Methodological Paper Governing the Literature Review for Horizon Scanning

Milestone 4.2

31 March 2019

WP Participants:

INSERM, UNEW, ISINNOVA, EURORDIS

V1	07/02/19	INSERM
V2	13/02/19	INSERM, UNEW, ISINNOVA, EURORDIS
V3	07/03/19	INSERM, UNEW, ISINNOVA, EURORDIS
Final version	08/03/19	All partners

The Rare2030 project is co-funded by the European Union Pilot Projects and Preparatory Actions Programme (2014- 2020). This leaflet is part of the pilot project PP-1-2-2018-Rare 2030. The content represents the views of the author only and is his/her sole responsibility; it cannot be considered to reflect the views of the European Commission or any other body of the European Union.

Contents

1. Objective and overview of the literature review

The literature review aims to inform horizon scanning for determinants of health and drivers of change in the field of rare disease policy. The information gathered will be analysed in depth and will be subject to an innovative foresight approach. This review will provide the necessary background to the Panel of Experts seeking to identify the determinants of health and drivers of change. The literature review -encompassing both scientific and grey literature (specific for RD or of interest for the RD community) will be performed- combining several methods:

1. Retrospectively: results from the RD and RD-relevant policy literature survey performed by Orphanet will be made available and exploited to answer specific foresight questions during the whole length of the project. Orphanet surveys this literature since 2005 to the present day, and a database is already available from 2010-today in which publications are annotated with, and searchable through, a controlled vocabulary. (http://international.orphanews.org/search.html) (led by INSERM).

2. Prospectively, scientific and grey literature will be reviewed and annotated with the same controlled vocabulary in order to address specific questions and for future exploitation (led by INSERM).

In addition to this, both retrospectively and prospectively – the national reports and country summaries of the State of the Art of Rare Disease Activities in Europe (SoTAR) developed in the past and updated under RARE2030 will be analysed. The most immediate use of the updated country data will be to support the production of topic-oriented analyses, to illustrate the status quo across Europe around, for instance, newborn screening, the existence and degree of implementation of a national plan or strategy for RD, etc. this work will be led by UNEW). Whilst collecting updated data from the focal European countries, a review of key grey literature relevant in theory to rare diseases as a group will be undertaken, for the purposes of collating references and summarising for use by the Panel of Experts.

The literature review will be conducted between M2 and M8 of the project, led by UNEW as WP4 leader with the support of INSERM, ISINNOVA and EURORDIS. A draft of factsheets will be provided by the end of M5.

The results of the literature review (both published and grey literature) will be presented in the form of knowledge base fact sheet. These will be oriented in accordance with the topics into which the large Panel of Experts (PoE) will be organised (see 2a). outlining the scope and overview of the theme, main trends detected in the literature review, and providing bibliographical references to main articles of interest detected in the literature review. These will be resources of a manageable size, to stimulate discussions in the PoE subgroups, on the status quo for each of these large topics and, most importantly, to allow people in these PoE subgroups to propose what *they* see as the main drivers of change and determinant of health & wellbeing looking forwards.

Additional horizon scanning outside of the rare diseases field in order to bring in knowledge from outside of the rare disease field (led by ISINNOVA with EURORDIS and TELETHON ITALIA). This work will not be described in this document, but for context a summary of activities is provided in the last part of this paper.

2. Orphanews literature survey & Orphadata analysis methodology

a. Scope of the Literature and Data Review

A number of broad themes of interest to the rare disease field will be the focus of the literature review conducted by INSERM in the framework of WP4. These thematic groupings are those which will be used to organise horizon scanning with panels of experts. The themes, as explained in the Terms of Reference, have been expanded to describe sub-themes of interest for the literature review. This list is indicative of the subjects and initiatives to be considered in the scope of the literature review, but should be developed in an iterative fashion (see Section C) to include emerging sub-themes and initiatives within these principle themes.

