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ORPHANET BELGIUM ACTIVITY REPORT 2017-2019

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Kris Doggen (Head of service)

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WHO WE ARE

SCIENSANO can count on more than 700 staff members who commit themselves, day after day, to achieving our motto: Healthy all life long. As our name suggests, science and health are central to our mission. Sciensano's strength and uniqueness lie within the holistic and multidisciplinary approach to health. More particularly we focus on the close and indissoluble interconnection between human and animal health and their environment (the "One health" concept). By combining different research perspectives within this framework, Sciensano contributes in a unique way to everybody's health.
For this, Sciensano builds on the more than 100 years of scientific expertise of the former Veterinary and Agrochemical Research Centre (CODA-CERVA) and the ex-Scientific Institute of Public Health (WIV-ISP).

Sciensano

Epidemiology and public health – Health services research

Rare Diseases Team

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- The **Orphanet Belgium Board** consists of representatives of:
  - the Orphanet Belgium team;
  - the sponsors of Orphanet Belgium (FPS/SPF/FOD/, NIHDI/INAMI/RIZIV) and Sciensano;
  - ad hoc: experts or representatives of institutes designated for the validation of the data.

- **Sponsors and non-financial Partnerships:**

	SPONSORS & NON-FINANCIAL PARTNERSHIPS	
Members of National Board	sciensano	Sciensano's service "Health Services Research" hosts the Orphanet Belgium team. Sciensano has been a beneficiary in RD-ACTION 677024 (financial support from the European Health Program). At Sciensano, there is internal collaboration with Infectious Diseases Service to validate data on reference laboratories and screening tests for infectious disease.
	federal public service HEALTH, FOOD CHAIN SAFETY AND ENVIRONMENT	The Federal Public Service Health, Food Chain Safety and Environment has been a beneficiary in RD-ACTION 677024 (financial support from the European Health Program).
	INAMI-RIZIV	The National Institute of Health and Disability Insurance (NIHDI) finances Sciensano to participate in the Orphanet project. The National Institute of Health and Disability Insurance provides information on the recognized reference centers working under a revalidation convention.
Ad-hoc experts	RaDiOrg	The Belgian umbrella association of patient organisations for rare diseases plays a role in the validation of data on Belgian patient organizations registered in Orphanet.
	COLLEGE GENETICS	The College of Human Genetics in Belgium, which represents the 8 recognized genetic centers, collaborates with the Orphanet team to improve and simplify the process of registration and update of data on genetic testing activities in the Orphanet database.

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EXECUTIVE SUMMARY

Orphanet, the portal for rare diseases and orphan drugs, was created in 1997 and has gradually grown to a consortium of 39 countries, within Europe (including the 27 Member states) and across the globe. Belgium has been a partner of Orphanet since 2005. The Orphanet portal plays a key role in providing expert-reviewed information on rare diseases, orphan drugs and expert resources for rare diseases. The integral role played by Orphanet in the research and care spheres has led to its recognition as an IRDiRC Recognised Resource. Every month, more than a million pages of the Orphanet website are consulted from over 200 countries and Belgium is among the top ten countries of the website's audience. Several recent surveys have shown that almost 40% of the users are professionals. Patients and their families account for one third. Orphanet also plays a leading role in the establishment and maintenance of a specific nomenclature of rare diseases: each disease receives a unique identifier called Orphacode. This nomenclature is aligned with other terminologies to ease exchanges between different databases. Orphanet and the ORPHA nomenclature are recognized as key measures in many national plans/strategies for rare diseases.

At European level, the maintenance of the infrastructure, coordination and networking activities of Orphanet (INSERM, Paris) is partially supported by the European Commission since 2001. During 2017-2019, Orphanet project was supported by a Rare Disease Joint Action, a Direct Grant and the European Joint Program for rare diseases. In Belgium, participation in Orphanet is supported by the health authorities. Sciensano has been endorsed by the Ministry of Health to host the Belgian team. During 2017-2018 the FPS participated in work packages of the Rare Diseases Joint Action. A national board consisting of members from Sciensano, FPS and the National Institute for Health and Disability Insurance (NIHDI) oversees the project.

The Orphanet portal is a "work in progress" and is constantly evolving. Data in Orphanet are manually curated and expert validated, in accordance with formalised procedures explaining how to work, the workflow to be followed and the inclusion/exclusion criteria for each type of data.

During the 2017-2019 period, the Orphanet Belgium team performed the following tasks:

1. Fulfilled all ad-hoc requests of professionals for new registrations (if eligible) or updates of their data. This concerns expert centers, medical laboratories and diagnostic tests, patient organisations, clinical trials, research projects, patient registries, mutation registries, biobanks.

2. Processed all information provided by professionals as a result of the general yearly updates of the directory of resources.

3. Carried out the quality control action points and specific projects of the "Quality Assurance Review (QAR)" documents that are distributed by the Orphanet coordinating team (INSERM) in order to continually enrich the database and keep it relevant and up-to-date.

4. Collaborated in 2018 with RaDiOrg, the Belgian umbrella organisation for patients organisations concerning rare diseases, in order to validate the data on patient organisations and to identify missing patient organisations in the database.

5. During 2018-2019 special attention was paid to the information with regard to Belgian rare disease reference centres. The Belgian Orphanet board approved the registration of the centres that work under a convention with the NIHDI ; the genetic centres officially recognized by the regional authorities for their diagnostic and counselling activities and the hospitals recognized by the regional health authorities to have a "rare diseases function". These centres were updated or newly registered and receive the "officially designated centre of reference" flag  .

6. Started mid-2019 with the registration of Belgian centres participating in ERNs, receiving the "member of a ERN" flag 

. This task is ongoing.

7. Searched proactively for information in order to compare with the data in the database (completeness and validation actions). For this purpose official and non-official sources were consulted (websites of patient organisations or medical laboratories, BELAC website, Clinical trials.gov,…).

8. Shared expertise in rare disease classifications, terminologies and cross-reference lists as well as Orphanet datasets for use by other rare disease projects/studies. For example the Central Registry of Rare Diseases (CRRD) and the Belgian Genetic Test Database (BGTD) use the Orphanet nomenclature of rare diseases to uniformly collect certain patient and test data. Orphanet data was also used in a study on rare diseases in primary care in Belgium[1].

9. Networked with professionals and experts at national level and developed partnerships (BELMOLGEN, other services of Sciensano, RaDiOrg, …).

10. Maintained the Orphanet Belgium national website presenting the news, events and documents of national significance as well as the pages dedicated to Orphanet's activities available on Sciensano websites.

11. Facilitated participation of Belgian experts in the Orphanet encyclopedia/terminology.

[1] *N. Boffin et al. General Practice Care for Patients with Rare Diseases in Belgium. A Cross-Sectional Survey, 2018, https://doi.org/10.3390/ijerph15061180*

12. Organised national board meetings. The national board met several times during 2017-2019.

13. Published an updated version of the document specifying -for each type of data- the definitions, the sources of information in Belgium as well as their inclusion criteria as decided upon by the national board.

14. Participated in the trainings organized by Orphanet INSERM (online, call conferences, hands-on sessions in INSERM, Paris).

15. Raised awareness of rare diseases and participated in communication activities (presentations at meetings, conferences, distributing flyers).

16. Fulfilled its tasks at European level: participation in annual meetings, participation in bi-monthly conference calls of the Management Board and follow-up on the decisions made, participation in the Orphanet Operating Committee (call conferences, tasks), validation of yearly Orphanet reports, as well as dissemination of national initiatives through the Orphanetwork internal newsletter.

For the near future, besides continuing its regular tasks and finishing the abovementioned ongoing projects, the Orphanet Belgium team aims to:

- Register information on specialized non-DNA tests and the laboratories that perform them (in collaboration with N. Vandevelde, Service Quality of Medical Laboratories, Sciensano).

- Renew attention to the information on tests for specific pathogens causing rare infections.

- Follow the “Train the trainers” program (2020) on classifications and terminologies provided by the Orphanet coordinating team (INSERM), in order to organize national trainings on the topic for professionals.

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ABBREVIATIONS

BE	Belgium
BeSHG	Belgian Society for Human Genetics
BGTD	Belgian Genetic Tests Database
BNMDR	Belgian NeuroMuscular Diseases Registry
CC	Country Coordinator
CEGRD	European Commission Expert Group on Rare Diseases
CRRD	Central Registry of Rare Diseases
CT	Clinical trial
EC	European Commission
EQA	External Quality Assessment
ESHG	European Society of Human Genetics
EU	European Union
FAMHP	Federal Agency for Medicines and Health Products
FPS	Federal Public Service (FPS) Health, Food Chain Safety and Environment
GDPR	General Data Protection Regulation
HPO	Human Phenotype Ontology
ICD	International Classification of Diseases
ICTRP	International Clinical Trial Registry Platform
INAMI	Institut national d'assurance maladie-invalidité
INSERM	The French National Institute of Health and Medical Research / Institut National de Santé et de Recherche Médicale
IRDiRC	International Rare Diseases Research Consortium
IS	Information Scientist
MB	Management Board
MedRA	Medical Dictionary for Regulatory Activities
MeSH	Medical Subject Headings
NIHDI	National Institute for Health and Disability Insurance
OMIM	Online Mendelian Inheritance in Man
ORDO	Orphanet Rare Disease Ontology
ORPHA code	Orphanet disease classification number
PO	Patient organisation
QAR	Quality Assurance Review
RD(s)	Rare Disease(s)
RIZIV	Rijksinstituut voor ziekte- en invaliditeitsverzekering
SNOMED-CT	Systematized Nomenclature of Medicine-Clinical Terms
SOPs	Standard Operating Procedures
UMLS	Unified Medical Language System
WHO	World Health Organisation
WP	Work Package

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OVERVIEW CONTACT ADRESSES AND WEBLINKS

Table 1: *Contact details and weblinks related to the Orphanet Belgium database for specific target groups of Orphanet users*

Target audience	Topic	Contact addresses and weblinks
General public and professionals	Through our generic email address, we receive different types of requests regarding the Belgian Orphanet database: submission of new information, update of already registered data, personal queries related to a rare disease (search for patient support group, questions about prevalence…),.. Orphanet Belgium national website presents the news, events and documents of national significance.	Via a request by email at the generic email address: orphanetbelgium@sciensano.be Users can provide comments seeking to improve the quality and accuracy of information on the Orphanet website through the "suggest an update" button. Remarks can also be send via an online contact form. Dutch version: http://www.orpha.net/national/BE-NL/index/homepage/ French version: http://www.orpha.net/national/BE-FR/index/page-d-accueil/
Professionals/experts	Registration and update of their activities related to rare diseases.	Via a request by email at the generic email address: orphanetbelgium@sciensano.be It can also be done at any time using the Orphanet online registration tool (aka PROFESSOR): https://www.orpha.net/professor/htdocs/
Experts	Substantive contributions to the rare disease inventory (writing or reviewing abstracts for specific diseases, suggestions regarding nomenclature, synonym and text modification).	Via a request by email at the generic email address: orphanetbelgium@sciensano.be The expert will then be put in contact with the Orphanet editorial team. Experts can also provide their feedback through the "suggest an update" button and through an online contact form.

