Current definitions, sources of information and eligibility criteria for Belgian expert resources in the global Orphanet directory of services and research for rare diseases and orphan drugs

INTRODUCTION:

Orphanet, the international rare diseases and orphan drugs database, publishes **data on services and research of 42 countries in Europe and beyond.** In Europe, a disease is considered to be rare when it affects not more than 1 person per 2,000 in the European population (Regulation (EC) N°141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products).

Data collection, validation and publication is ruled by the **Orphanet Standard Operating Procedures** (SOPs). For general information related to the Orphanet missions and activities, please consult the following document intended for Orphanet national teams and Orphanet users : https://www.orpha.net/orphacom/special/eproc_SOPs.pdf

The Orphanet coordinating team is located in Paris, France (Inserm). Orphanet national teams are located in each participating country. **In Belgium, the Orphanet National Team is hosted by Sciensano**, formerly the Scientific Institute of Public Health (WIV-ISP). The national team is responsible for the collection, registration, validation, publication and update of the Belgian collected data. The team is led by a national coordinator, coordinated by Inserm and supported by a Belgian national Orphanet board with representatives of different health authorities (including SPF-FOD and INAMI-RIZIV).

The **Orphanet registration tool** is a service that allows the professionals to register and/or update their activities related to rare diseases in the Orphanet database. Please click on the following link to access the Orphanet online registration service: https://www.orpha.net/professor/htdocs/ A **request for registration or update of data** can also be made by contacting the Orphanet Belgium team at the following email address : 'orphanetbelgium@sciensano.be'.

The purpose of the present document is to explain how data on expert resources (expert centres, medical laboratories and diagnostic tests, patient organisations, research projects, registries and biobanks) are collected at the level of Belgium. It also enlists definitions of each expert resources as well as the main sources of information and the selection criteria used for the different types of data.

Types of data on services and research registered with Orphanet:

1. Diagnostic tests and Quality data of laboratories (accreditations, External Quality Assessments);
2. Patient organisations;
3. Rare disease expert centres (a genetic counselling clinic, a medical management clinic or both);
4. Clinical trials;
5. Registries (patient & mutation);
6. Biobanks;
7. Research projects.

1. DIAGNOSTIC TESTS AND QUALITY DATA OF MEDICAL LABORATORIES

A. DEFINITION

A diagnostic test in Orphanet **is:**

- A biological analysis performed in a clinical setting to diagnose or confirm the diagnosis of a rare disease or a group of rare diseases, to test the responses to therapies or to assess the likelihood of developing a specific condition based on a genetic risk (only tests requiring specific technical competence may be included);
- A constitutional genetic test, whatever the disease prevalence (as Orphanet is the reference database for genetic testing in Europe, molecular genetic tests covering non-rare diseases are also collected but not published online).

B. IDENTIFICATION OF SOURCES OF INFORMATION

No official source (i.e. governmental organizations) is available in Belgium to obtain information for the testing activity of medical laboratories.

Therefore, the main sources of information on medical laboratories and genetic tests are non-official:

- Partnership with the workgroup on Molecular Genetics (BelMolGen) of the Belgian Society for Human Genetics (BeSHG), see: http://www.beshg.be/;
- "Limitative list Belgian Genetic Centres", i.e. a list that shows all the indications for which genetic analyses are reimbursed in Belgium. The version 2018 of this document can be found on https://www.college-genetics.be/pdf/LimitativeListGenetics-2018.pdf;
- Websites of medical laboratories publishing their offer of genetic tests;
- The International Genetic Testing Registry (GTR) that provides a central location for voluntary submission of genetic test information by providers, see: https://www.ncbi.nlm.nih.gov/gtr/;
- Website of BELAC, the Belgian Accreditation Organization, see https://economie.fgov.be/belac.

Since these sources do not allow an exhaustive coverage of the testing activity in Belgium, our national team is in charge of identifying the laboratories in the country performing diagnostic tests and inviting them to declare and update their activity through the Orphanet online registration service. An additional source of information is the list of laboratories participating in External Quality Assessment (EQA) schemes, obtained by the Orphanet coordinating team through a partnership established with several EQA providers. This list is sent to the national teams once received from the providers.