1. Political & strategic frameworks relevant to RD.

To include: *National and European frameworks and policies relevant to RD - especially National Plans/Strategies for RD (in terms of level of implementation, financing etc) but also existence of national plans for cancer, genomics, AI; funding and sustainability of national health & social systems, governance models, extent of inter-Ministerial interaction; operations of European level forums for RD policy definition/implementation e.g. SGPP, a RD stakeholder network in the EU Health Policy Platform once set up, etc.,*

- Political Framework for rare diseases at European level
    - EC Communications, Council Recommendations
    - Cross-border Healthcare Directive
    - RD Forums at transnational level, Expert groups (EUCERD, EGRD, SGPP)
    - DG Santé project funding
    - Other relevant official documents
- Political Framework at European Member State Level
    - National policy/national plans or strategies related to RD
        - RD specific
        - Rare cancers
        - Genomics
        - eHealth
        - Other relevant policy plans and strategies
    - Governance of national policies related to rare diseases
    - Financing of national policies related to rare diseases
- Political Framework in Other World Regions

2. Data collection and utilisation:

To include: *Deployment of strategies and approaches towards standardisation and interoperability of data; current and future roles of registries (thinking of all types of registries, and how they operate); evolution of ontologies; FAIR data concepts; real-life extent of data-sharing and data-querying; linking disparate data sources (including EHRs, biobanks); Monitoring of RD - definition and codification.*

- Patient data collection
    - Population registries
    - Rare disease national databases
    - Patient registries
    - Electronic health records

    - Biobanks
    - Genome-phenome repositories
    - Patient Centred Outcome Measures, including Patient reported outcome measures (PROMs) Patient Relevant Outcomes, etc
- Data management/ Data protection
    - GDPR
    - Open Science/ Open data
    - Informed consent
- Data interoperability
    - RD codification and monitoring
        - Nomenclatures/terminologies
            - ORPHA nomenclature (ORPHA codes)
            - other medical terminologies and resources (ICD, SNOMED, OMIM, UMLS…)
    - Ontologies
        - Human Phenotype Ontology
        - Orphanet RD Ontology
        - Other relevant ontologies (gene-related, etc)
    - FAIR data
- Information / data resources
    - Orphanet
    - GARD
    - OMIM
    - other
- Informatics/ Digital transformation/ Electronic and digital technology
    - eHealth
    - Personalised/precision medicine
    - Bioinformatics
    - Breakthrough technologies in genetics

3. Availability and accessibility of Orphan Medical Products (OMPs) and medical devices:

To include: *Therapy development status quo; accessibility of OMPs; HTA; pricing; medical devices; supplements relevant for RD; repurposing of medicines; public-private partnerships.*

- Drug development
    - Drug repurposing
    - Drug research funding and organisation
        - IMI calls
    - Clinical trials
    - Study design
    - EMA COMP opinions
    - Public-private partnerships
- OMP health economics
    - Orphan drug policy
        - Orphan Medicinal Product legislation and incentives at national level
        - Orphan Medicinal Product legislation and incentives at European level
        - Orphan Medicinal Product legislation and incentives in other world regions/countries
    - Orphan drug pricing

    - Orphan drug reimbursement
        - Health technology assessment
        - Healthcare budget
    - Medical devices
- OMP accessibility

4. Basic, clinical and translational research:

To include: *Research infrastructures; national and transnational research programmes; tools to support more efficient and cost-effective research; innovation-centric health systems.*

- European Research Infrastructures
    - ELIXIR
    - BBMRI
    - ECRIN
    - INFRAFRONTIER
    - EU-OPENSCREEN
- International Rare Disease Research Infrastructure (IRDiRC)
- Global Alliance for Genomics and Health
        - Tools to support more efficient and cost-effective research
        - Innovation-centric health systems
        - National and transnational research programmes
- National calls
- European calls
    - FP7/ H2020
    - eRare ERA-NET
    - EJP calls
    - other
- International calls

5. Diagnostics:

To include: *Prevention; NBS; genetic testing capabilities (single gene or panel or NGS), testing across borders and the introduction of NGS to the clinic; AI; undiagnosed patients; genetic counselling.*

- Screening
- Newborn screening
- Neonatal diagnosis
- Prenatal testing
    - NIPT
- NGS in clinical context
- Testing capacity
    - Single gene
    - Panel
    - NGS
    - WES

    - WGS
- Prevention
- Testing across borders
- Undiagnosed patients
- Application of AI to diagnosis
- Genetic counseling

6. Social integration of RD and holistic care:

To include: *Identifying and embedding examples of integrated and holistic approaches to care; RD-appropriate assessments of functioning; social research and burden of illness research; helplines and information on living with a RD, etc.*

- Organisation of RD Social Care (integrated care and social support) at national level
    - Assessments of functioning
    - Respite care programmes, therapeutic camps, Resource centres, etc
    - Information services on disabilities and 'hidden' impact of RD
        - European policy to promote holistic care
        - Social research / burden of illness research
        - Alternative medicine
        - Helplines and information on living with a RD