INTRODUCTION

In Europe, a disease is defined as rare when it affects no more than 1 in 2,000 people[2]. A recent scientific paper written by Orphanet confirms that **rare diseases represent a major public health issue**, as the number of people living with a rare disease is estimated at 300 million worldwide[3]. Almost 80% of rare diseases are of genetic origin and approximately 70% of rare diseases start in childhood. Most often, rare diseases are severe, chronic, progressive and significantly affect the quality of life of those affected. Over 6,000 rare diseases[4] have been clinically defined to date and new pathologies are regularly described by researchers. Specific issues are raised in relation to their rarity. In particular, the field of rare diseases suffers from a deficit of medical and scientific knowledge. For people affected by rare diseases, it is often difficult to find information on these pathologies, which are scarce and disseminated around the world, or to find qualified professionals to ensure their medical care. In addition, for physicians and researchers, it is essential to benefit from means facilitating collaborations and exchanges on advances in the field.

The Orphanet portal (official address of the central website: www.orphanet.net) plays a key role in the research and care spheres in providing expert-reviewed information on rare diseases and orphan drugs to all stakeholders. Every month, more than a million pages of the Orphanet website are consulted from over 200 countries and Belgium is among the top ten countries of the website's audience[5].

The table below (Table 2) shows the evolution of the number of Orphanet visitors in Belgium between June 2017 and June 2019. A recent substantial increase in number of visitors is perceptible. Even if all the visitors are not patients, the estimated number of RD patient population is given for reference.

Table 2: *Number of Orphanet visitors in Belgium*

COUNTRY	POPULATION 2018	ESTIMATED NUMBER OF RD PATIENTS (6%)	ORPHANET VISITORS JUNE 2018-JUNE 2019	ORPHANET VISITORS JUNE 2017-JUNE 2018	INCREASE
Belgium	11 398 589	683 915,34	272 923,00	179 378,00	52,15%

An on-line survey was launched in January 2019, with questions focused on the professional activity of the users, their habits when they visit the Orphanet website, their opinion of the content as well as

[2] *As defined in Regulation (EC) N°141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products, https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32000R0141&from=FR*

[3] *Nguengang Wakap S et al. « Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database ». European Journal of Human Genetics, 2019, https://doi.org/10.1038/s41431-019-0508-0*

[4] *« Prevalence of rare diseases: Bibliographic data », Orphanet Report Series, Rare Diseases collection, January 2019: Diseases listed in alphabetical order, http://www.orpha.net/orphacom/cahiers/docs/GB/Prevalence_of_rare_diseases_by_diseases.pdf*

[5] *Data from Orphanet 2017 Activity Report: https://www.orpha.net/orphacom/cahiers/docs/GB/ActivityReport2017.pdf*

their overall satisfaction and their suggestions for improvement. Belgium was in the top ten countries replying to the survey (n=105).

The profile of Orphanet's users is distributed as indicated in the figure below: seven categories were proposed (i.e. health professional, patient/entourage, researcher, industry, health care manager/policy maker, education/communication and students). Figure 1 shows the distribution of respondents amongst these categories.

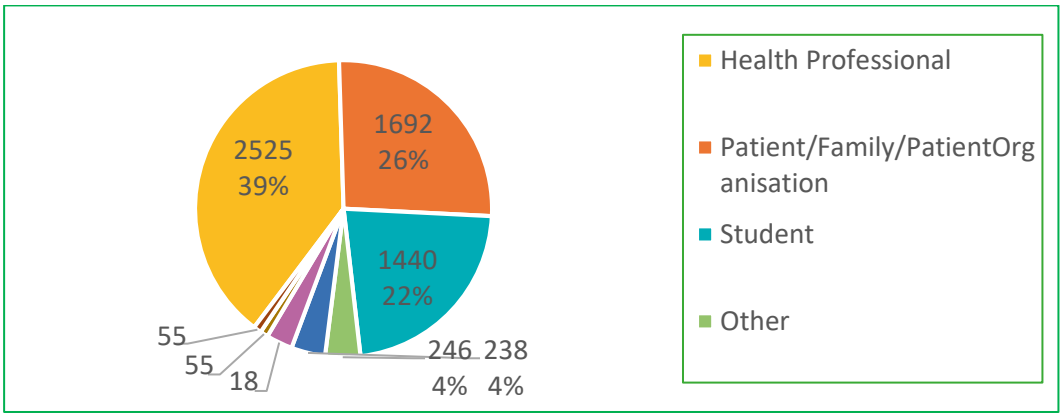

Figure 1 : *Types of Orphanet users (number of responses and percentage of total responses), n =6436*

The largest category of respondents is the health professional category (39%). The second largest category of respondents is patients and their entourage (including patient organisations, alliances and support groups) with 26% of responses. Many students (22%) also replied to the survey. Other users include policy-makers, pharmaceutical companies, teachers, journalists, industry managers or anyone interested in the field of rare diseases[6].

The vast majority of users answering the annual satisfaction survey (93% out of 4369) were satisfied of Orphanet services, as shown in Figure 2.

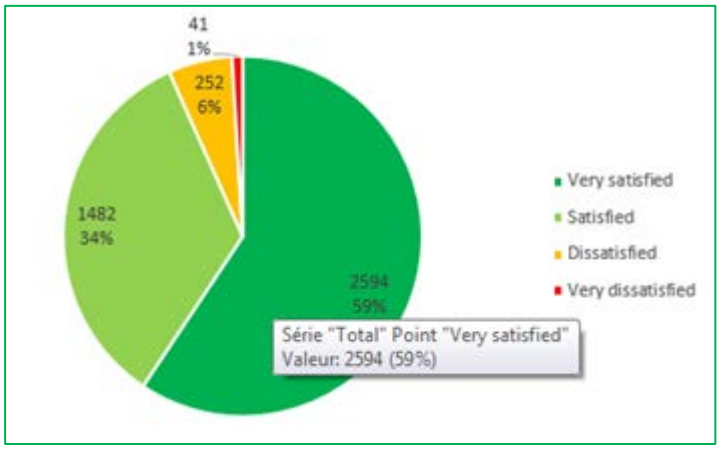

Figure 2 : *Global satisfaction of the Orphanet website users*

[6] *Latest annual survey document currently available: «2017 User Satisfaction Survey of the Orphanet Website», Orphanet Report Series, Reports Collection, 2018, http://www.orpha.net/orphacom/cahiers/docs/GB/Orphanet_survey2017.pdf*

Orphanet was established in 1997 in France on the initiative of the INSERM (French National Institute for Health and Medical Research) in order to gather scarce knowledge on rare diseases so as to improve the diagnosis, care and treatment of patients with rare diseases and to provide information on developments in research and new therapies. This initiative became a **European endeavour from 2000**, mainly supported by grants from the European Commission (EC)[7]. Orphanet has gradually grown to a **consortium of 39 countries, within Europe and across the globe:** 34 full members (endorsed by national authorities) in 33 countries[8] including the 27 Member States of the European Community and bound by a Network Agreement since 2018, plus 5 contact points.

Over the past 20 years, Orphanet has become the **international reference source of information on rare diseases**. Orphanet plays indeed a crucial role to help all audiences access quality information amongst the plethora of information available online, for example by providing the means to easily find rare disease patient organisations to break the isolation often experienced by people with rare diseases. It also participates in generating knowledge by producing massive, computable, re-usable scientific data. Its contribution in the field of rare diseases has led to its recognition as an IRDiRC (the International Rare Diseases Research Consortium) Recognized Resource[9].

Orphanet also plays a leading role in the **establishment and maintenance of a specific nomenclature of rare diseases**: each disease receives a unique identifier called "Orpha code". This nomenclature is aligned with other terminologies to ease exchanges between different databases. Orphanet and the ORPHA nomenclature are recognized as key measures in many national plans/strategies for rare diseases.

Orphanet is a **multilingual project**: translations of the Orphanet content (structural pages, terminologies, scientific abstracts) in a set of language(s) are managed by relevant teams. At the moment, the database and the website are progressively translated in 8 languages: English, French, Spanish, Italian, German, Dutch, Portuguese, Polish with texts also currently freely available online in Greek, Slovak, Finnish and Russian.

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[7] *For detailed information on funding, please consult the latest Orphanet activity report: https://www.orpha.net/orphacom/cahiers/docs/GB/ActivityReport2018.pdf*

[8] *This figure is correct as of June 2019; this number evolves as new countries join regularly. To have the most up to date figure, please refer to the following document: https://www.orpha.net/orphacom/cahiers/docs/GB/Orphanet_Network_MB_members.pdf*

[9] *http://www.irdirc.org/research/irdirc-recognized-resources/*

1. The Orphanet missions

Orphanet works towards meeting three main goals:

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

IMPACT:
For patients: increased visibility/recognition in health pathways
For healthcare professionals: facilitated identification of RD patients
For policy-makers: estimation of prevalence and burden of RD for policy planning
For researchers: facilitated data sharing and patient recruitment
For industry: facilitated estimation of the market size; facilitated recruitment

- **Provide high-quality information on rare diseases and expertise** (i.e. expert-validated and continuously updated data)**,** ensuring equal access to knowledge for all stakeholders. Orphanet provides visibility to experts and for patients by providing access to a directory of expert services by disease, such as centres of expertise, medical laboratories and diagnostic tests, patient organisations, patient and mutations registries, biobanks, research projects and clinical trials.