C. DATA SELECTION

General inclusion criteria for diagnostic tests:

Sciensano • Rue Juliette Wytsmanstraat 14 • 1050 Bruxelles • Brussel • Belgique • België
T +32 2 642 51 11 • F +32 2 642 50 01 • info@sciensano.be • www.sciensano.be
toute une vie en bonne santé • levenslang gezond

- Tests should be performed in a clinical setting (tests done on a research basis should be registered as research projects);
- Tests should be specific for one disease or one group of diseases (and in that case, apply to all diseases of this group);
- Tests should require a high level expertise;
- Tests should be performed by the medical/diagnostics laboratory itself.

Specific inclusion criteria depending on the type of test:

Molecular genetics : all constitutional genetic testing analyses are collected, even for non-rare diseases and pharmacogenetics.

Constitutional cytogenetics: conventional cytogenetic analyses (karyotypes, G-banding, etc) are not registered in Orphanet. Molecular cytogenetic analyses like FISH as well as molecular genetics such as MLPA or array-CGH,… are registered in Orphanet only if they are designed for specific microdeletion/microduplication syndromes. Tests for chromosome number anomalies and ring chromosomes done by FISH (e.g. Trisomy 11) are not registered in Orphanet, as their detection does not require a specific expertise in molecular cytogenetics.

Biochemical genetics : only tests requiring special metabolic investigation are considered (enzyme assays, key metabolites analyses or functional assays).

Microbiology (bacteriology/virology/parasitology/mycology): Belgium has recognized laboratories of reference for a list of rare infectious diseases. For these diseases only their tests will be registered.

Laboratory quality assessment:

The Orphanet dataset includes data regarding the laboratory quality management: EQAs and accreditations, which provide information on the accreditation status of the laboratory or on its participation in EQA schemes. This data can be consulted as it is shown for the corresponding laboratories or to specific diagnostic tests. EQA participations can be declared by the laboratory itself by providing a certificate. Three EQA providers (GenQA, CF Network and EMQN) supply their lists of the former year EQA participations directly to Orphanet. So for these providers, the laboratory does not have to send in certificates.

2. PATIENT ORGANISATIONS

A. DEFINITIONS

A patient organisation on rare diseases in Orphanet **is**:

- A non-profit active organisation or foundation which provides support and/or information to patients suffering from a rare disease or a group of rare diseases;
- Patient organisations on non-rare diseases also dealing with rare forms of common diseases, or with disabilities, are to be included if there is no specific organisation;
- Orphanet lists national patient organisations as well as European and international organisations based in Europe. Regional patient organisations may also be registered in the

Sciensano • Rue Juliette Wytsmanstraat 14 • 1050 Bruxelles • Brussel • Belgique • België
T +32 2 642 51 11 • F +32 2 642 50 01 • info@sciensano.be • www.sciensano.be

database if there is no national equivalent or if they are independent. Also rare-disease-specific sub-sections/contact groups of general organisations are registered. Organizations not based in Europe but covering a disease or a group of diseases not covered by a European organisation are also registered including European contact points.

A patient organisation on rare diseases **is not:**

- A fund-raising trust/foundation that helps one/few patients with no real advice or help given to others;
- A research-funding trust/foundation;
- A learned society;
- A blog or/and forum only.

B. IDENTIFICATION OF SOURCES OF INFORMATION

The main sources of information are:

- National and regional alliances. A partnership has been established with RaDiOrg, the umbrella organisation for patients with rare diseases in Belgium, in order to identify Belgian patient organisations not yet registered on Orphanet. For more information, please visit the RaDiOrg website: http://www.radiorg.be/;
- Eurordis, the non-governmental patient-driven alliance of patient organisations representing 970 rare disease patient organisations from 74 countries. For more information, please visit the Eurordis website: https://www.eurordis.org/;
- Physicians and researchers working in close collaboration with these support groups;
- Congress, symposiums, forums;
- A patient organisation or an alliance declaring their activity through the Orphanet online registration service.

Invitation letters for registration are regularly sent by the national team to the POs which are not still registered on Orphanet, after verification that they meet our inclusion criteria.

