Deliverable 1.1

The current situation, the challenges and the expectations on Patient registries and Databases. I - The current context

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Overview of the documents produced by EPIRARE

D1.2 Survey on the expectations and needs of patients (WP5)

D1.1 The current context of activities and policies on RD (WP7, WP8)

D1.3 Survey on the situation and needs of registries (all WP5)

D1.4 Statistical Analysis of the EPIRARE survey data (Parts 1 and 2) (WP6)

D1.5 Data mining on the EPIRARE survey data (WP6)

D3 Proposed Aims, Scope, Governance and Sustainability options for a European Platform for Rare Disease Registries (WP5)

D5 Developing a European Platform for Rare Disease Registries (WP8)

D4 Guidelines for data sources and quality for RD Registries in Europe (WP7)

D9.1.1 Overview of the scientific literature on Common Data Elements in the Rare Diseases Registries setting (WP6)

D9.1 Report on the survey on Common Data Elements (WP8)

D9.2 Analysis of the EPIRARE survey on registries data elements (WP6)

D9.3 Proposal for a Platform set of Common Data Elements (WP8)

D2.1 The Legal and Ethical Framework of EU Rare Disease Policies (WP4)

D2.2 Epidemiological and public health considerations for the EPIRARE briefing document on RD and data protection. (WP7)

D2.3 Amendments to the Draft Regulations on General Personal Data Protection (WP4, WP5, WP8)

D2.4 Briefing to the European Parliament (WP4, WP5, WP8)

Disclaimer

The contents of this document is in the sole responsibility of the Authors; The Executive Agency for Health and Consumers is not responsible for any use that may be made of the information contained herein.
I. Background

The general objective of the EPIRARE project is to build consensus and synergies to address legal, ethical and technical issues associated with the registration of rare disease (RD) patients and to elaborate a proposal for a EU web-based multi-disease platform which can promote quality rare disease patient registration. To this aim, the EU platform should be endowed with a number of features. It should integrate and synergize with existing initiatives and should support future developments expected from the implementation of current policies. Moreover, it should fulfil the needs of as many as possible different stakeholders. Finally, it should have its peculiar added value, e.g.: it should discharge tasks and provide a number of information outputs, which cannot or can scarcely be provided by individual registries. It is important to clarify that, in line with the EUCERD Core Recommendations on Rare Disease Patient Registration and Data Collection\(^1\), EPIRARE intends to develop a platform addressed to different types of data sources, from well established, multicentre and quality registries to small locally-held data collections. With such a wide range of targets, the approach of the platform has to be flexible, although preserving data quality. Actually, for it to be very effective, the platform should aim not only at collecting and sharing data from quality registries, but, rather, it should also aim at spreading quality registration. These aspects are taken into consideration by the EPIRARE project and will be the subject of dedicated documents.

The objective of this document is to review existing EU policies and initiatives of relevance for RD research and public health. This document is part of the EPIRARE deliverable D1, reporting on the current situation, the challenges and the expectations of RD patient registries and databases. Other documents making up this deliverable report on the results of surveys of the needs and expectations of RD registries and of RD patients. The analysis of the needs and expectations of other stakeholders will be dealt with in the EPIRARE deliverable D9, dealing with the different functions of the European RDR Platform.

II. Methodological note

The contents of this document is not intended to give an exhaustive review of initiatives and policies potentially relevant for RD registration, but to collect evidence on future developments in the field, to assess the relevance of a European Platform for Rare Disease Patient Registration (European RDR Platform) and to identify its major potential stakeholders to be consulted regarding their needs and expectations from this platform.

III. EU Public Health policies

A. The EU Recommendation for an action in the field of rare diseases (RD) and the Cross-Border Health Care Directive

The public health policies in the field of rare diseases in the EU essentially result from the EU Recommendation on an action in the field of rare diseases (2009/C 151/02), which triggered all EU Member States to develop national plans for RD, and recommended, among other actions, the promotion of databases and registries.