IMPACT:
For patients: identification of expertise including cross-borders; tackling isolation
For healthcare professionals: facilitated referrals including cross-border
For policy-makers: follow-up of the allocation of resources, patients' needs coverage and gap analysis on healthcare planification and research agenda, impact on evidence-based policy making
For researchers: facilitated networking by identification of experts and working groups
For industry: facilitated identification of experts, researchers, patient organisations for collaboration and recruitment (i.e. for clinical research)

- **Contribute to generating knowledge on rare diseases**: piecing together the parts of the puzzle to better understand rare diseases. To develop and curate the scientific data in the Orphanet database, Orphanet works with experts from around the globe, from health care professionals and researchers, to patient representatives and professionals from the medical-social sector. Orphanet also provides clinical practice guidelines (ERNs or other learned societies).

IMPACT:
For patients: better understanding of diseases; support for communication with professionals/institutions on their disease or their relative's disease
For healthcare professionals: increased knowledge, support for diagnosis and referral, access to best practice guidelines
For researchers: rapid access to the literature and state of the art of knowledge
For policy-makers: facilitated access to state of the art per disease and to guidelines (standards of care)

2. The Orphanet services

Orphanet offers a large range of freely accessible services:

- **A comprehensive inventory of rare diseases classified according to a polyhierarchical classification system.** Where possible, the Orphanet terminology has been mapped with other international standards: ICD-10, Online Mendelian Inheritance in Man (OMIM), SNOMED-CT, Medical Subject Headings (MeSH), Unified Medical Language System (UMLS), Genetic and Rare Disease Information Center terms (GARD), Medical Dictionary for Regulatory Activities (MedDRA). This cross-referencing is a key step towards the interoperability of databases. Each disease has an 'identity card' that includes –if the information is known- associated genes, an estimated prevalence category, age of onset category and mode of inheritance. Diseases are annotated with phenotypic features and frequency using the Human Phenotype Ontology (HPO), epidemiological data and their functional consequences.

  For more information on the Dutch translation of the Orphanet site, terminology and scientific abstracts, see: "Orphanet in het Nederlands Activiteitenrapport", Kim Van Roey, 2019.

- An **encyclopaedia** covering more than 6,000 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 progressively translated into French, German, Italian, Portuguese, Spanish, Dutch, Polish, Slovak, Greek and Finnish.

  For more information on the Dutch translation of the Orphanet site, terminology and scientific abstracts, see: "Orphanet in het Nederlands Activiteitenrapport", Kim Van Roey, 2019.

- An **inventory of high quality articles** published by other journals or learned societies. More than 3000 articles are available via Orphanet, with the permission of the authors and editors, comprising national and international clinical guidelines produced by learned societies that are not published in peer-reviewed journals but available as reports.

- An **inventory of orphan drugs** at all stages of development, from orphan designation to market authorisation.

- A **directory of specialised services** (currently available in in 35 of the 39 consortium countries), providing information by disease on expert centres, medical laboratories and diagnostic tests, ongoing research projects, clinical trials, registries, networks, technological platforms and patient organisations in the field of rare diseases, in each of the countries in Orphanet's network.

- An **encyclopaedia of recommendations and guidelines** for emergency medical care and anaesthesia.

- A **fortnightly newsletter,** "OrphaNews", reporting the latest scientific and political developments in the field of rare diseases and orphan drugs, in English, French and Italian.

- A **collection of thematic reports**, the "Orphanet Reports Series", focusing on overarching themes, directly downloadable from the website.

- A **platform, "Orphadata", providing high-quality datasets** related to rare diseases and orphan drugs, in a reusable and computable format.

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

3. The Orphanet network

Orphanet is a multi-stakeholder, global network of 39 countries, coordinated by the Orphanet Coordinating team at the French National Institute of Health and Medical Research (INSERM) in Paris.

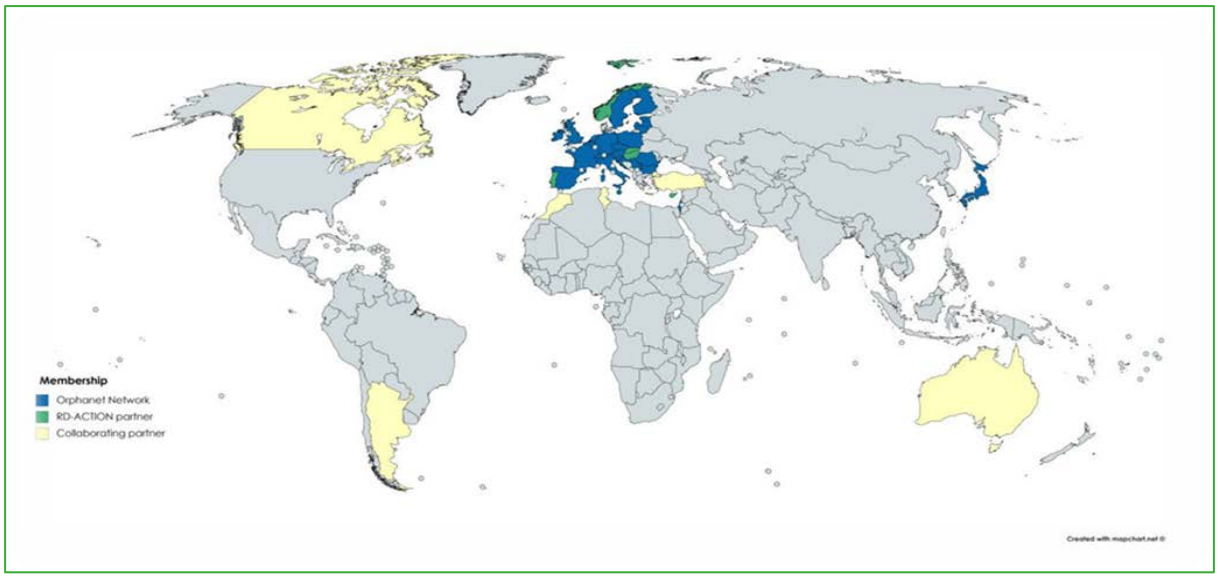

Figure 3 : *The Orphanet consortium (situation in September 2019)*

ORPHANET COORDINATING TEAM

At European/international level, Orphanet is coordinated by the French INSERM team. The coordinating team is responsible for the coordination of consortium activities, the hardware and software aspects of the project, the classification 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.

ORPHANET NATIONAL TEAMS

National teams are responsible for the collection of information on expert centres, medical laboratories, diagnostic tests, ongoing research projects, clinical trials, patient organisations and registries in their country. In several countries, they also manage the translation of Orphanet content in their national language(s). All Orphanet teams work according to the Orphanet Standard Operating Procedures (SOPs), https://www.orpha.net/orphacom/special/eproc_SOPs_V2.pdf.

Each national team maintains a national entry point to Orphanet, providing latest news and updates concerning national activities, in the national language(s) of the country concerned. Orphanet national teams are located in each participating country. A national Orphanet team is composed, at least, of a country coordinator and one or several information scientists (IS).

4. The Orphanet quality commitment

The Orphanet portal is a "work in progress" and is **constantly evolving**. Data in Orphanet are manually curated and expert validated, in accordance with formalised procedures explaining how to work, the workflow to be followed and the inclusion/exclusion criteria for each type of data. These procedures are available on OrphaNetwork (https://network.orpha.net/network/), a site assigned to national teams and serving as a collection point for common tools and documents. This website is only accessible to Orphanet national teams after entering a login and password.

The database is regularly updated with new information collected by the information scientists and validated by experts as well as the coordinating team. A **pre and post release quality control** is performed to insure the quality of all the data registered. This quality control is performed according to a predetermined program, updated every year.

A general dissemination document, called the "**Quality Assurance Review (QAR)**", is sent to all information scientists every three months to help them collecting and updating information for Orphanet. This document includes new and updated procedures and specific projects to be implemented. National teams are obliged to systematically read every issue and to carry out all the action points posted in this document within a given time.

GENERAL METHODOLOGY FOR DATA MANAGEMENT ON ORPHANET

The Orphanet framework is a complex process involving many collaborators playing specific roles and using several different tools to carry out their tasks.

1. Roles of the Orphanet Belgium team

The FPS Public Health, Food Chain Safety and Environment has designated Sciensano to manage Belgian data in the Orphanet database. The Orphanet Belgium team is hosted by the service "Health Services Research" of Sciensano .

Pages dedicated to Orphanet's activities are available on the Sciensano website (these pages are currently under review and a new version will be available by the end of 2019):
https://rarediseases.sciensano.be/en/orphanet/international-EN
https://www.sciensano.be/en/biblio/orphanet-een-portaal-voor-zeldzame-ziekten

The **Country Coordinator (CC)** is responsible for different tasks:

- the organisation of the governance of the project at national level, including liaison with learned societies, health authorities and patient organisations and the build-up of the Orphanet team within the country concerned;
- the data quality validation about expert resources in the country.

The country coordinator acts as the national contact point for the health authorities on rare diseases. He/she participates in the Orphanet Management Board (MB), which is composed of all the country coordinators in charge of data collection at a national level. It is chaired by the project coordinator at the Inserm. The MB is in charge of identifying funding opportunities, of guiding the project to provide an optimum service for the end-users, and of considering the inclusion of new teams as well as ensuring the continuity of the project. These tasks are achieved mainly through regular conference calls.

Moreover the Country Coordinator contributes to the dissemination of national initiatives in the field of rare diseases via Orphanews and the OrphaNetWork internal newsletter. He/she also participates to the Orphanet annual meeting.

The **Information Scientist (IS)** is responsible for the following tasks:

- Identify the trusted sources of information in the country ;
- Collect and update the information about:

  - expert centers;
  - medical laboratories and diagnostic tests;
  - patient organisations;
  - clinical trials;
  - research projects;
  - patient registries;
  - mutation registries;
  - biobanks;
  - translational projects and/or infrastructure such as platforms and networks.
- Validate the collected data according to the workflow established by the Country Coordinator and the coordinating team ;
- Publish the validated data in Orphanet using MAJOR (the editing tool);
- Update the data once a year;
- Communicate with the coordinating team and the different stakeholders (patients, experts, scientists, laboratory managers,…);
- Report to the Country Coordinator;
- Read the OrphaNetWork internal newsletter and the Orphanet Quality Assurance review and carry out the action points posted in them ;
- Contribute to the OrphaNetWork internal newsletter by sending short reports on activities performed by the national team.

The information scientist at the country level is technically supervised by the coordinating team (Paris-based expert resources managers).

