A European Union framework for action in the field of Rare Diseases registration

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Health and Consumers

New priorities after Commission Communication and Council Recommendation

Rare diseases registers

- **The action in the field of supporting RD registries started in the framework of the FP5 (1998-2002) and the first Community Rare Diseases Programme (1999-2003).**

- **A total of 597 rare diseases registries have been created during this period in the EU by several stakeholders from which 49 registers are financed by the Health Programmes or the FP5, FP6 or FP7. List available under http://www.orpha.net/orphacom/cahiers/docs/GB/Registries.pdf.**

- **The former Task Force on RD had their own Working Group on RD Registers and the new EUCERD will have a similar group, the EMA/EUCERD Workshop on Rare Diseases Registers (meeting in London next 4th October 2011) because RD registers constitutes an essential element in the Orphan Drugs designation and are a priority for EMA.**

- **EPIRARE (European Platform for Rare Diseases Registries) Project selected for funding in 2010 in order to build consensus and synergies to address regulatory, ethical and technical issues associated with the registration of RD patients and to elaborate possible policy scenarios as well as to evaluate the experience of the 514 registries in place and the most appropriate criterion to use EU funding.**

- **The USA/EU International Rare Disease Research Consortium (IRDiRC) has considered transatlantic RD registers as one of the privileged fields of the common agenda.**

New priorities after Commission Communication and Council Recommendation

Rare diseases registers

Patient registries and databases constitute key instruments to develop clinical research in the field of rare diseases, to improve patient care and healthcare planning. They are the only way to pool data in order to achieve a sufficient sample size for epidemiological and/or clinical research. They are vital to assess the feasibility of clinical trials, to facilitate the planning of appropriate clinical trials and to support the enrolment of patients.

Patient registries can form the basis for the development of support networks where national or regional patient advocacy groups where none existing. Indeed, the creation of a registry can be a powerful tool to create and structure networks of experts, whether they being European Reference Networks of Centres of Expertise or national expert networks for RD.

RD patients can draw great benefit from RD registries since where they exist, and are developed with high standards, there is evidence that quality of care and life expectancy improves dramatically (e.g., the European Cystic Fibrosis Society Patient Registry or the TREAT-NMD Neuromuscular Network). For all RD, performing epidemiological, clinical or social research to advance knowledge requires multi-country collaboration in the establishment of a registry in order to increase the number of patients included (e.g. European Registry of Cushing's syndrome, ERCUSYN).

New priorities after Commission Communication and Council Recommendation

Rare diseases registers

Identifying and monitoring the care and treatment of patients across Europe and beyond can also better prepare the landscape for eventual drug clinical trials once new potential treatments arise as well as assess the real-world effectiveness of treatments outside the rigid context of a randomised controlled clinical trial.

Because of their low individual prevalence and the scarcity of information about each of them, the benefits of collaboration and maximization of limited resources in establishing patient registries are most obvious for RD, especially for ultra RD for which expertise may only be available in a very small number of European countries.

No single institution, and in many cases no single country, has sufficient numbers of patients to conduct generalizable clinical and translational research. Geographic dispersion of RD patients has been a major impediment to patient recruitment into clinical trials.

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Rare diseases registers

Recently, the value of patient registries has acquired new appealing perspectives when thought in connection with repositories of RD bio-specimens. Patient registries and biological resource repositories and databases pursue different specific objectives and use different methods but both pursue the same general objective of supporting genetic, biological and clinical research in a specific disease.

In recognition of the challenges this undertaking presents, there are ongoing initiatives on both sides of the Atlantic in order to propose workable models. For example, in the US, the Genetic Alliance Biobank provides infrastructure coordination for multiple rare diseases, and it includes clinical records and questionnaires as well as biological materials. This type of federated approach also lowers the barriers for access to patient samples by individual researchers.

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Rare diseases registers

The US experience

Furthermore, the US Office of Rare Diseases Research (ORDR, NIH) has developed the Biospecimens/Biorepositories Website: Rare Disease-HUB (RD-HUB). This Website contains a searchable database of bio-specimens collected, stored, and distributed by bio-repositories in the United States and around the globe.

One of the major objectives of the project is to link the RD-HUB with the Global Rare Diseases Patient Registry and Data Repository (GRDR). The Global Rare Diseases Patient Registry and Data Repository (GRDR) is a pilot program launched by ORDR to enable analyses of data across many rare diseases and to facilitate clinical trials and other studies.