The basis of the EU Recommendation has been described in the EC Communication “Rare Diseases: A Europe’s Challenge” (2008). Actions to develop European Cooperation and to improve access to high-quality healthcare for rare diseases refer to:

- Development of national/regional Centres of Expertise and establishing European Reference Networks (ERNs)
- Access to specialised social services
- Access to Orphan Medicinal Products
- Compassionate Use programmes
- Medical devices
- Incentives for Orphan Drug development
- e-Health
- Screening practices
- Quality management of diagnostic laboratories
- Primary prevention
- Registries and databases
- Research and Development

Directive 2011/24/EU of the European Parliament and of the Council of 9 March 2011 on Cross-Border Health Care, which acknowledges a special prioritisation for the establishment of European Reference Networks of designated Centres of Expertise for rare diseases, will necessarily result in a change in the way patient information is stored and made available across different national health systems. The need to access patient health information and data from different places will result in a major boost of the use in electronic data processing within the health system. As a consequence, the implementation of technological solutions allowing both the collection and exchange of patient data within registry networks will be facilitated.

A platform for rare disease registries, not only fulfils one of the indications of the Council Recommendation on rare diseases, but could also support in several ways the development of the new EU system of rare disease care envisaged by the EU Directive on Cross-Border Health Care. Indeed, the core function of a technological service platform, supporting the collection and sharing of patient data within networks of professionals dedicated to specific diseases, will result in the promotion of clinical research on rare diseases and in greater networking among EU countries and possibly beyond. Actually, the European Platform could even represent an opportunity for networking neighbouring Countries.

B. Orphan Medicinal Products (OMP) policy

The specific features of OMP and the small population of patients for whom they are developed, make the extensive collection of clinical data difficult prior to marketing authorization. For these medicinal products, therefore, the acquisition of safety, effectiveness and appropriateness data after the marketing authorization is of special value compared to that of other drugs. For almost half of the orphan drugs arriving on the market, the pharmaceutical company is required to collect additional post marketing

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authorisation data. In this instance industry has often sought the collaboration of experienced academic
groups already running good quality registries, or to set up networks supporting product registries.

C. EU Health strategy

The current Programme of Community Action in the field of Public Health, ending in 2013, will be
superseded by the third Health Programme (Health for Growth) for the period 2014-2020, as part of the
EU health strategy within the overall “Europe 2020” Strategy. This programme is at present under
discussion at the European Parliament.

Among the four specific objectives proposed in the current draft of the Programme, two appear particularly
relevant for the EU rare disease registry platform:

- To develop common tools and mechanisms at EU level to address shortages of resources, both human
  and financial, and to facilitate up-take of innovation in healthcare in order to contribute to innovative
  and sustainable health systems.
- To increase access to medical expertise and information for specific conditions also beyond national
  borders, and to develop shared solutions and guidelines to improve healthcare quality and patient
  safety in order to increase access to better and safer healthcare for EU citizens.

This platform may enable synergies between isolated registries and avoid duplication of efforts, thus
improving the overall efficiency of data collection and analysis and funding. Moreover, it may provide a tool
facilitating access to medical expertise from distant sites where this is not available, and may extend its
scope beyond the EU. The adoption of robust data quality criteria, required for participation in the
platform, along with the strengthening of professional relationships between the platform users, will
facilitate building consensus and knowledge and the achievement of shared solutions or guidelines.
Moreover, the platform could facilitate a more balanced representation of the interests of all stakeholders
and the application of the EUCERD Recommendations on RD Patient Registration and Data Collection
and of the Key principles set out by EURORDIS, NORD and CORD in the Joint Declaration for Rare Disease Patient
Registries (see section V).

D. The regional dimension of the health policies

One of the overarching values of the EU health systems, in which all member states have committed
themselves, is the reduction of inequalities. Addressing the regional dimension of inequalities has
particular importance for rare diseases, since the expertise for the diagnosis and care of rare diseases is
scattered and the quality of services is heterogeneous across the EU.

The platform may fulfil this cross-cutting need to reduce inequalities in health among the EU regions if it
could foster the participation of stakeholders from different regions. Indeed, it may facilitate the exchange
of expertise and enable the benchmarking of standards of care across countries, thus providing a positive
contribution towards reducing the inequalities among EU regions and supporting neighbouring countries.