2. Description of the Orphanet tools

A wide range of tools for data management can be used by Orphanet employees after appropriate training. The technical SOPs for using the tools are available with a login and a password (one login/national team) via OrphaNetWork, a website that is available for the national teams of Orphanet via the following link: https://network.orpha.net/network/cgi-bin/index.php?lng=en

A short description of the most commonly used tools by Orphanet employees for daily data management is given below:

- **COLLECTOR:** back office tool for data and quality management. The tool allows the collection of data as well as requests for registration or updating of data requested by professionals via the Orphanet registration service;

- **MAJOR**: tool for registration and update of most types of activities (except diagnostic tests);

- **MAJOR 2:** tool for registration of data related to diagnostic tests and panels of genes;

- **ARBOR:** tool allowing to navigate into the diseases classifications used by Orphanet. This is the only way to visualize all classifications, to view the entire tree structure and to visualize all the occurrences of a selected disease or gene. This tool was developed to help the ISs decide at which accurate level in the classification (disease/group of diseases) the expert resource should be linked. It is also an appropriate tool to provide a list of diseases to professionals to help them determine which disease(s) should be linked to their activity;

- **PLATOR:** tool that allows to extract/inject a large amount of data specifically per country from/in the Orphanet database;

- **REDMINOR:** tool developed to facilitate communication on non-confidential matters between national teams and the coordinating team. This tool increases the traceability and transparency of interactions with the coordinating team and also makes it possible to evaluate the interaction in terms of the speed and quality of the response.

The general process for data collection, registration, validation and its quality control is presented in the flowchart below (Figure 4).

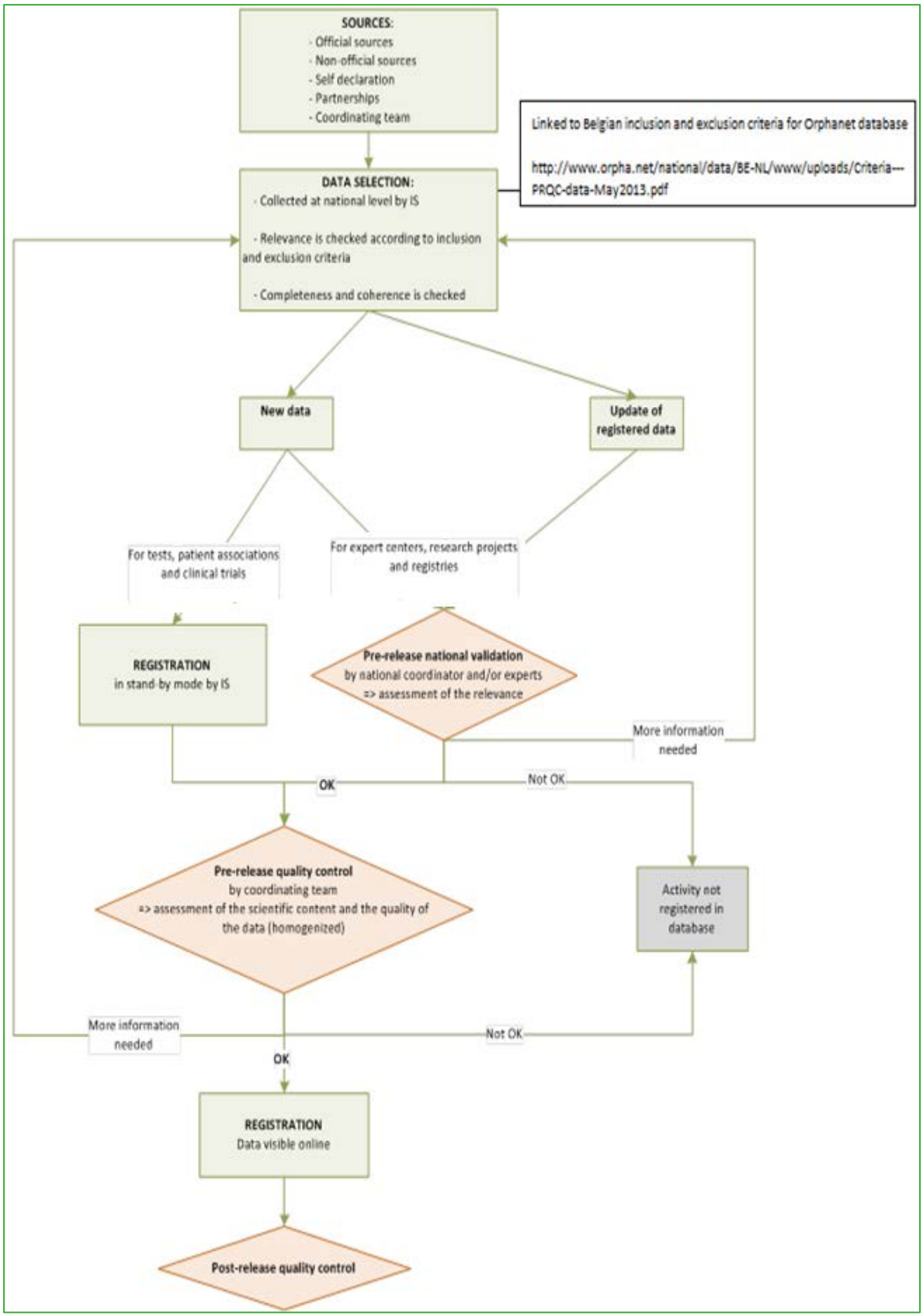

Figure 4 : *General overview of Orphanet database workflow.*
Legend: IS = Information Scientist of the Orphanet team.

1. **Data collection: identification of the sources**

Data collection is done preferably through partnerships with official sources (i.e. governmental organisations). Sources can also be non-official (e.g. national genetic centres, External Quality Assessment providers,…). It can also be self-declared by professionals involved in the expert resource through the online registration tool (**PROFESSOR**) or by direct contact (mail, phone). For data registered through Professor, any request for activity creation or update is sent to the Information Scientist as a registration form visible in **COLLECTOR**, the registration form backoffice. It is dedicated to Orphanet's IS and allows them to view all the forms assigned to their country, to processed them.

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

2. **Data selection**

Data selection is performed by the Information scientist. He/she checks if the data meet the inclusion criteria for Orphanet, which are listed in different technical procedures depending on the type of data (expert centres, medical laboratories, patient organisations, research projects, clinical trials, registries and biobanks). He/she also analyses the information to check that the mandatory dataset is provided and coherent. If this is not the case, the information scientist will contact the professional who submitted the request to invite him/her to complete or clarify the data.

It is of great relevance for the end-users of Orphanet (and professionals) to know how data on expert resources is collected at the country level as well as the selection criteria used. On the Belgian national website, a specific section listing each type of data, their definitions, the sources of information (i.e. public institutions, national official lists, funding bodies, national umbrella patient organisation, national clinical trial register,...) as well as their inclusion criteria is available.

3. **Pre-release control : national data validation**

Before publication, a validation step is ensures that data is relevant for the rare diseases community and the Orphanet users. This validation is provided by the national coordinator for certain types of data (expert centres, registries,…).

4. **Pre-release control: quality control by the coordinating team**

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

5. Data registration and online publication

Once information or modifications contained in the registration forms meet Orphanet quality standards, they are registered manually by the Information scientist into tools called **MAJOR/MAJOR 2** and published online. Professionals submitting forms are contacted in order to inform them that their requests were accepted and registered in Orphanet or explaining them the reason why they were rejected (for example, because their request is not related to a rare disease, etc.).

6. Data update

Besides ad-hoc updates, an obligatory general update of the directory of resources is performed once a year. Every professional registered in the database is contacted and encouraged to access the online registration tool and update his/her activities. The tool is available for professionals to request the update of their information whenever they want in Orphanet.

The information scientists are also encouraged to work proactively and to search for information themselves in order to compare this with the data in the database (completeness and validation actions). For this purpose one can use official and non-official sources on the internet (for example websites of patient organisations or medical laboratories, BELAC website, Clinical trials.gov,…).

7. Post-release quality control

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

3. Belgian contribution to the Orphanet database [January 2017 – September 2019]

3.1. CURRENT STATISTICS FOR THE CONTENT OF THE ORPHANET BELGIUM DATABASE

Table 3. shows a number of statistics on Belgian services and research that were included in the international database in September 2019.

Table 3 : *Registered data in Orphanet (situation in September 2019).*

Orphanet type of data	Number for BE	Weblinks in Orphanet
Expert reviewers	32 (data for 2017)	«Expert Reviewers for Orphanet in 2018», Orphanet Report Series: https://www.orpha.net/orphacom/cahiers/docs/GB/Expert_reviewers_2018.pdf
Persons with an activity in the field of rare diseases	795	http://www.orpha.net/consor/cgi-bin/Directory.php?lng=EN
Expert centres	81	http://www.orpha.net/consor/cgi-bin/Clinics.php?lng=EN
Medical laboratories with available quality information	66 (18 with accreditation, 27 participating in EQAs)	http://www.orpha.net/consor/cgi-bin/ClinicalLabs_Diagnostictest.php?lng=EN
Diagnostic tests	942	http://www.orpha.net/consor/cgi-bin/ClinicalLabs.php?lng=EN
Patient organisations	111	http://www.orpha.net/consor/cgi-bin/SupportGroup.php?lng=EN
Clinical studies	464 (of these, 126 are recruiting)	http://www.orpha.net/consor/cgi-bin/ResearchTrials_ClinicalTrials.php?lng=EN
Patient registries	21	http://www.orpha.net/consor/cgi-bin/ResearchTrials_RegistriesMaterials.php?lng=EN
Mutation registries	1	
Biobanks	3	
Research projects	125 (of these, 29 are ongoing)	http://www.orpha.net/consor/cgi-bin/ResearchTrials_ResearchProjects.php?lng=EN

3.2. OVERVIEW OF SOME QUALITY CONTROL TASKS CONDUCTED BETWEEN JANUARY 2017 AND SEPTEMBER 2019

3.2.1. REGISTRATION AND UPDATE OF EXPERT CENTRES

The possibility to register an expert centre on Orphanet depends on the specific situation in the different countries. In Belgium, eligibility criteria are appraised by the Orphanet Belgium management board.