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Rare diseases registers

In the EU, the EuroBioBank network is the first operating network of biobanks providing human DNA, cell and tissue samples as a service to the scientific community conducting research on rare diseases. EuroBioBank and RD-HUB are actively collaborating.

Finally, registries have become mandatory requirements for orphan drug development, clinical trials and drug regulatory affairs (either to develop a new medicine or for its post marketing surveillance).

For these specific purposes, specific recommendations have been communicated by the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) of the European Medicines Agency (EMA).

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Rare diseases registers

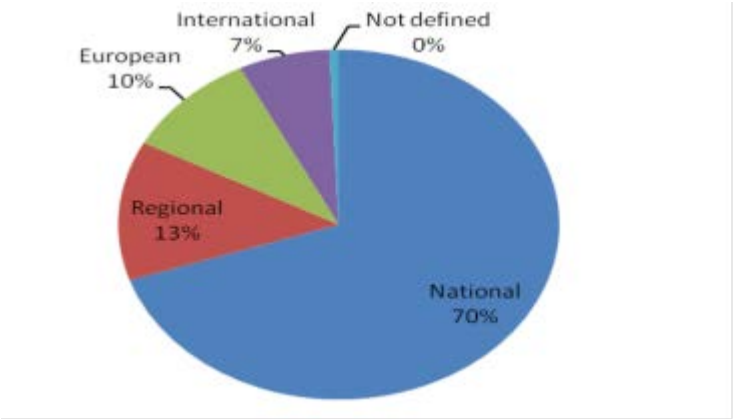
- The Orphanet Report - Disease Registries in Europe - January 2011,
- EUCERD Joint Action proposal (start January 2012, duration 36 months
- PARENT Joint Action proposal (Cross Border PAtient REgistries iNiTiative, start 1 September 2012, duration 30 months)
- EPIRARE (European Platform for Rare Disease Registries) Project (Start April 2011, duration 36 months)
- The International Rare Diseases Research Consortium (IRDiRC) (Start April 2011 still End 2020)
- RD Connect (FP7 Call 2012, started on January 2013)

New priorities after Commission Communication and Council Recommendation

Rare diseases registers

The document "RDTF Report on Patient registries the field of rare diseases: Overview of the issues surrounding the establishment, governance and financing of academic registries" published by the Rare Diseases Task Force in 2008 and updated by the EUCERD (European Union Committee of Experts on Rare Diseases) in June 2011 presents a detailed list and overview of the rare diseases registers exiting in Europe.

They are 597 in May 2012 presenting the following distribution:



According to the data in the Orphanet database, this 597 disease registries are: 59 European, 40 International, 417 national, 77 regional, 4 undefined.

New priorities after Commission Communication and Council Recommendation

Rare diseases registers

Almost all of these registries concern diseases or groups of diseases for which there is an innovative treatment either in development or already on the market. This is not surprising as registries of patients treated with orphan medicinal products are particularly relevant: they allow the gathering of evidence on the effectiveness of the treatment and on its possible side effects, keeping in mind that marketing authorisation is usually granted at a time when evidence is still limited although already somewhat convincing. Most of the registries are established in academic institutions. A minority of them are managed by pharmaceutical or biotech companies, with others being run by patient organisations.

DG SANCO has been financing in the last years, 16 networks of researchers and clinicians on a single or on a group of related rare diseases including registration of RD. The 6th and 7th Framework programmes, managed by DG Research, have funded 18 and 27 projects for rare disease research including registration of RD.

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Rare diseases registers EPIRARE Survey

What kind of data are collected? (select all that apply)

		Frequency	Percent	Valid Percent
Valid	Anagraphical data	71	32,3	32,3
	Diagnosis	209	95,0	95,0
	Anthropometric information	72	32,7	32,7
	Socio-demographic information	106	48,2	48,2
	Genetic data	159	72,3	72,3
	Clinical data	191	86,8	86,8
	Medications, devices and health services	135	61,4	61,4
	Patient-reported outcomes (e.g. quality of life data, Health status, etc)	78	35,5	35,5
	Family history	121	55,0	55,0
	Birth and reproductive history	67	30,5	30,5
	Clinical research participation and bio-specimen donation	67	30,5	30,5
	Patient's preferences for communication	28	12,7	12,7
	Other (specify):	12	5,4	