7. Patient engagement, patient empowerment and patient centred approaches to RD issues:

To include: *Strategies for patient empowerment; support of patient organisations; involvement of citizens in mHealth, direct QoL data collection; definition of PCOs/PROMs etc.*

- Patient characteristics
    - Quality of life
- mHealth
- QoL data collection
    - Eurobarometer
    - Rare Barometer Voices
    - other experiences
    - Information level
- Patient empowerment/ engagement
    - Patient organisations/advocacy/support groups
        - RD specific patient organisations
        - Umbrella groups/Federations
- Patient academies/courses
- Rare disease awareness campaigns
    - Social media
        - Informed consent/choice
- Use of personal data

- Consent forms for data re-use, for research, etc
    - Information services and resources on rare diseases
        - Orphanet
        - Helplines
        - other (ERN's websites, etc)

8. Accessing healthcare:

To include: *Centre of Expertise creation and functioning; integration of ERNs to health systems; development and use of clinical practice guidelines/clinical decision support tools to reduce inequalities in access to care; eHealth, etc.*

- National level: Centres of expertise and national networks
    - Centre of Expertise
        - Designation
        - Governance
        - Financing
    - National networks for RD
        - Designation
        - Governance
        - Financing
    - Integration of ERNs into national offer
    - Inequality in healthcare services provision
    - Geographical disparity
- European level: European Reference Networks
    - Designation
    - EC support to ERNs
- International level: Undiagnosed diseases networks
- eHealth strategies
- Healthcare Technology Assessment
- Reducing inequalities in access to care
    - Clinical practice guidelines
    - Clinical decision support tools
- Health economics in regards to clinical care

b. Literature review strategy - INSERM

A four-fold literature review strategy will be undertaken by the team at INSERM. This team has been in charge of the production of the OrphaNews newsletter since 2004. Examples of search algorithms are given here, and all search formulae used will be documented in the Annex of the report/factsheets to be delivered based on this literature review.

• OrphaNews literature review - Prospective

The political monitoring for OrphaNews International is carried out via a systematic literature review, including a survey of medical literature, grey literature, subscriptions to newsletters, information directly sent from the editorial board, alerts, RSS feeds, newspapers, and direct visit of websites.

OrphaNews is a freely available, twice-monthly electronic newsletter presenting an overview of scientific and political news about rare diseases and orphan drugs. OrphaNews is produced by Orphanet and is intended for the rare disease community. In each new issue, OrphaNews reports the latest developments in the field of rare diseases and orphan drugs, including new syndromes, new genes, basic and clinical research, national and international policy, disease surveillance, clinical trial updates, orphan drug approvals, funding opportunities, ethical, social and legal issues, news from the patient associations, upcoming events, and new publications.

OrphaNews is suited to all sectors of the rare disease and orphan drugs community - including policy makers, scientists, health professionals, patient representatives, geneticists, members of the biopharmaceutical industry and anyone interested in staying informed of important developments and new initiatives in the field of rare diseases and orphan drugs.

OrphaNews has been produced since 2004, with the support of EU Health Programme grants. It has been, in the past, the communication tool of the EC Rare Disease Task Force and the European Union Committee of Experts on Rare Diseases.

To produce OrphaNews, a twice-monthly literature review is conducted using the sources cited in Annex 1. The results of the survey are presented to the Editorial Committee, that selects the articles to write and the angle to take on the subjects that are chosen. The articles, once written, are presented for validation to the Editor in Chief of the newsletter, before the draft edition is sent to the Editorial Board. The Editorial Board's comments are integrated before final publication.

The OrphaNews literature review strategy will be used to prospectively survey scientific and grey literature relevant for RD, and will feed the literature review report.

• Search using thesaurus terms (Contao database) - Retrospective

A retrospective review of the OrphaNews article database will be conducted back to 2010.

The OrphaNews newsletter is edited using an open source newsletter tool, Contao. This tool allows for the indexation of articles with terms included in a controlled vocabulary. This thesaurus of terms (Annex 2) covers a wide range of subjects, both political and scientific, and was devised by the team at Orphanet, inspired by a selection of terms from the French Public Health Database (http://www.bdsp.ehesp.fr/). The thesaurus has a hierarchical structure (four levels), and synonyms are included.