To assess the quality of the Orphanet database, indicators and objectives are established for the expert resources database. A key issue is how to apply the quality indicators to the national level. Indeed the characteristic "coverage" in particular is very country-dependent. For Belgium, our objective is for 100% of the officially designated rare disease centres to be registered in the database. What has been agreed upon by the Belgian Orphanet board is the registration of:

- the centres that work under a convention with the National Institute for Health and Disability Insurance (NIHDI) with a specific focus on rare diseases (neuromuscular diseases, cystic fibrosis, hemophilia, hereditary metabolic diseases, pediatric nephrology, refractory epilepsy and spina bifida);
- the genetic centres officially recognized by the regional authorities for their diagnostic and counselling activities;
- the hospitals recognized by the regional health authorities to have a "rare diseases function".

These reference centres are considered as validated data and registered in the Orphanet database with the "officially designated centre of expertise" flag  .

A consultation of the NIHDI website has been carried out by the IS, in order to determine which centers working under a convention with the NIHDI were not yet listed on Orphanet. This resulted in **8 officially designated reference centres newly created on Orphanet** ("Centre of reference of cystic fibrosis - CHC Espérance", "Centre of reference of Haemophilia- UZ Leuven", "Centre of reference of Haemophilia-UCL Saint-Luc", "Centre of reference of Haemophilia-UZA", "Centre of reference of Haemophilia-HUDERF", "Centre of reference of Haemophilia-UZ Gent", "Centre of reference of Neuromuscular diseases- Erasme-HUDERF", "Centre of reference of pediatric nephrology- UCL Saint-Luc"). Once the information on expert centres was made accessible on the Orphanet website, the IS informed the involved professionals that the activity had been published and asked them for validation.

Moreover a post-release quality control of all Belgian expert centres already registered was conducted during the first quarter of 2019 to ensure data are still up-to-date, accurate and comprehensive. Accordingly, a total of **34 Belgian reference centres were contacted individually** (it should be keep in mind that some of these centres belonging to the same hospital structure include a children section and an adult section represented by different medical coordinators and should be considered as individual centers to be contacted separately). In all cases, **the data had been updated proactively** by

the IS based on information obtained from different sources (websites of the centres, NIHDI website, etc.) and only a confirmation of the accuracy of the data was asked to the professionals. This task resulted in a response rate from professionals of about 75%.

Particular attention has been given to the participation of reference centers in a European Reference Network (ERN), in order to make this information visible on the Orphanet website. Indeed, since 2019, the Belgian expert centres participating in an ERN may also be registered on Orphanet. These centres appear on the Orphanet website with the "member of a ERN" flag  but not with the "officially designated centre of expertise" flag. A list of the ERNs and the health providers in each participating country can be consulted here: https://www.orpha.net/consor/cgi-bin/Clinics_ERN.php?lng=EN

The registration of Belgian centres participating in ERNs has started in mid-2019 and is an ongoing task. As examples, here are some of the centers newly created in the Orphanet database in 2019: "Huntington Clinic- UZ Leuven" which belongs to ERN-RND (European Reference Network on Rare Neurological Diseases); "FrontoTemporal Lobar Degeneration clinic - UZ Leuven" which belongs to ERN-RND (European Reference Network on Rare Neurological Diseases); "Centre for screening and diagnosis of hereditary red blood cells disorders - ULB Erasme" which belongs to EuroBloodNet (European Reference Network on Rare Hematological Diseases); "Centrum voor zeldzame en complexe hartziekten – UZ Brussel" which belongs to GUARD-HEART (Gateway to Uncommon And Rare Diseases of the HEART); "Disorder of sexual development center - UZ Gent" which belongs to Endo-ERN (European Reference Network on Rare Endocrine Conditions); "Center for Vascular Anomalies – UCL Saint-Luc" which belongs to VASCERN (European Reference Network on Rare Multisystemic Vascular Diseases); "Aorta Team – UZ Gent" which belongs to VASCERN (European Reference Network on Rare Multisystemic Vascular Diseases); "Multidisciplinary clinic for bone dysplasias and growth disorders – UZA" which belongs to ERN BOND (European Reference Network on Rare Bone Disorders),…

3.2.2. REGISTRATION OF A "RARE DISEASES FUNCTION" FOR 7 BELGIAN UNIVERSITY HOSPITALS

In 2016, the creation of "rare disease functions" within the Belgian university hospitals aimed to implement a multidisciplinary approach to diagnosis and treatment. Patients with rare diseases/undiagnosed patients can be referred to a hospital where expertise for a specific rare disease (or group of rare diseases) is available. This should lead to a diagnosis as soon as possible and the referral of patients towards the care units most able to take charge of their pathology.

The rare diseases functions are a direct consequence of the Belgian Plan for Rare Diseases (Action 9). The conditions for recognition are defined by a royal decree[10] and only academic hospitals with a human genetics center have obtained a recognition from regional health authorities for a rare diseases function. In Belgium, it concerns 7 university hospitals: "Cliniques universitaires UCL Saint-Luc",

[10] *http://www.ejustice.just.fgov.be/eli/arrete/2014/04/25/2014024248/moniteur*

"University hospital ULB Erasme", "University hospital CHU-Liège", "University hospital UZA", "University hospital UZ Brussel", "University hospital UZ Gent" and "University hospital UZ Leuven".

In 2018, the national board of Orphanet Belgium agreed to **publish the 7 Belgian university hospitals on Orphanet, as reference centres for rare diseases**. For each of them, a "Multidisciplinary expert team/centre for rare diseases" was created. No specific expert is listed, only the name of the medical coordinator is mandatory. The centres are linked to different large sets of rare diseases representing the head of all the functional classification, so that these centres will appear in all rare diseases research on Orphanet website. Moreover each university hospital has been linked to all the ERNs it participates in.

3.2.3. REGISTRATION AND UPDATE OF PATIENT ORGANISATIONS

In order to identify Belgian patient organisations (POs) not yet registered on Orphanet, a collaboration has been established with RaDiOrg[11], the umbrella organisation for patients with rare diseases in Belgium which is also the validator of the Orphanet Belgian patient organisations data. A comparison was made with the file of patient organisations that are members of RaDiOrg. All the inclusion criteria for the Orphanet registration have been checked and 17 POs have been retained. An invitation to register was sent to the responsible persons of these patient organisations. **11 patient organisations responded favorably and were successfully registered** between May 2018 and March 2019 (« Association Kabuki Belgium », « Association Lupus Erythémateux », « Association Neurofibromatose Belgique », « Association Retina Pigmentosa », « Association Moebius Syndrome Belgique », « Collectif Drépanocytose », « Duchenne Parent Project Belgium », « Ensemble pour Lola et les enfants de la lune », « Imagene Caps Association in Belgium », « MPN Belgium Vereniging», « Sclero'ken Vereniging »). Other patient organisations have been newly registered following a spontaneous request or a recommendation by a professional ("Rarity United", "Rohhad Association Belgium",…).

In order to have a high quality expert resources database, we need to ensure that the information we are offering is still valid and up-to-date. This is why Orphanet coordinating team has decided to start a process to check if the activities that have not been validated by the professionals for at least 5 years are still valid. This process has started with the patient organisations that have not been updated since 2013. This task involved verifying that the POs are still active by contacting their head or contact points and asking them if the registered data are still valid or need updates. Once it was done, we made the requested modifications and adapted the "date of manual update" which is displayed on the Orphanet website. If we had enough evidence that the PO no longer exists (no response after at least three attempts to contact the responsible persons by emails, phone calls or other means such as a Facebook page or a contact form available on the website of the organisation), the PO was removed from the database (indeed, reactivity is one of the inclusion criteria in order to keep the associations of patients registered in Orphanet). **In Belgium, this task concerned 30 patient organisations. All cases were successfully processed (23 POs were updated, 7 POs were deleted from the database).**

[11] http://www.radiorg.be/

This quality task on the initiative of the Orphanet coordinating team was taken as an opportunity by the Belgian IS to carry out a general update of all registered POs. Accordingly, a total of **102 Belgian patient organisations registered on Orphanet were contacted individually** between November 2018 and March 2019, multiple times if necessary. In the majority of cases, **the data had been updated proactively** by the IS based on information obtained from different sources (websites and Facebook pages of the patient associations, publications to the Belgian monitor, etc.) and only a confirmation of the relevance of the data was asked to the professionals. This task resulted in a high response rate of about 95%.

3.2.4. UPDATE OF DIAGNOSTIC TESTS: COMPLETE THE INFORMATION ON THE TECHNICAL PROCEDURE [ONGOING]

Orphanet has further developed its diagnostic test database in order to respond to the evolution of genetic testing techniques. Therefore, the **technical procedure of diagnostic tests is now defined with a three-level representation**: "specialty" (main method category; ex: molecular genetics)/ "objective" (the goal of the test; ex: targeted mutation analysis) / "technique" (specific technology used in the test to reach the goal; ex: Sanger sequencing). As of today, there are about 42 000 diagnostic tests registered in the Orphanet database and more than 16 000 still have an incomplete technical procedure. This situation is harmful for Orphanet and its users, specially taking into account that Orphanet is mentioned as the reference database in the framework of the European Commission Expert Group on Rare Diseases (CEGRD) Recommendation on Cross Border Genetic Testing of Rare Diseases in the European Union[12].

In order to update all these incomplete data, the Information Scientist contacted individually between December 2017 and June 2018, on several occasions, all the Belgian laboratories (26) registered on Orphanet that have tests described with an incomplete technical procedure. They were asked to complete their technical procedure. For that purpose we have created an Excel file with a drop-down list of techniques, specific to each laboratory, listing all the tests concerned to help the laboratories in their task. The technical procedure had been pre-completed where possible (based on information found through different sources: laboratories websites; "limitative list", i.e. a list that shows the indications for which genetic analyses are reimbursed in Belgium; GTR NCBI website and BELAC accreditation) and only confirmation of the accuracy of the data was expected of the professionals. It is important to note, however, that these different sources do not generally provide the level of information needed for a 3-level representation as previously described. Moreover, only the laboratories themselves can confirm that the tests are still part of their current offer and whether they wish to see them published on Orphanet. The collaboration of the laboratories is therefore essential to ensure the relevance of the data related to diagnostic tests registered on Orphanet.

[12] *https://ec.europa.eu/health//sites/health/files/rare_diseases/docs/2015_recommendation_crossbordergenetictesting_en.pdf*

For Belgium, this quality task concerned 687 diagnostic tests. At the time of writing this report, **the technique of 430 diagnostic tests could have been completed by the information scientist but without the final validation of most of the professionals involved. Indeed the participation of professionals to complete and validate their diagnostic test data is difficult (lack of responsiveness)**.