New priorities after Commission Communication and Council Recommendation

Rare diseases registers EPIRARE Survey

What are the aims of the register? (select all that apply)

		Frequency	Percent	Valid Percent
Natural history of the disease		133	60,4	60,7%
Epidemiological research		155	70,4	70,8%
Clinical research (patient recruitment for clinical trials)		134	60,9	61,2%
Disease surveillance		122	55,4	55,7%
Treatment evaluation (efficacy)		94	41,8	42,9%
Treatment monitoring (safety)		73	33,1	33,3%
Mutation database		94	42,7	42,9%
Genotype-phenotype correlation		117	53,1	53,4%
Social planning		42	19	19,2%
Healthcare Services planning		74	33,6	33,8%
Other (specify):		18	8,1	
Total valid		219	99,5	
Missing	System	1	0,5	
Total		220		

New priorities after Commission Communication and Council Recommendation

Rare diseases registers EPIRARE Survey

Number of active cases (prevalence)

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	10-200	20	9,1	9,2	9,2
	201-1000	87	39,5	39,9	49,1
	1001-5000	55	25,0	25,2	74,3
	5001-10000	27	12,3	12,4	86,7
	>10000	29	13,2	13,3	100,0
	Total	218	99,1	100,0	
Missing	System	2	,9		
Total		220	100,0		

Number of new cases entered in the last year (incidence)

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	None	13	5,9	6,0	6,0
	5-50	98	44,5	45,4	51,4
	51-200	45	20,5	20,8	72,2
	>200	60	27,3	27,8	100,0
	Total	216	98,2	100,0	
Missing	System	4	1,8		
Total		220	100,0		

N rare diseases included

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Just one	75	34,1	34,2	34,2
	A group of related RDs	102	46,4	46,6	80,8
	Several RDs (or groups of RDs) not related among them	26	11,8	11,9	92,7
	All rare diseases	16	7,3	7,3	100,0
	Total	219	99,5	100,0	
Missing	System	1	,5		
Total		220	100,0		

New priorities after Commission Communication and Council Recommendation

Rare diseases registers EPIRARE Survey

The register was set up with funding coming from: (select all that apply)

		Frequency	Percent	Valid Percent
Valid	No specific fund	46	20,9	22.8
	Regional Authority	27	12,2	13.4
	National Authority	55	25	27.2
	University/Research Institute	35	15,9	17.3
	Hospital	19	8,6	9.4
	Patients Association	36	16,3	17.8
	Foundation	22	10	10.9
	Industry/Industrial Association	25	11,3	12.4
	EU Commission/EU Agency	33	15	16.3
	Information not available	6	1,3	3.0
	Other (specify)	14	6,3	14
	Total valid	202	91,8	100
Missing	System	18	8,1	
Total		220	100	202

Possible scenario for a repository data at EU level for Rare Diseases Registration

All the ongoing EU projects go in a similar direction:

- **To avoid waste of resources due to the funds invested in similar activities (consent form, storage of data, training of staff, harmonisation procedures, etc.);**
- **To have a sustainable existence of registries;.**
- **To serve all the purposes of RD registration for epidemiology purposes, research, clinical trials, post-marketing surveillance of orphan medicinal products, to contribute to ERN activities, etc.**
- **The Commission should propose, under certain rules, a common platform permitting to improve and increase integrated uses of RD registries.**

European Commission

Possible scenario for a repository data at EU level for Rare Diseases Registration

The goal of a future EU RD Registration Repository Platform (EURDRRP) is to enable data analysis within and across many rare diseases and to facilitate clinical trials and other studies. An interface will be developed to accept de-identified patient data from existing patient registries to promote data sharing.

The EURDRRP will also serve rare disease patients and their advocacy groups seeking help and information. It will also serve investigators conducting research, clinicians treating patients, epidemiologists analysing disease data, and investigators seeking patients for new clinical trials and initiating natural history studies.

The EURDRRP will be also a researcher portal will allow authorized researchers to gain access to de-identified patient data to identify potential study candidates and to learn about the natural history of disease.