C. DATA SELECTION

Selection criteria of patient organisations:

- The patient organisation/alliance has to provide support for a rare disease, a group of rare diseases or rare forms of common diseases;
- Umbrella organizations and national alliances, as well as patient organizations able to support and advocate for patients with any rare disease are also registered;
- The organisation should have a legal status, according to Belgian laws. In Belgium, patient organisations may be vzw/asbl, private or public foundations or contact groups;
- The organisation has to be responsive and must able to be contacted by telephone, e-mail,…;
- The organisation should have a designated head and/or a contact person;

Sciensano • Rue Juliette Wytsmanstraat 14 • 1050 Bruxelles • Brussel • Belgique • België
T +32 2 642 51 11 • F +32 2 642 50 01 • info@sciensano.be • www.sciensano.be
toute une vie en bonne santé • levenslang gezond

- For an organisation with an official contact point in Belgium, the official contact point is also registered;
- The regional patient organisations are accepted if there is no national equivalent.

It is not mandatory to have a website, but in case of having one, the information on the disease(s) must be freely available for all users and should not contain advertising for treatments. A Facebook page of a patient organisation can also be registered.

3. EXPERT CENTRES

Orphanet offers, amongst a range of expert resources on rare diseases, a directory of expert centres and networks of expert centres dedicated to the medical management and/or genetic counselling for one particular rare disease or a group of rare diseases. The procedural document on data collection and registration of expert centres in Orphanet can be found here: https://www.orpha.net/orphacom/cahiers/docs/GB/eproc_expert_centres_R2_PatCar_Cns_EP_02.pdf

A. DEFINITIONS

A medical management expert centre on rare diseases in Orphanet **is:**
A specialised centre for a rare disease (or a group of rare diseases) organised for the medical management of patients or recognised as an expert centre for consultation. Centres of expertise mentioned in Orphanet should deliver a service of indisputably higher quality for rare diseases than a standard hospital service in the relevant speciality. This data is intended to contribute to appropriate referrals of patients towards expert centres, to ease the process of second opinions between professionals, and to establish reference networks.

A medical management expert centre on rare diseases **is not:**
- A conventional specialised medical department without specific focus on rare diseases, even if it is a reputed one;
- A self-declared centre that does not fulfil the quality standard criteria.

A genetic counselling expert centre on rare diseases **is**:
A centre delivering genetic advice either for all rare genetic diseases or for a rare genetic disease/group of diseases.

A genetic counselling expert centre on rare diseases **is not:**
A self-declared centre as a genetic counselling centre with no formal validation.

A network of expert centres **is:**
- A network of expert centres specialised in a disease (or group of diseases) with an official designation by health authorities in a country or specific funding from a well-established body;

Sciensano • Rue Juliette Wytsmanstraat 14 • 1050 Bruxelles • Brussel • Belgique • België
T +32 2 642 51 11 • F +32 2 642 50 01 • info@sciensano.be • www.sciensano.be
toute une vie en bonne santé • levenslang gezond

- It can be national, European or International.

A network of expert centres **is not**:

- A self-declared network (same hospital or same disease without any funding);
- Clinical centres participating in the same clinical trials;
- Clinical centres with expert knowledge in the same field but without official recognition.

B. IDENTIFICATION OF SOURCES OF INFORMATION

The mains sources of information are:

For officially designated expert centres:

- National list of centres of expertise, or reference centres, recognised by the Health authorities. **In Belgium, the health authorities do not provide a list of expert centres officially designated**;
- European Reference Networks (ERNs).

For non-officially designated expert centres:

- Learned societies, foundations and other networks;
- Expert centres involved in clinical trials;
- Scientific publications;
- Patient organisations;
- Websites of Human Genetics societies (for genetic counselling centres);
- Pharmaceutical and biotechnology companies involved in orphan drugs;
- Professionals declaring an expert centre through the Orphanet online registration service.

C. DATA SELECTION

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 national Orphanet coordinator and the Orphanet Belgium management board.