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4 Proposal for a REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL on establishing a Health for
Growth Programme, the third multi-annual programme of EU action in the field of health for the period 2014-2020
5 Council Conclusions on Common values and principles in European Union Health Systems (2006/C 146/01) Official
IV. Other relevant EU policies

A. e-Health policy

The EU e-Health policies are dramatically changing the ways in which the national health systems operate, with the development of powerful communication technology applications and infrastructures. Electronic health records, electronic prescriptions, patient’s card, diagnosis networks are being used more and more widely in EU member states. Such a transition demonstrates a perspective in which health service organization will increasingly exploit communication technologies and electronic records, thus facilitating, from a technological standpoint, patient data collection and exchange within the European Reference Networks (see above), whilst reducing the burden of data entry for the purpose of registry feeding.

The platform for rare disease registries will therefore synergize with the e-health and cross-border health care actions, impacting positively on registration activities beyond data entry. Indeed, the platform may reduce the burden of the organizational aspects of establishing and holding a registry, by providing resources supporting common registry activities, such as applications for data sharing and elaboration; staff training; data quality guidelines; recommended ethical procedures, and ensuring visibility and use of the results obtained.

B. Research policy and Industrial policy

Innovation has been placed at the heart of the Europe 2020 strategy. With over thirty action points, the Innovation Union (one of the Europe 2020 branches) aims to improve conditions and access to finance for research and innovation in Europe, to ensure that innovative ideas can be turned into products and services that create growth and jobs.

The EU industrial policy actively encourages the participation of Small and Medium Enterprises (SME), given their role as indispensable partners of the larger industrial players and their importance as developers of cutting edge technologies and drivers of innovation. In connection with rare diseases, it should be noted that Orphan Medicinal Products (OMP) are often developed starting from small pharmaceutical companies, following advances in research on the etiology and pathophysiology of rare diseases.

A platform for rare disease registries, which is able to identify patient cohorts for clinical trials and assist with the timely collection of related data, will support the activities of SME developing OMP, can contribute to the EU industrial policy.

Moreover, since it directly supports cooperation among EU national health systems, the platform contributes to the implementation of commitment 29 (Pooling forces to achieve breakthroughs: European Innovation Partnerships) within the Innovation Union policy, due to its relevance for developing clinical research on rare diseases, advancements in which can also be of use for other more common diseases.

C. The Revision of the Personal Data Protection Directive

The current Directive has been implemented in the EU Member States in 1998. The 27 EU Member States have implemented the 1995 rules differently, resulting in divergent national regulations. These divergences have made it difficult to share health data for medical research and public health purposes. The text of the current Directive is available at: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31995L0046:en:NOT. Since its implementation, technological progress and globalisation have profoundly changed the way our data is collected, accessed
and used. The European Commission has proposed a comprehensive reform of the EU’s 1995 data protection rules to strengthen online privacy rights and to boost Europe’s digital economy. The proposed text is available at: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:52012PC0010:en:NOT. This revision will take the form of a Regulation, which implies that a single set of rules will apply to all EU member states, thus facilitating compliance with the legislation for activities across member states. At the current stage of debate, the provisions for strong controls to data collection may impact on health research especially with regard to secondary use of the patient data. The outcome of the debate is not yet determined. However, the Members of the European Parliament have been informed, by EPIRARE and other organizations, of the specific needs of rare disease care and of the danger that current provisions can hamper health research on rare diseases and the improvement of health care for rare disease patients.

V. Current Activities in Research and Public Health

Thanks to the EU Council Recommendation on Rare Diseases (2009), we are assisting to an unprecedented and concurrent development of the national health services for rare disease patients; the active development of National Plans for Rare Diseases witnesses the involvement of health authorities and the awareness that the conditions of rare disease patients are a health and social priority. An EU committee has been formally established (EU Committee of Experts on Rare Diseases - EUCERD), supported in its activity by the EUCERD Joint Action (EJA), funded by Directorate General for Health & Consumers (DG SANCO) to support the European Commission with the preparation and implementation of Community activities in the field of rare diseases, in cooperation and consultation with Member States and other relevant stakeholders acting in the field. Member States are aware that coordinated efforts and common instruments need to be developed to reduce costs and avoid fragmentation of initiatives. Although the actions on rare diseases have rightly warranted dedicated attention and urgent implementation, they are also a reference model for cooperation on more common diseases. Therefore, while the actions on rare diseases address a specific public health topic, they represent the wider need of EU Member States for reliable data, rather than estimates, on their healthcare services, which will allow more cost-effective service planning and monitoring and will represent a first important step in the implementation of the Cross-Border Health Care Directive.