Possible scenario for a repository data at EU level for Rare Diseases Registration

Registries can also be established to provide data for assessing the clinical effectiveness or the cost-effectiveness of new interventions in a real-world setting. This is required because the clinical studies performed to assess the clinical efficacy of new treatments are based on studies of selected patients following an "ideal protocol", which differ from the clinical practice afterwards when the treatment is implemented in the healthcare setting.

This is why more and more regulatory authorities and healthcare insurers request that a registry be implemented when an orphan drug receives a marketing authorisation. This type of registry is much more interesting than the previous type as it includes all patients, not only the treated patients. However, registries have to be designed specifically to assess cost / effectiveness in order to accomplish this purpose even if cost-effectiveness may be difficult to assess in rare diseases.

In order to aggregate data from different registries to facilitate pan-disease analysis, data must be captured and collected in a standardized manner. Use of Common Data Elements (CDEs) facilitates the standardization of data collection and allows for harmonization, sharing, and exchange of information across registries. The EURDRRP should develop a minimal set of CDEs to be accepted and adopted by numerous national and international patient advocacy groups and professional organizations globally.

New priorities after Commission Communication and Council Recommendation

ERIC (European Research Infraestructure)

An ERIC has legal personality based on EU law (Article 171 of the EC Treaty). Its main tasks are establish and operate a research infrastructure.

The ERIC is an easy-to-use legal instrument providing:

the spirit of a truly European venture (also allowing the participation of non-European countries)

- **a legal personality recognised in all EU Member States**
- **flexibility to adapt to the specific requirements of each infrastructure**
- **some privileges/exemptions allowed for intergovernmental organisations**
- **a faster and more cost-efficient process than creating an international organisation**

An ERIC can benefit from exemptions from VAT and excise duty in all EU Member States and it may adopt its own procurement procedures, which have to respect the principles of transparency, non-discrimination and competition but are not subject to public procurement procedures.

New priorities after Commission Communication and Council Recommendation

ERIC (European Research Infraestructure)

Members will be states and intergovernmental organisations.

At least three Member States agree to establish and operate together a research infrastructure. Associated countries, third countries and intergovernmental organisations may also be members.

The members agree on statutes ruling governance, IPR policy, financing, etc.

The seat has to be in an EU-Member State or in a country associated to the EU Framework programmes.

The members submit the file to the Commission, which, with the aid of independent experts, examines whether the conditions of the ERIC Regulation are fulfilled. After that, a committee composed of representatives of the EU Member States gives an opinion on the file by qualified majority, following which the Commission decides on the application.

New priorities after Commission Communication and Council Recommendation

ERIC (European Research Infrastructure)

Rare diseases infrastructures having interest for research purposes and being potential beneficiaries of an ERIC:

- **ORPHANET**
- **Surveillance networks on rare diseases (EUROCAT and SCPE)**
- **The European Platform of Rare Diseases Registration**
- **EUROGENTEST (under discussion)**
- **First meeting between Commission and Member States + potential beneficiaries to take place in Ispra (italy) next 17 june.**

Possible scenario for a repository data at EU level for Rare Diseases Registration

A pilot program could be established to test the different functionalities of the EURDRRP. During a pilot project, a web-based template will be developed to assist other patient groups that wish to establish their own patient registry.

This global rare disease registry infrastructure will draw new interest in rare diseases from academic researchers and the pharmaceutical industry because it will assist in the recruitment of patient participants much faster and at much lower cost and enable the design of more effective clinical trials.

Proposal in the Work Plan 2013:

Support to rare diseases registries and networks in view of their sustainability

The aim of this action is to set up a sustainable platform to coordinate and maintain registries and networks on rare diseases. Registries and networks are key instruments in increasing knowledge of rare diseases and in developing clinical research. They are the only way to pool data in order to achieve a sufficient sample size for epidemiological research and/or clinical research. This action will build on activities and experiences developed through initiatives funded by the EU Health programmes and Research and Innovation programmes.

[Project grant / Administrative agreement with the JRC] Indicative amount: EUR 2 000 000

DG SANCO priorities on rare diseases Web site

Public health actions

http://ec.europa.eu/health/rare_diseases/policy/index_en.htm

Contact points at DG SANCO

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Research actions

http://ec.europa.eu/research/health/medical-research/rare-diseases/index_en.html

Contact point at DG RTD

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JRC Platform

Contact point at JRC

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