Political articles are prospectively indexed, and have been retrospectively indexed back to 2010.

The advanced search tool (http://international.orphanews.org/search.html) of the newsletter allows the user to consult the thesaurus, and to search for a term, or a combination of terms. Results can be sorted by chronological order (the time period can also be restricted) or by relevance. The terms below the selected term in the hierarchy are also shown in the results.

In addition to that, a free-text review can be conducted on the articles published before 2010 (and backwards until 2004).

The terms the most relevant in the scope of each one of the themes will be used by expanding from the node in the thesaurus to the leaves level; by doing that, we will apply a Boolean search strategy based on "OR" logical operators.

Example of terms to searched for by theme

Please note that the highest term of theme or subtheme in the hierarchy of the thesaurus is used.

Data collection and use: [DATA] OR [eHealth]

N.B "DATA" includes the following 'terms' in the thesaurus:

- Search using key terms in free text search (Contao database)

To complement the analysis of the article database using the controlled thesaurus of terms a retrospective review of the OrphaNews article database will be conducted back to 2010 employing the use of key terms in free text searches.

A simple Boolean search function (http://international.orphanews.org/search.html) can also be used in Contao, to complement the search by term. This technique can be applied to the archives of the newsletter from 2004 to the present day.

We will build appropriate search equations using the terms in the thesaurus as these are already identified as the most relevant for the field, using Boolean operators and adjusting to reduce noise. New relevant and significant terms will be added to these equations and the thesaurus as the project progresses.

Example of search terms for free text search by theme

Data collection and use: "data" "data anonymization" bioinformatics "computing" interoperability matchmaking nosology "data sharing" "intellectual property" "data protection" "data storage" database biobank registry

- ## Additional literature search using search formulae

To complement the OrphaNews archive and OrphaNews literature survey approach, a review of the medical and grey literature as well as news reports will be carried out using Pubmed, Google Scholar, Google and Qwant for the period 2010-2019 using the following search formulae:

Example of search terms/formulae by theme

Informatics/ Digital transformation: ("rare disease" OR "genetic disease") AND ("data" OR "data anonymization" OR "bioinformatics" OR "computing" OR "interoperability" OR "matchmaking" OR "nosology" OR "data sharing" OR "intellectual property" OR "data protection" OR "data storage" OR "database" OR "biobank" OR "registry" OR "eHealth" OR "mHealth")

- ## Iterative process or refining the literature review when new areas of interest are detected

The list of themes, keywords and sources used to conduct the literature will be refined via an iterative process in response to the reviews conducted by UNEW and ISINNOVA. When a new theme of interest or disruptive innovation in the sector is detected, the literature review will be completed by carrying out an additional literature search via Pubmed, Google Scholar, Google and Qwant (see B iv).

- ## Ad hoc analysis of Orphadata from Orphanet

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

Orphanet offers a range of freely accessible services

- An inventory of rare diseases mapped with resources as OMIM, ICD10, MeSH, MedDRA, GARD and UMLS and a classification of diseases elaborated using existing published expert classifications. Diseases are also annotated with phenotypic features and frequency using HPO.
- An encyclopaedia of rare diseases in English, progressively translated into the other languages of the website.
- An inventory of orphan drugs at all stages of development.
- A directory of expert resources, providing information on expert clinics, medical laboratories, 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 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.
- Orphanet and ORDO are IRDiRC Recognized Resources and ELIXIR Core Data Resources

Orphadata - Orphanet's data download platform

Orphadata provides the scientific community with comprehensive, quality data sets related to rare diseases and orphan drugs from the Orphanet knowledge base, in reusable formats. Freely available (CC BY licence) datasets include the Orphanet nomenclature of rare diseases, cross-referenced with other terminologies, classifications of rare diseases, gene-disease relationships, disease-phenotype relationships, and epidemiological data. Catalogue data (available after signature of a Data Transfer Agreement for academia and non-profit organisations) includes the following data sets: textual data, the directory of expert centres, laboratories and diagnostic tests, patient organisations, research projects, patient registries, biobanks, and orphan drugs.

Orphanet data can be analysed to answer policy questions such as:

- What is the estimated prevalence of people living with a rare disease in Europe?
- Where is the expertise for rare diseases in Europe? What is the status quo of expert services for rare diseases in Europe (by type of service, by group of diseases, by disease prevalence, by country)?
- Where are the gaps in rare disease expert services in Europe? In what domains and for which diseases is a cross-border approach necessary?
- Where are the gaps in rare disease research?