The EU Committee of Experts on Rare Diseases (EUCERD), as well as the Cross-Border Health Care Expert Group, are developing recommendations on the establishment of European Reference Networks (ERN) of Centres of Expertise, which comply with selection criteria. Within ERN, potential for networking has been identified in areas such as databases and registries, newborn screening, biobanks, tele-expertise tools, guidelines, information packages, quality assurance schemes and training tools covering the medical dimensions of diseases.

EUCERD is also developing a set of “EUCERD Recommendations on RD Patient Registration and Data Collection”; this will become an important reference document, since it is being developed with the agreement of the many different stakeholders participating in EUCERD. The proposal developed by EPIRARE for the EU Platform for rare disease registries is developed fully in line with thisEUCERD Document.

The European Medicines Agency coordinates the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP), which has been developed in collaboration with European

experts in the fields of pharmaco-epidemiology and pharmaco-vigilance. The goal of ENCePP is to further strengthen the post-authorisation monitoring of medicinal products in Europe by facilitating the conduct of multi-centre, independent, post-authorisation studies focusing on safety and on benefit:risk ratio, using available expertise and research experience across Europe. This network comprises relevant research centres, medical-care centres, healthcare databases, electronic registries and existing European networks covering certain rare diseases, therapeutic fields and adverse drug events of interest.

A multi-stakeholder group within the EJA and in collaboration with the EMA is discussing possible registry models to avoid the fragmentation of data in industry-led post marketing surveillance studies. Any new model will need to take into account the new pharmacovigilance regulation which is reinforcing the companies’ obligation to provide safety and effectiveness follow up of their drug.

DG Health and Consumers has been financing, during the last years, 11 networks of researchers and clinicians on a single disease or on a group of related rare diseases\(^7\). The 6th and 7th Framework programmes, managed by EC DG Research, have funded 24\(^8\) and 38 projects\(^9\) for rare disease research, respectively. Among these projects, E-RARE established a European Research Area for rare diseases among 17 EU and non-EU countries, which is aiming at reducing the fragmentation in rare disease research and co-funded 65 international projects until 2013\(^10\). A preliminary analysis of many networks has been performed by EJA\(^11\). None of these projects will be mentioned specifically here; however, many of these projects have been remarkably successful in developing registries and interesting applications stemming from these.

More recently the EU Commission published a page stating that the creation of a European Platform for Rare Disease Registries is a strategic objective for its action in this field\(^12\). Moreover, the EU Commission is concluding a contract agreement for the development of the platform infrastructure for rare disease registries with the EU Joint Research Centre (Ispra, Italy) as part of the Work Plan 2013 of the Programme of Community Action on Health, with a budget of 2 million Euro. The activities in ISPRA are expected to begin by the end of 2013.

BURQOL (Social economic burden and health-related quality of life in Patients with Rare Diseases in Europe) is a 3-year project that began in March 2010, funded by the 2nd Programme of Community Action in the Field of Public Health, promoted by EC DG Health and Consumers. It is coordinated by the Canary Foundation of Investigation and Health, and includes 21 associated and collaborating partners. The primary objective of BURQOL is to generate a methodological framework to quantify the socio-economic burden and impact on health-related quality of life (HRQOL) of both patients and carers, for ten rare diseases in eight different European countries. Planned outcomes include an integrated and harmonised set of instruments to assess and monitor socio-economic burden and HRQOL of patients affected by rare diseases and their caregivers, and a detailed analysis of the services (health and social care) received by people with specific rare diseases in different EU countries, including the identification of formal and informal care. The

