland with RD-Action for the provision of a project manager, 0.5 information scientist, and part time administrative support.
 Shire	Shire Pharmaceuticals Ireland supported the start up of the National Rare Disease Office and Orphanet Ireland through the provision of a once-off unrestricted grant

LATVIA	
	"Centre for Disease Prevention and Control of Latvia" (Slimību profilakses un kontroles centrs) is a beneficiary in RD-ACTION 677024.
LITHUANIA	
	The Vilnius University Hospital, "Santariškių Klinikos" Centre for Medical Genetics is a beneficiary in RD-ACTION 677024
NETHERLANDS	
	The LUMC is a beneficiary in RD-ACTION 677024. It hosts Orphanet Netherlands and co-funds the work of Prof van Ommen.
	The Centre for Medical Systems Biology is a joint activity of six institutions in the Netherlands, led by LUMC and including VUMC. The CMSB co-funds the rare disease work of project manager Dr Petra van Overveld and of the chair of the Dutch Scientific Advisory Board, Prof Cornel.
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. It is beneficiary in RD-ACTION 677024
	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. It is beneficiary in RD-ACTION 677024
POLAND	
	The "Instytut Pomnik Centrum Zdrowia Dziecka" (Children's Memorial Health Institute) is beneficiary in RD-ACTION 677024. The CMHI 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, is beneficiary in RD-ACTION 677024 and hosts the Orphanet Portugal team since June 2015
ROMANIA	
	The “Universitatea de Medicina si Farmacie “Gr.T.Popa” Iasi” is a beneficiary in RD-ACTION 677024
SLOVAKIA	
	CUMS (UNIVERZITA KOMENSKÉHO V BRATISLAVE) is a beneficiary in RD-ACTION 677024
SLOVENIA	
	The University Medical Centre Ljubljana is 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 and is beneficiary in RD-ACTION 677024. CIBER (Institute of Health Carlos III, Ministry of Economy and Competitiveness) finances the main activities of the Spanish team.
SWEDEN	
	The Karolinska Institutet” is a beneficiary in RD-ACTION 677024
	Karolinska University Hospital of Stockholm supports the Orphanet Sweden activities.
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.
	Since 2011, Orphanet Switzerland is funded by the Swiss Conference of the Cantonal Ministers of Public Health. In 2015, the support financed an information scientist part time position






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. It is a beneficiary in RD-ACTION 677024

Table 11 Partnerships providing funding for national activities

6.2.2. 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.
AUSTRIA	
	The "Gesundheit Österreich GmbH" (GÖG) is a collaborating stakeholder in the RD-ACTION
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.
CYPRUS	
	The Department of Medical and Public Health Services is an associated partner in the Orphanet Europe Joint Action as of April 2011.
CROATIA	
	The Zagreb Children's Hospital contributes to the project by allocating the time of the country coordinator
IRELAND	
	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 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.
MOROCCO	
	The National Institute of Hygiene hosts Orphanet Morocco's activities and contributes to the project by allocating the time of some professionals.
SERBIA	
	The Institute of Molecular Genetics and Genetic Engineering, University of Belgrade, hosts Orphanet Serbia's activities and contributes to the project by allocating the time of some professionals.
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

6.2.3. 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.
ESTONIA	
	The Ministry of Social Affairs of Estonia officially supports Orphanet.
FINLAND	
	The Ministry of Social Affairs and Health of Finland officially supports Orphanet.
	Terveystietä (www.terveystietä.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 Terveystietä's searches concerning the 300 "most common rare diseases". As a result, Orphanet will have a higher profile among the Finnish health care professionals.
FRANCE	
	The Ministry of Health officially supports Orphanet.
	The French High Authority for Health (HAS) and Orphanet cooperate for the online publication of the National Protocols for Diagnosis and Care (NHDP) produced by the HAS.
	The "Agence nationale de sécurité du médicament et des produits de santé" (ANSM) provides Orphanet with data on clinical trials in France.
	"Air France" provides patients and professionals with a quota of airline tickets for patients to travel to medical experts or for experts to travel to patients with rare diseases. Orphanet provides expertise on the merits of applications.
	Orphanet has delegated to "Maladies Rares Info Services", the French helpline for information on rare diseases - 0156538136, the role of replying to unsolicited electronic messages received by Orphanet.
GERMANY	
	The "Allianz Chronischer Seltener Erkrankungen e.V." (ACHSE) works together with Orphanet Germany on informational services for patients.