Currently, the Belgian Orphanet National board (composed of representatives of Sciensano, as well as members of the health authorities FOD-SPF and RIZIV-INAMI) only recognizes as validated data in Orphanet the data on rare diseases expert centres for:

- the **hospitals recognized by the regional health authorities to have a "function rare diseases**" (however no specific experts will be listed);
- the **centres that work under a convention with the RIZIV-INAMI** (i.e. the centres for cystic fibrosis, neuromuscular disorders, hereditary metabolic diseases, haemophilia, refractory epilepsy, spina bifida, paediatric nephrology);
- the **genetic centres officially recognized by the regional authorities** for their diagnostic and counselling activities.

Sciensano • Rue Juliette Wytsmanstraat 14 • 1050 Bruxelles • Brussel • Belgique • België
T +32 2 642 51 11 • F +32 2 642 50 01 • info@sciensano.be • www.sciensano.be
toute une vie en bonne santé • levenslang gezond

These reference centres will be registered with the "officially designated centre of expertise" flag .

Since 2019, the **Belgian expert centres participating in a European Reference Network (ERN)** may also be registered on Orphanet. However, the Orphanet Belgium Management Board allows to link to an expert centre **only those diseases for which the expertise is recognized by the ERN concerned.**

These centres will appear on the Orphanet website with the "member of a ERN" flag and not with the "officially designated centre of expertise" flag.

Centres recognized by the Belgian Orphanet National board as officially designated and belonging to an ERN will be registered with both flags.

If your centre does not meet the inclusion conditions described above, please be aware that data on all other expert activities for rare diseases can be registered in Orphanet such as research projects, diagnostic tests, clinical trials, registries, ... We kindly invite you to do so.

An expert centre can offer medical management and/or genetic counselling services. Both options have specific selection criteria.

Since 2019, genetic counselling activity quality must be assessed based on an Orphanet quality questionnaire for Genetic Counselling Units/Clinics. This questionnaire aimed at evaluating the appropriateness of registering in Orphanet a genetic counselling expert centre that is not officially-designated. It is based on peer reviewed literature about genetic counselling practices in Europe and the European Board of Medical Genetics documentation for European unified competency standards for ensuring patient safety. Genetic centres with a national designation will not need to complete the genetic counselling questionnaire.

The questionnaire must be filled-in by professionals when the genetic counselling centre is not officially designated and it is assessed by national validators. The criteria will be appraised qualitatively according to the disease(s) and the national context.

4. CLINICAL TRIALS

A. DEFINITIONS

A clinical trial on rare diseases in Orphanet **is:**
An interventional study aiming to evaluate a drug (or a combination of drugs or a biological product, etc) or a medical device as treatment (or prevention) of a rare disease (or rare form of a common disease). Single-centre and national or international multicentric clinical trials are registered. A clinical trial is defined nationally as it has to be approved by competent authorities in each country involved.

Sciensano • Rue Juliette Wytsmanstraat 14 • 1050 Bruxelles • Brussel • Belgique • België
T +32 2 642 51 11 • F +32 2 642 50 01 • info@sciensano.be • www.sciensano.be
toute une vie en bonne santé • levenslang gezond

A clinical trial on rare diseases **is not:**

- A non-therapeutic clinical study;
- A therapeutic pre-clinical study (on animals for example). Observational clinical studies that could be identified are registered as research projects;
- A clinical trial on a common disease which has rare forms (e.g. Parkinson, breast cancer, etc.);
- A clinical trial evaluating an intervention other that a drug or medical device (e.g. surgery, behavioural therapy, etc.).

B. IDENTIFICATION OF SOURCES OF INFORMATION

The Orphanet coordinating team is in charge of the centralized collect of clinical trials through a partnership with the International Clinical Trial Register Platform (ICTRP), see http://apps.who.int/trialsearch/. This platform, supported by the World Health Organization, provides access to a central database containing the trial registration data sets provided by other national and international registries as well as links to the full original records.

The ICTRP database centralises data on clinical trials provided by other national and international registries such as:

- The European Clinical Trials Database (EudraCT), see: https://eudract.ema.europa.eu/;
- Clinical trials.gov, see: https://clinicaltrials.gov/.