3.2.5. REGISTRATION OF EXTERNAL QUALITY ASSESSMENT (EQA) DATA

The registration of the quality management data for laboratories (accreditations and EQAs) is very important as it allows Orphanet users to make the best possible choice when selecting a laboratory for a diagnostic test. The participation in an EQA can be declared by the laboratory itself but Orphanet also has a partnership with three EQA providers (CF Network[13], CEQAS[14] and EMQN[15]) in order to directly obtain the annual list of participating labs. Concerning the EMQN data for the last three years, the Orphanet coordinating team is currently discussing the signature of a Data Transfer Agreement with them. This implies that only EMQN data from laboratories that have provided their participation certificate have been registered in the database.

In 2017, the EQAs for 2016 concerning 16 participating laboratories were analyzed and successfully processed.

In 2018, the EQAs for 2017 concerning 27 participating laboratories were analyzed and successfully processed.

In 2019, the EQAs for 2018 concerning 7 participating laboratories (quality data for cystic fibrosis tests) were analyzed and successfully processed.

Cytogenomics External Quality Assessment Service (CEQAS) and UK National External Quality Assessment Service (UK NEQAS) for Molecular Genetics have partnered on 1st January 2018 to become Genomics Quality Assessment (GenQA)[16]. As a consequence, the number of EQAs to be registered in Orphanet has increased. For Belgium, a list of 33 EQA data from GenQA for 2018 was provided in mid-August 2019 and is yet to be registered. This task is scheduled for the last quarter of 2019.

3.2.6. REGISTRATION OF NATIONAL CLINICAL TRIALS THAT STARTED IN 2010 AND ONWARDS

Orphanet has been collecting clinical trials on rare diseases for many years. A clinical trial (CT) in the Orphanet clinical trial database is an interventional study aiming to evaluate a drug (or a combination of drugs or a biological product, etc.) to treat (or prevent) a rare disease or a group of rare diseases. The data collection by the Orphanet consortium concerning clinical trials is of utmost importance as it

[13] http://cf.eqascheme.org/
[14] https://www.ceqas.org/
[15] https://www.emqn.org/
[16] https://www.genqa.org/

helps professionals and patients to obtain a centralized, quality controlled, access to the current state of the art on these data.

Data provided by the WHO (World Health Organization) ICTRP (International Clinical trial Registry Platform)[17] on clinical trials were analyzed to obtain interventional clinical trials not yet registered for the period of January 2010 to December 2018. The file was first cleaned from the clinical trials already registered in Orphanet. Then the remaining trials were mapped against the Orphanet nomenclature, and the clinical trials potentially involving a rare disease were revised by the coordinating team. **For Belgium, this task concerned 97 clinical trials not yet registered.** The dataset of each clinical trial (title, phase, date of first enrolment, recruitment status, sponsor, disease, intervention) were checked or identified by the Information Scientist and completed if necessary. The inclusion/exclusion criteria were verified and the data meeting the inclusion criteria were registered in MAJOR in order to be displayed on the Orphanet website.

3.2.7. REGISTRATION OF MULTINATIONAL CLINICAL TRIALS WITH NATIONAL ENTRIES THAT STARTED BETWEEN 2010 AND END OF 2018

This quality task concerned multinational clinical trials (i.e. involving more than one Orphanet country) collected from ICTRP database and that were missing in Orphanet. **For Belgium, this task concerned 250 clinical trials.** For each of these clinical trials, the inclusion/exclusion criteria have been checked in order to confirm the disease link suggested, using the Arbor tool. As a national team, we were particularly involved in collecting and registering details on the investigators and the investigation centres in our country in order to create the corresponding national clinical entry.

3.2.8. COMPLETE THE MISSING DATA OF CLINICAL TRIALS FLAGGED AS “DRUG CLINICAL TRIALS” BUT NOT LINKED TO A DRUG IN THE DATABASE

In the frame of the post-release data quality control, a series of recurrent queries are put in place to ensure the accuracy of the database. One of these recurrent control tasks concerned the clinical trials flagged as "drug clinical trial" but not linked to a drug within the database. A "drug clinical trial" is defined as "a clinical trial which tests a new substance or group of substances for the treatment of a disease". Clinical trials involved in the development of drugs for rare diseases are an invaluable source for enriching the Orphanet orphan drugs database with potential candidate drugs. Therefore, we need to register those drugs in the database. Moreover, registering the drugs detected through clinical trials provides visibility on therapeutic development in the field of rare diseases. **For Belgium, 28 clinical trials flagged as "drug clinical trials" were completed with the appropriate drug.**

3.2.9. REGISTRATION AND UPDATE OF RESEARCH ACTIVITIES

Research-related activities are research projects, clinical trials, patient registries, biobanks, mutation databases and platforms. Research projects can be found in websites of funding bodies, patient organisations, public research organisations, etc. Like other resources, they can also be obtained via professionals declaring their activity through the Orphanet online registration service.

17 https://www.who.int/ictrp/en/

In June 2019, the Belgian IS contacted proactively several private or public funding bodies ("Association Muco/Mucovereniging","King Baudouin Foundation",…) to offer them the possibility of registration of the projects they support financially in the Orphanet database. This resulted in the **registration of 18 new ongoing research projects** related to several rare diseases (cystic fibrosis, tuberous sclerosis complex, Duchenne muscular dystrophy, multiple system atrophy, Wolfram syndrome, vascular anomalies, Steinert disease,…).

Research-related activities are regularly updated and a series of recurrent queries are put in place to ensure the accuracy of the database, in the frame of the post-release quality control. For Belgium, this quality control task involved a few research projects and patient registry already registered in the database. An analysis of the data was performed by the Information Scientist to decide whether they should stay in the database or should be deleted (because they no longer meet the current inclusion criteria). If the data were considered as to be kept, the dataset was completed as needed. **For Belgium, this task concerned 65 research projects that had no protocol and/or start and end date.** A systematic review of the sources of information for research projects in our country (e.g. the FRIS (Flanders Research Information Space) Research portal[18], the research portals of universities, the INVENT database[19],…) was conducted in order to find the missing data. Then, the associated professionals were individually contacted to ask them to confirm the relevance of the registered data. This update was also an opportunity to offer these professionals the possibility to register new ongoing and unpublished research projects in the Orphanet database.

3.2.10. UPDATE OF PROFESSIONALS CONTACT DETAILS

Correct email address is key to reach the professionals during the annual update mailing and to maintain an accurate and updated database. General mailings to all the professionals registered in the database are launched regularly and allow us to identify all the invalid email addresses. One quality control task has been led in 2018 to try to identify a functional email address for professionals whose email address mentioned in the database was no longer valid. **In Belgium, this task concerned 35 professionals. All cases have been successfully processed.**

3.2.11. COMPLIANCE WITH THE IMPLEMENTATION OF GDPR

The General Regulation on the Protection of Personal Data (GDPR, Regulation 2016/679)[20] is the new reference text in the European Union regarding personal data. It has been applicable since 25 May 2018 and replaces Directive 95/46/EC of 1995 which dated from the beginning of the Internet. Its purpose is to balance the use of data with the rights of individuals. Today, the exchange of personal data is necessary for economic activity and public action. However such use of data should not be at

[18] https://researchportal.be/

[19] https://www.belspo.be/belspo/invent/intro_en.stm

[20] https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32016R0679&from=EN

the expense of the people concerned. The new European regulation takes these two aspects into account.

This new law impacts Orphanet day to day activities as we process personal data. In order to comply with the GDPR, Orphanet coordinating team is working on a consent form that professionals will complete when registering or updating their activities in Orphanet. This consent form will be stocked adding the corresponding URL to the “Comment” field in the Persons screen in Major. Until now, the information scientists could use this section to add different kind of complementary information concerning the professional. All this information needed to be removed (and stocked in another place when necessary) to include only the consent information when the previously described process will apply. **In Belgium, this task concerned 20 professionals. All cases have been successfully processed.**

Another action taken in the frame of the GDPR was to minimize the personal data collected. A task was conducted to keep only one contact phone number per professional registered in the database, as we do not need more than one valid contact number and one valid email address to reach a professional. Therefore all the professionals with two phone contact numbers registered in the database have been assessed to decide which phone number to keep and to put it in the "Direct phone number" field. **In Belgium, this task concerned 62 professionals. All cases have been successfully processed.**

3.3. CONTRIBUTION OF BELGIAN EXPERTS TO THE RARE DISEASE INVENTORY

Experts can collaborate to the update of scientific information contained in the Orphanet database of Rare Diseases. They are identified through their publications and their activity related to the given disease/group of diseases (on the basis of research projects, clinical trials, expert centres and dedicated networks to which they collaborate). More information on the expert selection procedure will be available soon on www.orpha.net. Substantive contributions to the rare disease inventory (writing or reviewing abstracts for specific diseases, suggestions regarding nomenclature, …) can also be proposed spontaneously by experts involved in the field. In this case, an evaluation of the professional’s expertise is carried out by the Orphanet editing team. The expert having contributed to the text concerning the disease is cited on the disease page as well as the date of last update.

As an example, Doctor Julie Harvengt, geneticist at the CHU Liège, wrote in 2019 an abstract for the disease ROHHAD (Rapid-onset childhood obesity-hypothalamic dysfunction-hypoventilation-autonomic dysregulation syndrome, ORPHA 293987) (Figure 5).