	The “Kindernetzwerk e.V. - für Kinder, Jugendliche und (junge) Erwachsene mit chronischen Krankheiten und Behinderungen” provides data on associations in Germany.
	The “Deutsche Gesellschaft für Humangenetik e.V.” supports Orphanet by supplying the German team with addresses and information on laboratories and diagnostics.
	Nationale Kontakt- und Informationsstelle zur Anregung und Unterstützung von Selbsthilfegruppen (NAKOS) officially supports Orphanet.
	The AWMF (Association of the Scientific Medical Societies in Germany) cooperates with Orphanet DE by supplying the web links of their clinical practice guidelines to the Orphanet encyclopaedia
	DIMDI cooperates with Orphanet DE in implicating the disease terms from the German encyclopedia into the alpha-code of the ICD-10GM
HUNGARY	
	The State Secretary of Health within the Ministry of Human Resources officially supports Orphanet.
IRELAND	
	The Department of Health officially supports Orphanet and provides governance of Orphanet Ireland
	The National Rare Disease Office (NRDO) hosts the Orphanet Ireland team. Orphanet is the main source of rare disease resource information for the NRDO Information Line
	The Royal College of Physicians National Clinical Programme for Rare Diseases Clinical Advisory Group (Chair: Prof. Andrew Green) acts as Scientific Advisory Group for Orphanet Ireland
	The Genetic and Rare Diseases Organization (GRDO) (who together with MRCG and IPPOSI form the Irish National Alliance for Rare Disease) collaborate in the promotion of Orphanet and Rare Disease activities in Ireland. The Country Coordinator and an Information Scientist (ROS) are GRDO board members.
	The Medical Research Charities Group (MRCG) collaborates in the endorsement and promotion of Orphanet and Irish Rare Disease activities.
	The Irish Platform for Patient Organizations, Science and Industry (IPPOSI) collaborate in the promotion of Orphanet and Rare Disease activities in Ireland. IPPOSI is also actively engaged in implementation of the RD-action WP5 in Ireland by providing links between the Orphanet Ireland team and eHealth and software developers.

ISRAEL	
	The Israeli Ministry of Health officially supports Orphanet.
ITALY	
	The “Istituto Superiore di Sanità” officially supports Orphanet.
	Telethon collaborates with Orphanet for the collection of data concerning research projects.
	Uniamo, the Italian Federation of support groups on rare diseases, collaborates with Orphanet in the organization and promotion of events dedicated to rare diseases, in order to increase public awareness on this particular issue.
	Netgene collaborates with Orphanet for the diffusion of information on rare diseases.
	Farindustria promotes Orphanet publications.
	Osservatorio Malattie Rare (O.Ma.R.) collaborates with Orphanet for the diffusion of information on rare diseases and the promotion of events.
	The Italian Inter-regional Technical Board for Rare Disorders collaborates with Orphanet for the collection of data concerning the Centres of Reference officially recognized in Italy.
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.
	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	
	The Ministry of Health of the Republic of Lithuania officially supports Orphanet.
NETHERLANDS	
	The Ministry of Health, Welfare and Sport of the Netherlands officially supports Orphanet Netherlands.

	The Erfocentrum provides information to the general public on mainly rare, genetic disorders. Collaboration has been established to increase the number of Dutch texts available on Orphanet and to list the Dutch designated centers of expertise for rare diseases for the public and for experts.
	The VSOP (umbrella organisation of parent and patient organisations for genetic, congenital and rare disorders) provides information regarding patient organisations dedicated to rare disease and participates in the designation of Dutch centers of expertise for rare diseases.
	The Dutch Federation of University Medical Centers (NFU) is, in collaboration with Orphanet NL and the VSOP, responsible for the inventorying and documentation of Dutch centers of expertise for rare diseases.
POLAND	
	The patient organisation, Ars Vivendi, 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, Social Services and Equality - Office for Health Planning and Quality is an associated partner in the Orphanet Europe Joint Action as of April 2011.

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

Table 13 Non-financial partnerships for national activities



7. Communication

7.1. Communication documents

In 2015, A5-size flyers to present Orphanet and Orphanet services were updated when necessary and distributed:

- Orphanet in 3 languages (English, French and German)
- Orphadata (English)
- Orphanet application for iPhone and iPad (English)
- ORPHA codes(English)
- Orphanet database structure and main products (English)
- Orphanet rare disease ontology

An A5 leaflet about Orphanet 2014 achievements was also printed and distributed at congresses.