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\(^8\) [http://www.healthcompetence.eu/conversis/publicweb/area/1353?show=PROJECT&page=1&sortBy=start_date&sortBy=descAsc=false&items=10&fseachkey=&fypename=0&fsequence=0&fyear=0&forganisation=&fperson=&fkeyword=&farea=1377&fcountry=](http://www.healthcompetence.eu/conversis/publicweb/area/1353?show=PROJECT&page=1&sortBy=start_date&sortBy=descAsc=false&items=10&fseachkey=&fypename=0&fsequence=0&fyear=0&forganisation=&fperson=&fkeyword=&farea=1377&fcountry=) (accessed on 13/03/2014)


\(^10\) [http://www.erare.eu/all-funded-projects](http://www.erare.eu/all-funded-projects) (accessed on 13/03/2014)


results and deliverables that emerge from this project will stimulate the future comparability and monitoring of rare diseases in Europe as well as anticipate future information needs, which will also be relevant to include into the EPIRARE EU platform for rare disease registries.

The Cross Border PAatient REgistries iNiTiative (PARENT Joint Action), a project funded by DG SANCO, started in 2012 and aims to rationalize the development and governance of interoperable patient registries, thus enabling the use of secondary data for public health and research purposes in cross-organizational and cross-border setting. PARENT has launched a pilot Registry of Registries in 2013, accessible at www.parentror.eu. It provides comprehensive search and comparison of over 130 national or regional registries in the EU.

The European Partnership for Action Against Cancer (EPAAC Joint Action) brings together the efforts of different stakeholders into a joint response to prevent and control cancer. The EPAAC Joint Action encompasses 36 associated partners from across Europe and over 90 collaborating partners. One of the key aims of this consortium is to define and outline a European comprehensive information system, networking different stakeholders and including cancer registries with the aim of developing best approaches to care and dissemination of good practice. Similarly, the EUROCOURSE project, funded by DG Research, is addressing the optimisation of the use of registries for scientific excellence in research.

The EU Biobanking and Biomolecular Resources Research Infrastructure (BBMRI) and the FP7 Gen2Phen project (gene-specific and genomic variant databases including phenotypic information) aim at developing platforms to network the pertinent centres and have developed standards concerning data formats and exchange for this type of information. Although these are resources dedicated to fostering highly specialized research, a connection between them and a platform for rare disease registries may be highly beneficial for both sides. The development of the RD registries platform should consider attentively to ensure smooth communications with these platforms.

ORPHANET is a portal of information for professionals and patients interested in rare diseases. In 2009, ORPHANET published a list of rare disease registries active in Europe. This list included initially 402 registries with regional, national, European and global dimension, and a more recent list reported over 600 registries\(^\text{13}\). These registries, together with other registries not reported in these lists were included in the mailing list of the EPIRARE surveys. However, many of these registries either did not reply or else the e-mail addresses no longer seemed valid. The reasons for these results may be varied and should be investigated further. Termination of the registry, either due to a lack of sustainability or because of the successful achievement of the registry objectives would suggest that the opportunity has been missed for a better exploitation of the data collected and of the resources used for the establishment of that registry. Lack of interest or of time for the registry staff to reply would also suggest that a platform providing appropriate tools and resources for registration may improve data sharing and use in a wider context.

The International Rare Disease Research Consortium (IRDiRC) was launched in April 2011 as a bilateral EU-USA initiative dedicated to fostering international collaboration in rare diseases research. The European Commission and the US National Institutes of Health initiated the discussions, and several other stakeholders, including other funding agencies (Canada and Australia), have also since joined the consortium. IRDiRC will team up researchers and organisations investing in rare diseases research in order to achieve two main objectives, namely to deliver 200 new therapies for rare diseases and the means to diagnose most rare diseases by the year 2020. IRDiRC unites organisations which share common goals and

\(^{13}\) http://www.orpha.net/orphacom/cahiers/docs/GB/Registries.pdf
principles and have agreed to work in a coordinated and collaborative manner within a multinational consortium. RD registries are one of the main focal topics of this international consortium because they provide information about the natural history of diseases as well as promote all types of research.

**Within IRDiRC, the RD-Connect project**, funded by the Directorate-General for Research & Innovation of the European Commission (DG Research; start date November, 1st 2012), is also aiming to establish an integrated platform connecting databases, registries, biobanks and clinical bioinformatics for rare disease research. It will deploy its activities with a global partnership ensuring links with the main initiatives in the EU and beyond, including the EPIRARE project and the EUCERD.