ICTRP is the major source of information but clinical trials can also come from professionals' self-declarations and national watch. Therefore, national teams are in charge of identifying the other relevant sources of information for clinical trials in their country, in order to complete the centralized collect of clinical trials. In Belgium, a database of clinical trials managed by the Federal Agency for Medicines and Health products (FAMHP) is a helpful sources of information, in particular to identify details on the investigation centres in our country. For further information on clinical trials approved by the FAMHP, please click on the following link: https://www.famhp.be/en/news/new_database_for_clinical_trials_in_belgium.

Principal investigators can declare their activity through the Orphanet online registration service. Please note that concerning clinical trials, professionals cannot update the information through the Orphanet online registration service, for technical reasons. For update request, please contact directly the Orphanet Belgium team at the following email address : 'orphanetbelgium@sciensano.be'.

C. DATA SELECTION

Selection criteria of clinical trials:

- Only interventional clinical trials that concern a rare disease/group of rare diseases or rare forms of common diseases are collected;

Sciensano • Rue Juliette Wytsmanstraat 14 • 1050 Bruxelles • Brussel • Belgique • België
T +32 2 642 51 11 • F +32 2 642 50 01 • info@sciensano.be • www.sciensano.be
toute une vie en bonne santé • levenslang gezond

- Terminated clinical trials can be registered in Orphanet, but Orphanet put a threshold date 2010 (date at which the International Rare Diseases Research Consortium (IRDiRC) consortium started);
- Clinical trials conducted by both industry and research institutions are eligible;
- Clinical trial conducted in at least one country of the Orphanet consortium or funded by an IRDIRC member;
- Clinical trial approved by competent authorities;
- A protocol or brief description of the trial's objectives must be available.

5. REGISTRIES

A. DEFINITIONS

A patient registry (or disease registry) on rare diseases in Orphanet **is:**
Any kind of systematic registry of clinical data for clinical research on a rare disease or a group of rare diseases, as well as for rare forms of common diseases, governed by an identified body.
The concept of coverage (regional, national, European or international) that is associated with patient registries reflects the area of collection of a single physical database, to which several clinical entities contribute.

A patient registry on rare diseases **is not:**
A study performed by recruitment of patient of a registry, i.e. clinical trial or clinical study.

A mutation registry on rare diseases **is:**
A systematic data collection on gene mutations described as responsible for a rare disease (or group of rare diseases) with an online interface, governed by an identified body.
Mutation registries are tools for medical laboratories as well as research laboratories.

A mutation registry on rare diseases **is not:**

- A collection of gene mutations without an associated phenotype;
- An empty database associated with a project of data collection on gene mutations.

B. IDENTIFICATION OF SOURCES OF INFORMATION

Patient registries are found through, research projects, networks, funding bodies, pharmaceutical and biotech companies, patient organisations, peer reviewed publications and Orphanews.
The mutation registries listed in Orphanet are the mutation databases listed on the HGVS website (http://varnomen.hgvs.org/) or the LOVD website (http://www.lovd.nl/2.0/) and related to rare diseases.

Sciensano • Rue Juliette Wytsmanstraat 14 • 1050 Bruxelles • Brussel • Belgique • België
T +32 2 642 51 11 • F +32 2 642 50 01 • info@sciensano.be • www.sciensano.be

C. DATA SELECTION

Selection criteria of patient and mutation registries:
Patient registries on a rare disease (or group of rare diseases) should be governed by an identified body. Cancer registries are listed only if they focus on (a) rare form(s) of cancer.

For mutation registries, data selection is performed by the coordinating team.

6. BIOBANKS

A. DEFINITIONS

A biobank on rare diseases in Orphanet **is:**
Any kind of systematic, open-for-collaboration register of biological specimen for clinical research with a clear orientation toward the field of rare diseases.

A biobank on rare diseases **is not:**

- A collection of biological material with no specificity but that might be useful in the field of rare diseases;
- A private, not open for collaboration, collection.

B. IDENTIFICATION OF SOURCES OF INFORMATION

The coordinating team selects lists from websites, such as EuroBioBank (http://www.eurobiobank.org/), BBMRI (http://www.bbmri.eu/) and collects biobanks that have been established thanks to EU-funded networks.

National teams collect biobanks dedicated to rare diseases at the national level.