7.2. Invitations to give lectures at conferences in 2015

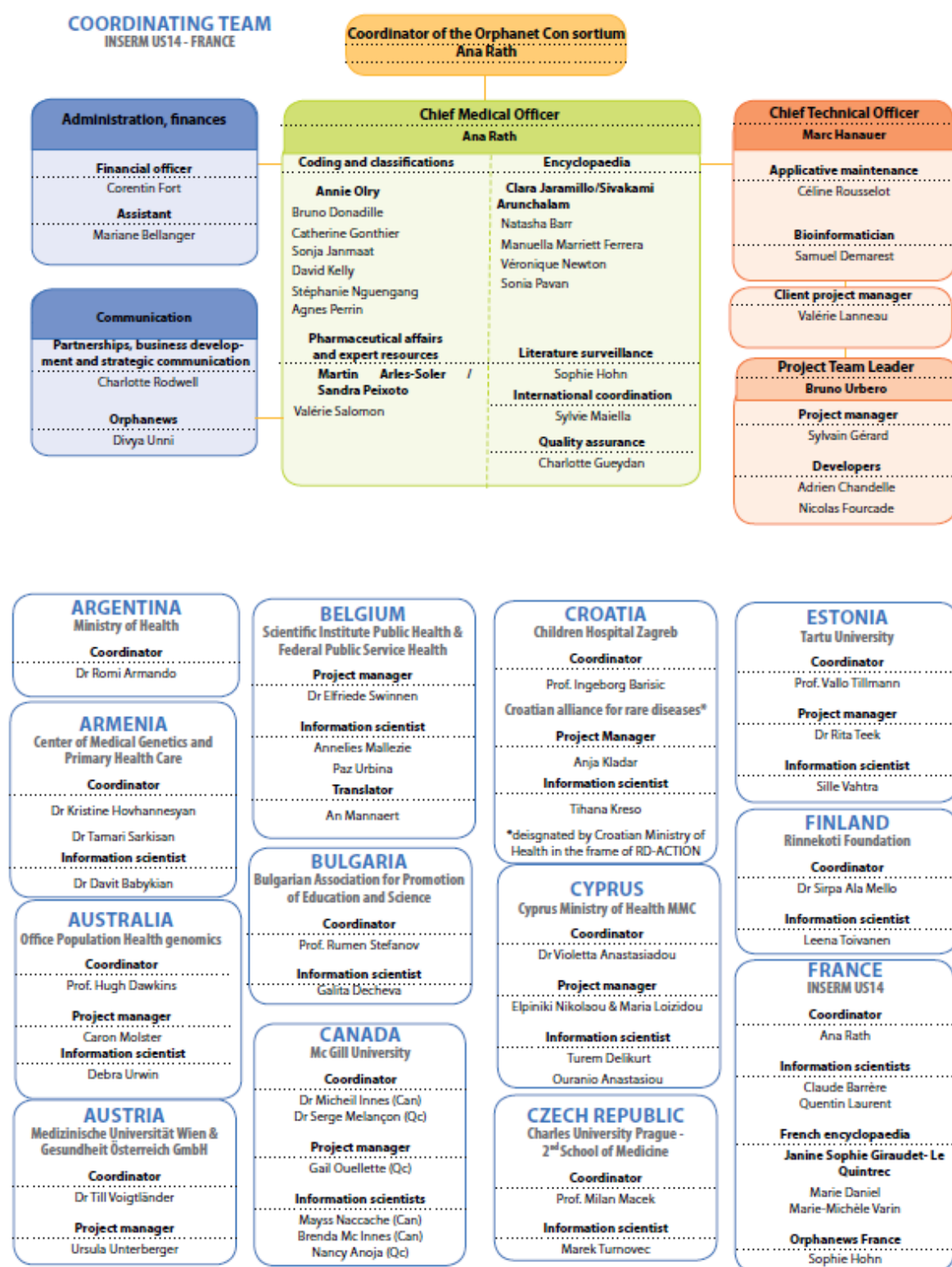
Orphanet representatives, as specialists in the field of rare diseases, were invited to give lectures and to participate in more than 50 conferences worldwide. These lectures focused on presenting the Orphanet database (29), public health policies (8), RD research (2), orphan drugs (1), and medical and genetic approaches (7 presentations).