The **EU Commission and the World Health Organization (WHO-Euro)** have been cooperating for a long time for the establishment of a common European Health Information System. Although this system is not specifically dedicated to RD, it might be the case to consider this initiative to identify possible synergies for the production of pre-defined platform outputs and for the extension of its geographical coverage to other non-EU European Countries.

Among European patients Associations, **EURORDIS** is particularly active and organizes the biennial European Conference on Rare Diseases & Orphan Products, a unique forum across all rare diseases and across all European countries. It brings together all stakeholders - academics, health care professionals, industry, policy makers, and patients’ representatives. It presents the state-of-the-art of the rare disease environment, monitoring and benchmarking initiatives. It covers research, development of new treatments, health care, social care, information, public health and support at European, national and regional levels. Also, every year EURORDIS organises its Membership Meeting in a different European city. This is an occasion for patient representatives to gather and learn from each other.

EURORDIS, together with NORD (US National Organization for Rare Disorders) and CORD (Canadian Organization for Rare Disorders) has prepared a **Joint Declaration for Rare Disease Patient Registries**, where 10 Key Principles have been proposed:

1. Patient Registries should be recognized as a global priority in the field of Rare Diseases.
2. Rare Disease Patient Registries should encompass the widest geographic scope possible.
3. Rare Disease Patient Registries should be centred on a disease or group of diseases rather than a therapeutic intervention.
4. Interoperability and harmonization between Rare Disease Patient Registries should be consistently pursued.
5. A minimum set of Common Data Elements should be consistently used in all Rare Disease Patient Registries.
6. Rare Disease Patient Registries data should be linked with corresponding biobank data
7. Rare Disease Patient Registries should include data directly reported by patients along with data reported by healthcare professionals
8. Public-Private Partnerships should be encouraged to ensure sustainability of Rare Disease Patient Registries.
9. Patients should be equally involved with other stakeholders in the governance of Rare Disease Patient Registries.
10. Rare Disease Patient Registries should serve as key instruments for building and empowering patient communities

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14 http://rarediseases.org/docs/registries-2012
These principles clearly reflect the interest of patient organizations in the development of RD registries and also their capacity to contribute to registry development. These principles represent the framework within which this proposal for an EU platform for rare disease registries has been developed.

Two USA-based initiatives provide important counterparts for building common strategies between Europe and USA in the field of RD patient registries.

The Global Rare Diseases Registry and Data repository (GRDR) has been established by the NIH Office of Rare Disease Research. It is connected with a RD-HUB platform addressed to RD biobanks. The GRDR provides the rare disease community a resource of standardized aggregated de-identified patient information to accelerate research and advance therapeutic development. This initiative includes all type of patient registries and rare diseases. All registries have to achieve good quality standards and use common data elements definitions. All patients data are de-identified and coded with a Global Unique Identifier (GUID), which avoids duplicate patient records.

In parallel to this rare disease repository, the US Agency for Healthcare Research and Quality (AHRQ) has recently launched the Registry of Patient Registries (RoPR), which is not primarily addressed to rare diseases but offers good criteria for building a rare disease registry platform based on metadata and not on individuals’ data. This platform is similar in functionalities to EU based www.parent-ror.eu Registry of Registries as created in PARENT Joint Action and complementary to the very well-known website named clinicaltrials.gov. Both the platform and the website provide important clues for whatever other kind of rare disease registry platforms to be created.

Finally, the number of private companies offering software platforms for web-based registries and patient management is rapidly increasing.

VI. Conclusions

Both the EU policies for the coming years and the on-going activities at global, EU and Member State levels indicate a clear transition to new modes of cooperation operated by international networking and exchange of information addressed to scientific and economic development and to reduce inequalities. Within this context, the European RDR Platform may play a strategic role in supporting data sharing, in facilitating the adoption of common standards, references and tools, in improving the quality and use of collected data and promoting registration. A platform succeeding in reaching these goals will have a significant impact on the economic, scientific and health care development in the EU and globally.