Ad hoc analyses can be be performed on the datasets described above. Data on expert services can be analysed by classification, or by prevalence interval, for example, to respond to these type of questions.

Analyses performed back to 2010 for the State of the Art of Rare Diseases in Europe will be also exploited to create the factsheets made available to experts as an output of the literature review. These include:

- Number of genes/diseases tested in each country;
- Countries in the ERA-Net eRare;
- Number of FP projects coordinated/participated in by country;
- Disease registries by coverage;
- Countries with a national alliance for RD;
- Number and geographical coverage of disease/group of disease specific rare disease patient organisations in Europe;
- Countries participating in the Orphanet consortium;
- Countries with a RD helplines/info centres;
- Countries with a national plan/strategy for a RD.

3. State of the art grey literature review methodology (UNEW)

In Task 4.1 of the project there will be an element of retrospective as well as prospective review of the materials created via the State of the Art of Rare Disease Activities in Europe Resource (SoTAR). Past country reports and summaries from RD-ACTION (2016) and also from the EUCERD Joint Action will be explored. Most emphasis for populating the knowledge base factsheets, however will come from the request to countries (all EU MS plus Iceland, Norway, and several additional countries participating to the SoTAR in the past) to update their country data via the online survey.

This will be collected from the data Contributing Committees, which are being updated based on best knowledge to reflect any changes in DCC member positions, and also enlarged to involve Board of Member States (BoMS) of ERNs representatives where desired. The online survey used to gather the data in a comparable format was also adapted slightly, to reflect developments. The raw data submitted by the end of April 2019 (M4) will immediately be analysed to populate summaries, graphs and diagrams for the knowledge base factsheets. Alongside this activity, and foreseeably across M5-8, all countries submitting their updated data will receive updated national reports and summaries for their webpages.

The legacy data from past SoTAR updates will enable the creation of comparator summaries and graphs etc., to illustrate changes and developments over time between the counties.

Therefore, the SoTAR-related information, both retrospective and prospective, will be the main source of the analysis conducted by UNEW. To complement it, and also to be summarised via the relevant knowledge base factsheets, will be an analysis of key grey literature including the following:

- Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on Orphan Medicinal Products
- Commission Communication on Rare Diseases: Europe's challenges [COM(2008) 679 final
- Council Recommendation of 8 June 2009 on an action in the field of rare diseases (2009/C 151/02)
- Directive on the Application of Patients' Rights in Cross-Border Healthcare (Directive 2011/24/EU)
- Pan-Disease Recommendations agreed at European Level and adopted by the EUCERD and CEGRD
- ERN-related documents published via the RD-ACTION project, through the ERN Board of MS, and any other disease-agnostic product of the ERN WGs publically available via the EC websites
- Reports emerging from the IRDiRC and EJP
- Outputs of the INNOVCare initiative
- Rare-Disease specific grey literature on the subject of OMP accessibility, HTA, etc.

In compiling a list of grey-literature outputs relevant to each knowledge base factsheet, the key factor for inclusion will be broad applicability to the issues facing 'rare diseases' as a group, with a relevance to the potential determinants of health organisation and drivers of change. Support in compiling this list of relevant grey literature will be ensured by INSERM and ERN-BOND and ERN MetabERN who will ensure the input of all 24 European Reference Networks. To supplement the sources of data above, ad hoc extraction and analysis of data from the Orphanet database will be utilised to illustrate development and trends over time.

4. Horizon scanning (ISINNOVA)

In addition to this process, a parallel horizon scanning exercise will be carried out by ISINNOVA with support from EURORDIS but all RARE2030 partners will participate by providing foresight studies references and insights on specific projects and experiences. This work, focused on non-rare-disease specific foresight and scenarios, will be conducted from two perspectives:

- The governance perspective will investigate trends influencing the governance of Rare Diseases, looking at which will be the main functions for EU and national institutions and networks in the future;
- The sectoral perspective will examine emerging issues, technologies and social and organisational practices that are likely to influence the diagnosis, care, treatment and quality of life of people living with a rare disease in the future

The trend monitoring and analysis will generally follow a social, technological, economic, ecological and political (STEEEP) classification, but we will pay particular attention to categories that are likely to specifically impact Rare diseases. This approach will help bring forward knowledge from outside the strict RD Health policy sector with two main aims:

- Complement and refine with this input the factsheets and the iterative process of the literature review described by INSERM/UNEW.
- Support the stakeholders dialogue in the identification of trends, disruptive events, wild cards, weak signals and innovations opportunities that could influence the RD areas described in the factsheet.