7.3. Booths at conferences in 2015

Orphanet booths were held in 6 different congresses in 2015 as indicated in the list below:

- 26th Annual Meeting of the German Society of Human Genetics in Cooperation with the Austrian Society of Human Genetics and the Swiss Society of Medical Genetics”, 15-17 April, Graz, Austria
- Rare Diseases Colloquium, 8-9 May, Tunisia
- European Human Genetics Conference 5-9 June, Glasgow, Scotland
- Annual Meeting of the Canadian Paediatric Society, June 24-25, Toronto
- CCMG 39th Annual Scientific Meeting & CCMG/CAGC Joint Symposia, September 10-12, Ottawa, Canada
- American Society of Human Genetics, October 7-9, Baltimore, USA

8. The Orphanet team as of December 2015



GERMANY Medizinische Hochschule Hannover Coordinator Prof. Joerg Schmitzke Project manager Dr Kathrin Rommel Information scientists Dr Mareike Derks Elisabeth Nyongui	LITHUANIA Vilnius University Hospital Coordinator Prof. Vaidutis Kucinskas Information scientist Birute Burnyte Birute Tumiene	PORTUGAL Instituto de Biologia Molecular e Celular, University of Porto Until June 2015 Coordinator Prof. Jorge Sequeiros Project manager João Silva Information scientist Patricia Arinto Directorate General of Health From June 2015 Coordinator Dr Paulo Nogueira Project manager Dr Rui Gonçalves	SWEDEN Karolinska Institutet Coordinator Dr Désirée Gavhed Information scientist Dr Rula Zain
HUNGARY Országos Tisztifőorvosi Hivatal Coordinator Dr Melinda Csaky-Szunyogh Assistant Anita Szilagyi Semmelweis University Project manager Dr Maria Judit Molnar Information scientist Dr Marta Szegedi	MOROCCO Institut National d'Hygiène Coordinator Prof. Abdelaziz Sefiani Information scientist Imane Cherkaoui-Jaoud	SERBIA Institute of Molecular Genetics and Genetic Engineering Coordinator Dr Dragica Radojkovic Project manager Dr Maja Stojiljković	SWITZERLAND Service of Genetic Medicine - Geneva University Hospitals Coordinator Dr Loredana D'Amato Sizonenko Information scientist Beatrice Geissbuhler
IRELAND National Centre for Medical Genetics Coordinator Prof. Eileen Tracey Project manager Debby Lambert	NETHERLANDS Leiden University Medical Center Coordinator Prof. Gert-Jan van Ommen Project manager Dr Petra van Overveld Information scientist Dr Judith Carlier - de Leeuw van Weenen Chairperson scientific advisory board Prof. Martina Cornel	SLOVAKIA Comenius University Bratislava Coordinator Prof. László Kovács Project manager Anna Hlavata Information scientist Gabriela Nagyova	TUNISIA CHU Farhat Hached Coordinator Dr Dorra H'mida Ben Brahim
ISRAEL Chaim Sheba Medical center Coordinator Dr Annick Raas-Rothschild Project manager Vivi Einy	NORWAY Norwegian National Advisory Unit on RD Coordinator Lena Lande Wekre The Norwegian Directorate of Health Coordinator Bodil Stokke	SLOVENIA University Medical Centre Ljubljana Coordinator Dr Luca Lovrecic Information scientist Ales Maver	TURKEY University of Istanbul Coordinator Prof. Ugur Özbek
ITALY Bambino Gesù Children's Hospital Coordinator Prof. Bruno Dallapiccola Project manager Dr Rita Mingarelli Information scientists Martina Di Giacinto Serena Ciampa Roberta Ruotolo Elena Cocchiara (until 02/2015) Sonia Festa (until 02/2015) Editorial Assistant Maria Lisa Dentici (until 11/2015) Francesca Clementina Radio	POLAND Instytut Pomnik Centrum Zdrowia Dziecka Coordinator Prof. Malgorzata Krajewska-Walasek Prof. Krystyna Chrzanowska Information scientists Dorota Karczmarewicz Aleksandra Jezela-Stanek	SPAIN CIBER & Ministry of Health and Social Policy Coordinator Dr Francesc Palau Project manager Dr Virginia Corrochano Information scientists Maria Elena Mateo	UNITED KINGDOM National Disease Registration Division at Public Health England Coordinator Sarah Stevens Information Scientist Ayomikun Akinrinmade
LATVIA Centre for Disease Prevention and Control of Latvia Coordinator Jana Lepikšone Information scientist Santa Pildava Irisa Zile	ROMANIA Universitatea de Medicina si Farmacie «Gr.T.Popa» Iasi Coordinator Ass. Prof. Cristina Rusu Information scientists Elena Braha Monica Panzariu Cristina Gavrilovici	ORPHANET CONTACT POINTS** Denmark Dr John Ostergard Georgia Dr Tamari Rukhadze Lebanon Prof André Megarbane Luxembourg Dr Yolande Wagener Malta Dr Neville Calleja	

** please refer to paragraph 2.3.3

Table 14 Organisational chart

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

Editor-in-chief: Ana Rath Managing Editor: Sylvie Maiella Contributing Editors: Charlotte Rodwell & Charlotte Gueydan

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