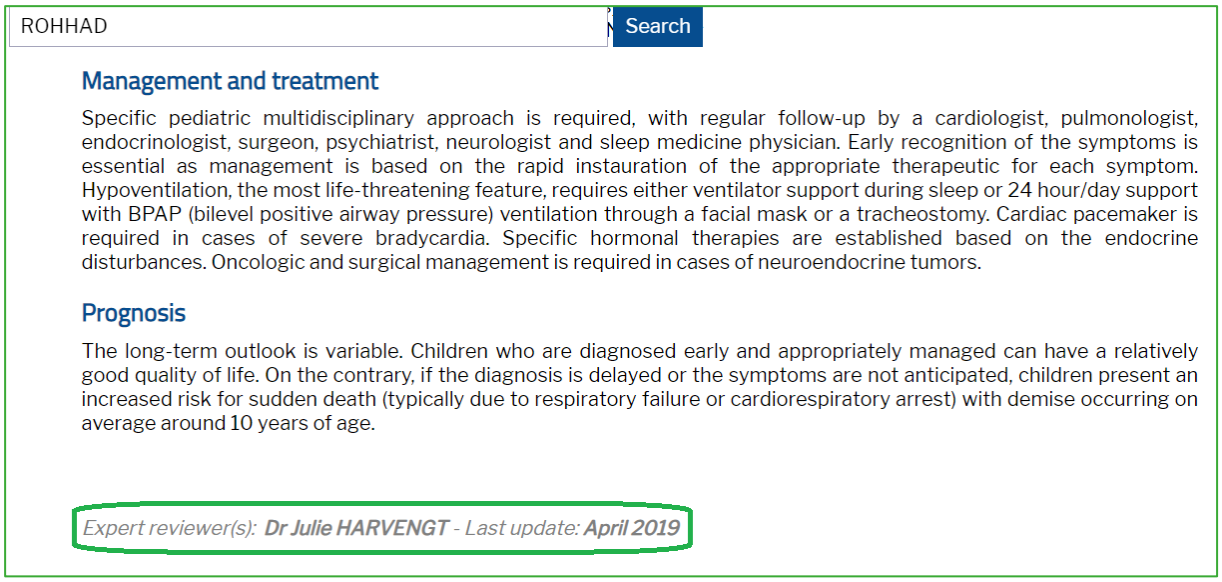

Figure 5 : *Screenshot of the Orphanet website: a contribution of a Belgian expert to the rare disease inventory.*

4. Indicators on the Orphanet online registration service activity

Collector is the back-office tool of the online Orphanet registration service (Professor) used by the information scientists, the national validators and the International Quality Control team to process the professionals' requests for registering or updating their activities related to rare diseases in Orphanet. This online registration service was launched in the beginning of 2014.

Between 2017 and end of August 2019, 140 registered forms submitted by Belgian professionals were completely processed. This number needs to be put into perspective. Indeed some individual requests involve changes in many different types of data. Moreover, some forms are also being processed, waiting to be assessed by the coordinating team.

It is also important to know that Collector is not the only source available for registration/update requests. **Many requests are still submitted to the Orphanet Belgium team by emails or phone calls**. In this case, the requests are processed but of course not counted in Collector. However, it is possible to check when the data was updated for the last time by the responsible person, as shown in the screenshot below (Figure 6).

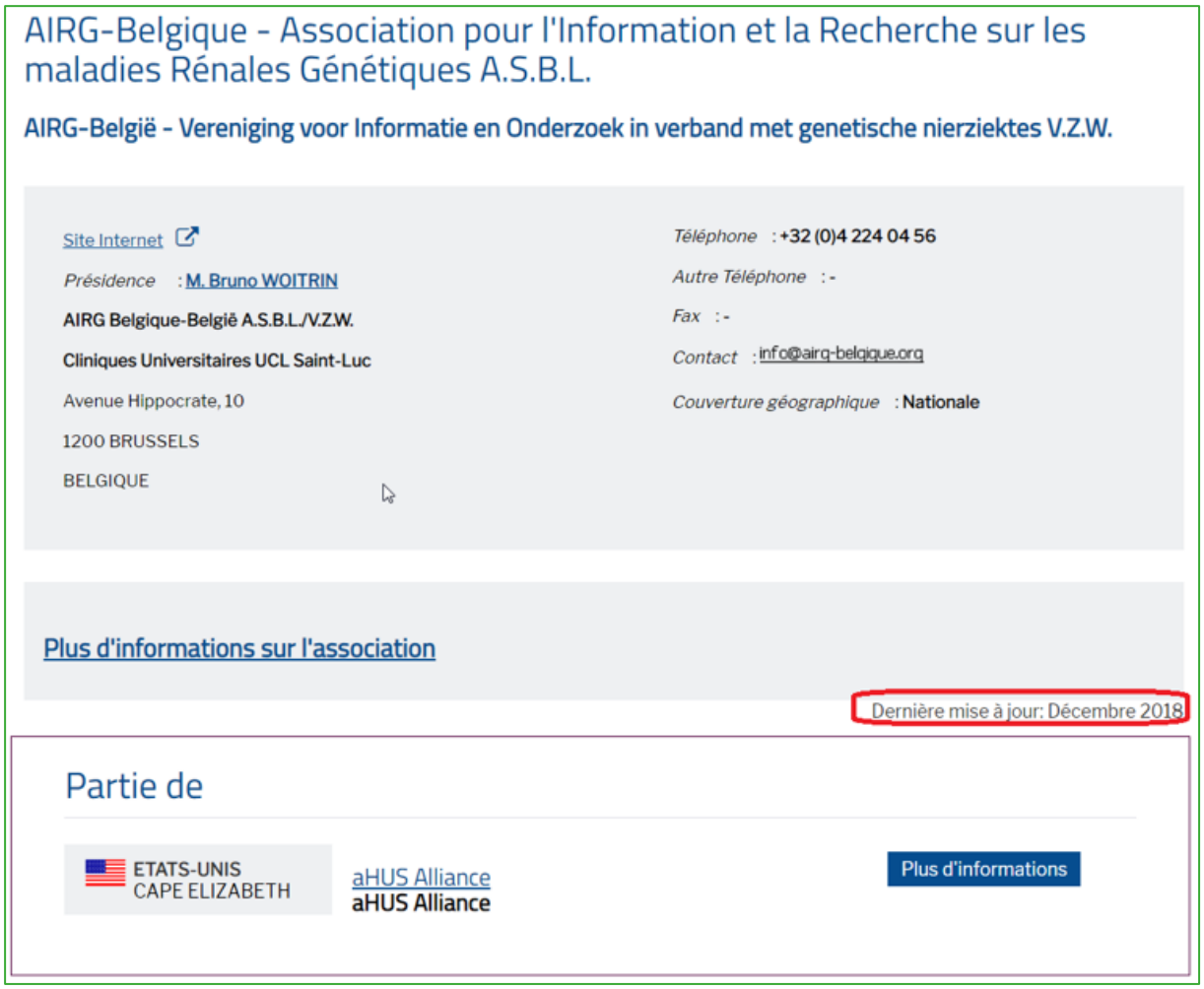

Figure 6 : *Screenshot of the Orphanet website: the Orphanet Belgium team updated information about a patient organisation (changes of name and phone number, mention of participation in a patient organisations network) in response to a request received by email on December 14, 2018.*

5. Other activities conducted by the Orphanet Belgium team

5.1. TRAINING

As part of the continuous training of Orphanet collaborators, the members of the Orphanet Belgium team participated in various **online training courses**.

The main focus is on:

- **learning how to use the complex Orphanet rare diseases classification**, in order to fully understand how rare disorders are organised into classifications and the consequences of linking resources at different levels of classifications on the way resources are displayed in the website; using the Arbor tool to visualize and navigate through the Orphanet classification;

- **using the Orphanet tools**: Major and Major 2 (input of data), Plator (import and export of large amounts of data), Collector (collection of requests for registration or updates submitted by professionals in Professor), Redminor (tracking tool for monitoring issues, suggestions and questions submitted to the coordinating team);

- **establishing and checking of inclusion/exclusion criteria** (Quality Control).

In addition, **an information scientists training** is organized every year in Paris (Orphanet headquarters) in which the Belgian IS always participates. A lot of attention is paid to the inclusion criteria for the various activities to ensure the high-quality of the provided data. The collaborators also learn to work with the new tools that will be used afterwards. In 2019, this annual training took place from March 11th to 13th included.

As part of the preparation of the annual training, several pre-trainings must be carried out. These video-trainings cover general or more specific topics: "What is a rare disease ?", "Orphanet classifications of rare diseases", “How to use Arbor ?”, “How to use Plator ?", “Data collection and registration of Patient organisations”, “Data collection and registration of Expert Centres”, “Data collection and registration of Research Projects”, “Data collection and registration of Clinical Trials” and “Data collection and registration of Diagnostic tests”. After going through these distance learning courses, an understanding questionnaire has to be completed and sent to the coordinating team for assessment.

Here are some examples of topics covered by the 2019 IS Orphanet three-day training:

- Summary and evaluation of the pre-trainings;
- Data workflows for patient care expert resources;
- Orphanet tools (Orphanetwork, QAR newsletter, Collector, Major, Plator, Arbor, Seqtor, Excel tool for gene panels);
- Overview of the Research & Development expert resources and ERNs;
- Clinical trials: ICTRP workflow;
- Research projects: How works “Myscienceworks”;
- Implementation of a quality questionnaire for the genetic counseling expert centres. Consequences in Major and Consor (Orphanet public website);
- Discussion on the Orphanet strategy and how to apply the quality indicators at the national level.

Two half-days were also devoted to Collector and Major hands-on sessions organized into working groups of 3 to 4 collaborators.

After the annual training, a compulsory test is conducted by the coordinating team to check whether the participants have correctly understood the content of the various topics covered during the training.

5.2. COMMUNICATION THROUGH MEETINGS AND CONFERENCES

- **BELMOLGEN WORKGROUP MEETING**

On June 08, 2018, a presentation was made to the members of the Workgroup on Molecular Genetics (BelMolGen) of the Belgian Society for Human Genetics (BeSHG) in order to make the professionals aware of the importance of registering and updating their diagnostic tests on Orphanet. Representatives of the 8 Belgian Centres for Human Genetics attended.

The Orphanet database is indeed the main source of information on genetic testing laboratories for the rare diseases field at European level. The main purposes of the diagnostic tests database are:

- to respond to the evolution of genetic testing techniques;
- to provide useful information for the identification of laboratories across Europe;
- to offer a directory of diagnostic tests to help patients affected by a rare disease to access the appropriate medical expertise.

Explanations were given on how to submit a request for diagnostic tests registration and how to make the update of already registered tests. Special attention was paid to the main problem currently affecting the diagnostic tests database: the fact that a large number of registered diagnostic tests have still an incomplete technical procedure.

- **ESHG CONGRESS**

A poster[21] describing the characterization of ORPHA code use for rare disease patients in the Belgian registry was presented at the "European Human Genetics Conference" (ESHG) congress on June 16-19, 2018 held in Milan, Italy. It appears from this work that it would be possible to share around 80 % of current cases at European level using the "Beta-Masterfile", a table retaining only ORPHA-codes at disorder level in the Orphanet classification of rare diseases. For a relatively high percentage of confirmed cases (20 %) the diagnosis was coded with a "group-of-disease" ORPHA-code; therefore training of Belgian professionals with regard to the Orphanet classification would be beneficial.

- **RADIORG MEMBERS DAY**

On February 02, 2019, a presentation of Orphanet's activities was given to the members of RaDiOrg (the umbrella organisation for patients with rare diseases in Belgium) on the occasion of the RaDiOrg Members Day. Ms. Maggie de Block, Minister for Social Affairs and Public Health of Belgium and M. Benoit Mores, advisor to the Minister, responsible for patient-related topics, attended the meeting. Focus was made on the importance of access to information to help rare diseases patients.

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[21] *Urbina P.M. et al. « Testing the ORPHA-code based Beta-Masterfile using data from the Belgian Central Registry of Rare Diseases (CRRD) for the use case of rare diseases patient data sharing at EU level », 2018, http://www.abstractsonline.com/pp8/#!/4652/presentation/3997*

- **RARE DISEASES DAY- CHU LIEGE**

On February 27, 2019, the Orphanet Belgium team participated in the conference for all audiences "Belgian actions around rare diseases" organized by the University Hospital of Liège, one of the seven Belgian university hospitals with a "rare diseases function". An overview of Orphanet's activities and possible contributions by health professionals and the general public at Orphanet Belgium was delivered.

- **RARE DISEASES DAY- PRESENCE IN BRUSSELS STATION**

In order to raise awareness on rare diseases in Belgium and involve the general public, RaDiOrg was present on February 28, 2019 in three main train stations in Belgium. They distributed flyers, temporary tattoos with the Rare Disease Day logo and face-paint sets. Orphanet Belgium team members joined them at the Brussels-Central station and took this opportunity to distribute flyers mentioning the activities of Orphanet.

5.3. COMMUNICATION THROUGH THE NATIONAL WEBSITE

The Orphanet Belgium team manages a national website available in two languages.
Link to the French version: http://www.orpha.net/national/BE-FR/index/page-d-accueil/
Link to the Dutch version: http://www.orpha.net/national/BE-NL/index/homepage/
The Orphanet national website contains information specific to Belgium.

The following topics are covered:

- Team/contact: on this page the contact details of the Orphanet Belgium team can be found;
- Board : short description of the Orphanet Belgium board;
- Partnerships: the sponsors (FPS Public Health, Sciensano and INAMI/RIZIV) are explicitly mentioned on this page, as well as the cooperation with RaDiOrg;
- Medicines: some frequently asked questions about orphan drugs and the specific situation in Belgium are discussed here. There is also an overview of the orphan drugs that are on the market in Belgium. Finally, you can also contact a hospital pharmacist who agrees to help people with questions about orphan drugs;
- Link to the Orphanet online registration tool, in order to submit a registration form or request an update of activities already registered in the database;
- National and international news and events: on the homepage news is regularly shared with the Belgian public. This can include, for example, information about the rare diseases day, call for patients to participate in clinical research, conferences in Belgium and abroad, patient association initiatives etc. The calendar of events is regularly updated;
- General information: information about Orphanet, rare diseases and orphan drugs (explanations on the activities, organization and financing; latest version of the activity report; instructional videos on the nomenclature and the use of the tool for finding a disease or a

gene,…) are available on this website, as well as information on the Orphanet quality commitment;

- Criteria for Belgian Expert Resources: document mentioning the definitions, sources of information and inclusion/exclusion criteria for expert resources.

Documenting inclusion criteria for expert resources in each country is of great relevance for the end-users of Orphanet and professionals to know how data on expert resources is collected at the country level as well as the selection criteria used. Therefore a pdf document listing each type of data (expert centres, medical laboratories and diagnostic tests, patient organisations, research projects, clinical trials, registries and biobanks) and our sources of information (i.e. public or private institutions, funding bodies, national umbrella patient organisation, national clinical trial register,...) as well as their inclusion/exclusion criteria can be found in the "Documents" section of our national website. An update of this document was completed in June 2019.

5.4. ASSISTANCE TO THE PATIENTS

The Orphanet Belgium team regularly receives questions about rare diseases via e-mail (orphanetbelgium@sciensano.be) or by phone calls. The team provides answers to these questions whenever possible or refers the patients to the authorized persons (as Orphanet may not answer medical personal queries).

Since RaDiOrg, the umbrella organisation for patient organisations concerning rare diseases in Belgium, acts as "helpline for personal queries", its contact details are available on the national website as well as on the Orphanet central website as shown in the screenshot below (Figure 7).

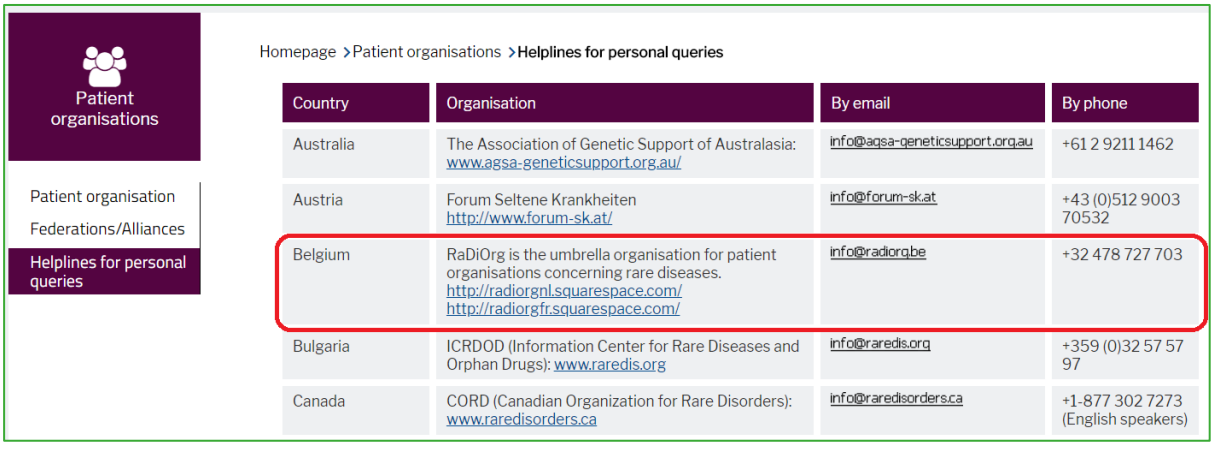

Figure 7 : *Screenshot of the Orphanet website: Belgian Helpline for personal queries*

5.5. ORPHANET STAKEHOLDERS SURVEY RESULTS (RD-ACTION WP2)

An evaluation phase of the stakeholder awareness, use and needs regarding Orphanet's services was undertaken prior to the elaboration of a sustainability plan. A survey was proactively sent to representatives of all stakeholders in the field of RD in all Member States (MS) in order to guarantee participation of all stakeholder groups in at least one survey instrument.

The survey aimed to provide a clearer vision on the services that deserve long-term sustainability as well as some clues of what some stakeholders are ready to support in the future. This stakeholder survey was launched at the start of 2017, targeting professionals at national authorities, umbrella organisations of the pharmaceutical industry, patients' organisations and other institutions. In addition to querying the usefulness of the different Orphanet services, the survey contains a section on the general funding of Orphanet, as well as possible institutional contributions to funding of the different Orphanet services. **Belgium team participated to the first round of this survey.**

CONCLUSION

The Orphanet network, developed thanks to sustained European and national efforts, is an example of successful cross-European cooperation. Belgium's participation in the Orphanet project has been an ongoing process for many years now.

However limited resources and funding disruptions have temporarily impacted the basic tasks of the Belgian team, which consist in particular in the registration of expert-reviewed data, the regular update of existing data and, of course, the creation of the most complete and accurate database possible in the field of rare diseases.

In 2017 there was no designated employee for Belgium as an Orphanet information scientist due to temporarily funding disruptions and hiring difficulties. The reduction in manpower has had consequences for the quantity and quality of the Orphanet Belgium database. For example, neither the quantity of requests for updating during the annual update campaign nor the requested level of quality could be fully processed and we falled behind the quality control missions assigned by the coordinating team. Nevertheless, the other members of the rare diseases team have carried out the most urgent assignments. For example, the makeover of the Orphanet portal at the beginning of 2017 forced the team to translate a large amount of texts for the structural webpages of this new portal. They also participated in the annual update round that is organized by Orphanet (INSERM) and a substantial part of the work was carried out. In addition, there were meetings at the national level with the Federal Public Service Health, Food Chain Safety and Environment as well as participation in the annual Orphanet Management Board calls, Annual Meeting and preparing the new Orphanet proposal to obtain funding.

A new Orphanet Belgium information scientist was hired in 2018 and the elimination of accumulated backlog became the number one priority. This important work had to be carried out in parallel with the new tasks regularly assigned by the coordinating team. At the time of writing this report, much of the accumulated backlog has been filled but there are still challenges to overcome. In particular, the cooperation with the Sciensano Health Services Research collaborator who implements the Belgian Genetic Testing Database must be continued to improve the quality of data for this type of expert resource in Orphanet database (this implementation is described in the NIDHI-Sciensano convention for quality management of genetic centers).

From 2019 onwards, particular attention has been paid to the registration of expert centres participating in a European Reference Network (ERN). These networks allow the generation and promotion of best practices for rare disease healthcare in Europe, providing data and resources that can contribute to avoiding duplicating efforts and making better use of resources. Giving visibility to all ERNs activities is a one-stop shop so that they can be easily identified by patients and professionals in Europe and beyond. Belgium participates in no less than 23 of the 24 existing European Reference

Networks. Our objective is that 100% of the Belgian centres belonging to a ERN will be registered in the Orphanet database based on the list of participating centres provided by each ERN. Our efforts are currently focused on identifying the necessary information for each of these centers and making contact with the appropriate person in order to propose the registration of the center in Orphanet. This work is in progress and some of these centers have already been referenced in Orphanet.

Among the other ways of enriching and improving the content of the Orphanet database, a better identification of the main sources of data in our country (for research projects, clinical trials, registries,...) is also desirable. For instance, establishing partnerships with these different sources could greatly facilitate data capture.

For more than 20 years, Orphanet has been a well-established and internationally recognized portal dedicated exclusively to rare diseases and orphan drugs. This unique database serves all EU countries and currently relies on a network of 39 national teams. The daily management of Orphanet database content, based on regularly updated procedures, must be guaranteed to provide all users with a reliable and up-to-date database on rare diseases. Orphanet is recognized as a fundamental resource to support access to quality care for those affected by rare diseases and to support research. The sustainability of the Orphanet national teams in the long-term is essential to meet the new challenges arising from a rapidly evolving political, scientific and informatics landscape.

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