The Horizon Scanning will include the following three activities:

1. Compile, analyse and categorise a non-rare-disease specific foresight and scenarios literature list;
2. Analyse, cross compare and summarise the most relevant findings of selected studies to i) complement the factsheets and ii) produce a preliminary list of drivers that will influence the future EU and national Rare Disease governance and diagnosis, care, treatment and quality of life of people living with a rare disease (general);
3. Conduct 10 interviews with selected experts in order to review, refine and validate the driver list.

This Horizon Scanning process and results will be documented in the D4.2 “Report on determinants of health and drivers of changes for RD, resulting from stakeholders’ interviews and workshop” (Month 10), but will not be detailed in this current document, which focuses on the literature review at INSERM/UNEW level

This process will be documented in the methodology of the horizon scanning report to be delivered in this project, but will not be detailed in this current document, which focuses on the literature review at INSERM/UNEW level.

5. Annexes

Annex 1: OrphaNews Literature Review Sources

1. Keywords

Used for: Pubmed alerts, Google alerts, Qwant, ScienceDirect, Scopus, BioMed Central

- Bioinformatics
- Prenatal Screening
- Non-invasive prenatal screening
- Rare Disease
- Next generation sequencing
- Methodologies for clinical trials
- Orphan Drug
- Policy AND Rare disease
- Reimbursement AND Rare disease
- Reimbursement AND Orphan Drug
- Stem Cell AND Rare Disease
- Rare Disease AND Asia
- Rare Disease AND Africa
- Intractable disease
- OMP Policies
- China rare diseases prevention and treatment alliance
- Rare Disease AND Regulatory
- Orphan Drug AND Regulatory
- Precision medicine
- Patient stratification
- Specialized care centers
- Care pathway
- Registries and cohorts
- Drug development strategies
- Drug pricing strategies
- Prevention, proactive management of carriers, prognosis markers
- Risk aversion

2. Google scholar alerts

- stem cell AND “rare diseases”
- intitle:“prenatal screening”
- intitle:“next-generation sequencing”
- “orphan drug” AND regulatory
- orphan AND drug
- “rare disease” AND bioinformatics
- rare AND disease
- intitle:bioinformatics
- ethical OR ethics AND “rare disease”
- “rare disease” AND regulatory
- Orphanet -”journal of rare diseases” -”j rare dis”
- “rare disease” AND “quality of life”

1) Governmental/institutional sites/newsletters

EMA, DG Santé (Newsletter What's new on DG Health & Food Safety Website update/EU newsletter eHealth, Wellbeing and Ageing), DG Enterprise, DG Research and Innovation, NHS (newsletter), U.S. Food & Drug

Administration (FDA) Daily Digest Bulletin, NIH (ORDR, NCATS), PBS website (Australia), CDC genomics update, Health Canada, MHLW (Japan), INSERM, CIBERER, IMI2.

2) Patient Organisations

NORD, NZORD, Rare voices Australia, EURORDIS, Chinese Organization for Rare Diseases, Rare Diseases South Africa, I-ORD, Rare Disease UK, Genetic Alliance Rare Diseases International.

3) Project sites

RD-Connect, Solve-RD, RD-Action, EJP-RD, euNetHTA, Joint Action on Rare Cancers, ERA-Net, Dyscerne, TREAT-NMD, JAseHN, RD-Code.

4) Foundations websites

PHG Foundation, French Rare Disease Foundation, Black Swan Foundation, Chan Zukerberg Foundation, Bill & Melinda Gates Foundation.

5) News sites

PMLive, Japan Times, NY Times, Fierce Biotech, Washington Post.

6) Other newsletters and websites

The Medical Futurist.

7) Journals surveyed at each edition

The index of each edition of the following journals is surveyed.