C. DATA SELECTION

Selection criteria of biobanks
In Orphanet, biobanks and collections of biological samples (DNA, cells, tissues, serum/plasma) produced by the scientific community conducting research on rare diseases, and who are willing to share their resources with the scientific community are listed. This excludes private collections, except if they are open for collaboration (samples available to third parties).

7. RESEARCH PROJECTS

A. DEFINITIONS

A research project on rare diseases in Orphanet **is:**

Sciensano • Rue Juliette Wytsmanstraat 14 • 1050 Bruxelles • Brussel • Belgique • België
T +32 2 642 51 11 • F +32 2 642 50 01 • info@sciensano.be • www.sciensano.be
toute une vie en bonne santé • levenslang gezond

An **ongoing and unpublished** research project explicitly focused on a rare disease or a group of rare diseases. It is either funded by a funding body (public or private, for or not-for-profit) with a scientific committee (after competitive evaluation) or by the regular funding of a research institution.

A research project on rare diseases **is not:**

- A study on general aspects of a common disease which has rare forms (Parkinson disease, Alzheimer disease, breast cancer, etc);
- A study on non rare diseases;
- A study that could one day be applicable in the field of rare diseases but without explicit intention;
- A study that has already been published e.g. with the label of the study being the title of the article in PubMed;
- A study that is too fundamental: no specific disease or general title including some rare diseases as examples.

A network of research projects **is:**

A collaborative research project funded by an international funding agency or transnational program (i.e. the Framework Programme of DG Research or E-Rare), clinical networks funded by DG Sanco, a multinational non-therapeutic clinical research study, a network of experts (such as Treat-NMD, ECORN-CF, PRINTO), or a network of clinical investigation centres.

A network of research projects **is not:**

An informal network, a network not funded.

B. IDENTIFICATION OF SOURCES OF INFORMATION

The coordinating team collects projects funded by IRDiRC members at the European level.

National teams are in charge of identifying the sources of information for research projects on rare diseases in their country. In Belgium, national funding institutions are regularly consulted to obtain information on funded projects. The Belgian Federal Science Policy has developed a database, "INVENT" (https://www.belspo.be/belspo/invent/intro_en.stm), that gathers all the research data collected by:

- the French-speaking Community (http://www.cref.be/);
- the Flemish Community on the FRIS Research portal (https://www.researchportal.be/nl);
- the Federal Authorities (http://www.belspo.be/).

Projects can be found in websites of funding bodies, patient organisations, public research organisations, etc. They are also obtained via professionals declaring their activity through the Orphanet online registration service.

Sciensano • Rue Juliette Wytsmanstraat 14 • 1050 Bruxelles • Brussel • Belgique • België
T +32 2 642 51 11 • F +32 2 642 50 01 • info@sciensano.be • www.sciensano.be

C. DATA SELECTION

Selection criteria of research projects:

Research projects can only be put online if a website, a link to a protocol or a brief description of the research purpose is provided. Projects from the following research categories can be registered:

Animal model creation / study
Biomarker development
Biorepositories development/creation
Biotechnology innovation
CRISPR-Cas9 study
Databases & Registries development/creation
Diagnostic tool / protocol development
Drug repurposing
Epidemiological study
Gene expression profile
Gene search
Genotype-phenotype correlation
Health economics study
Human physiopathology study
In vitro functional study
Induced pluripotent stem cells (iPS) creation / study
Medical device / instrumentation development
Mutations search
Natural history study
Observational clinical study
Ontology / bioinformatics study
Outcomes mesures development
Pre-clinical cell therapy
Pre-clinical drug development / drug delivery
Pre-clinical gene therapy
Pre-clinical vaccine development
Public health study (excluding health economics)
Small molecule screening
Social sciences and humanities

Important remark: these definitions and criteria have been largely agreed upon by the European consortium of Orphanet partners and have been further adapted to the Belgian situation.
This document will be updated as often as necessary. Comments or questions with regard to this document are welcome: 'orphanetbelgium@sciensano.be'.

Sciensano • Rue Juliette Wytsmanstraat 14 • 1050 Bruxelles • Brussel • Belgique • België
T +32 2 642 51 11 • F +32 2 642 50 01 • info@sciensano.be • www.sciensano.be
toute une vie en bonne santé • levenslang gezond