1. American Journal of Human Genetics
2. American Journal of Medical Genetics
3. Annals of Neurology
4. Biochimica et Biophysica Acta (BBA) - Proteins and Proteomics
5. BMC
6. BMC Genomics
7. BMC Medicine
8. BMJ
9. Cancer Cell
10. Cancer Gene Therapy
11. Cangen test
12. Cell press journals (all)
13. Cell Discovery
14. Cell Research
15. Clinical Pharmacology Therapeutics
16. CORDIS
17. Current Biology
18. Developmental Cell
19. EMBO Journal, EMBO report, EMBO molecular medicine
20. Epigenetics, Clinical epigenetics, Environmental epigenetics, etc…
21. European Journal of Human Genetics
22. Expert Opinion Orphan Drugs
23. Gene Therapy
24. Genetics in Medicine
25. Genomics
26. Health Policy
27. Health Policy and Technology
28. Human Gene therapy
29. Human microbiome
30. Human Genome Variation
31. INSERM pole PResse
32. JAMA
33. Journal of Biochemical Chemistry
34. Journal of cell Biology
35. Journal of Medical Genetics
36. Journal of Neuroscience
37. Journal of Pharmaceutical Policy and Practice
38. Journal of Rare Diseases
39. L'agence de Biomédecine (France)
40. Lancet Series
41. Microbiome journal
42. Molecular Cell
43. Molecular Therapy
44. Nature
45. Nature Biotechnology
46. Nature Genetics
47. Nature Medicine
48. Nature Medicine
49. Nature Methods
50. Nature Reviews Drug Discovery
51. OECD publication series
52. Orphanet Journal of Rare Diseases
53. Pediatric Research
54. PLoS Series

55. PNAS
56. Prenatal Diagnosis
57. Research Policy
58. Science
59. Science Signalling
60. Science Translational Medicine
61. Stem cell Reports
62. Stem Cells
63. The Lancet Global Health
64. The Lancet Haematology
65. The Lancet Neurology
66. The Lancet Oncology
67. The Pharmacogenomics Journal,
68. Toxicological sciences, Toxicology, Journal of Toxicology, etc…

8) European Reference Networks sites /newsletters

- ERN on Rare Bone Disorders - ERN BOND
- ERN on Rare craniofacial anomalies and ENT disorders - ERN CRANIO
- ERN on Rare Endocrine Conditions - Endo-ERN
- ERN on Rare and Complex Epilepsies - EpiCARE
- European Rare Kidney Diseases Reference Network - ERKNet
- ERN on Rare Neurological Diseases - ERN-RND
- ERN on Rare inherited and congenital anomalies - ERNICA
- ERN on Respiratory Diseases - ERN-LUNG
- ERN on Rare and Undiagnosed Skin Disorders - ERN-Skin
- ERN on Rare Adult Cancers (solid tumors) - EURACAN
- ERN on Rare Hematological Diseases - EuroBloodNet
- ERN for Rare Neuromuscular Diseases - EURO-NMD
- ERN on Rare Eye Diseases - ERN-EYE
- ERN on GENetic TUmour RIsk Syndromes - ERN GENTURIS
- Rare Urogenital Diseases - EUROGEN
- Gateway to Uncommon And Rare Diseases of the HEART - GUARD-HEART
- ERN on Rare Congenital Malformations and Rare Intellectual Disability - ITHACA
- ERN for Rare Hereditary Metabolic Disorders - MetabERN
- ERN for Paediatric Cancer (haemato-oncology) - PaedCan-ERN
- ERN on Rare Hepatological Diseases - RARE-LIVER
- Rare Connective Tissue and Musculoskeletal Diseases Network - ReCONNECT
- Rare Immunodeficiency, Autoinflammatory and Autoimmune Diseases Network - RITA
- ERN on Transplantation in Children (incl. HSCT, heart, kidney, liver, intestinal, lung and multiorgan) - TransplantChild
- ERN on Rare Multisystemic Vascular Diseases - VASCERN

RSS feeds

When available, RSS feeds for the above resources are subscribed to.

Twitter feeds

Monitoring of 400 accounts subscribed to by the @orphanet (https://twitter.com/Orphanet) Twitter handle.

Annex 2: Thesaurus of terms

Available as an Excel file: https://drive.google.com/open?id=15FN3FQKu4H-i6yzsKOmZ2XSdLF-ZF1D1

Available online (click on Advanced search>Consult the terms of the thesaurus)
http://international.orphanews.org/search.html

Annex 3: Factsheet outline

The exact structure for each knowledge base factsheet will vary (and will evolve over the course of the first 10 months of this project). However, it may be helpful to illustrate a broad outline for what these documents will look like. An example for the first factsheet, on 'Political and Strategic Framework relevant to rare diseases' is therefore included here, for reference: