EUROPLAN NATIONAL CONFERENCES 2012-2015

CONTENT GUIDELINES FOR WORKSHOP 3 / THEME 3

RESEARCH FOR RARE DISEASES

Table of Contents

A. How to read and use these Content Guidelines

The EUROPLAN Content Guidelines cover 6 main Themes. For each Theme, these Content Guidelines cover all the core topics to be addressed in the Workshop dedicated to that Theme. These Guidelines include:

1st column – RESOURCES	**2nd column - TOPICS FOR DISCUSSION**
This column includes the background documents and relevant material that should be referred to in preparation for the discussion. They mainly include: • Specific articles of the EU Council Recommendation on an action in the field of rare diseases; • Specific recommendations from the "EUROPLAN Recommendations"; • EUCERD Recommendations on "Quality Criteria for Centre of Expertise for Rare Diseases in Member States"; • EUCERD Core Recommendations on Rare Disease Patient Registration and Data Collection; • Specific recommendations from the "EUROPLAN Recommendations"; • Specific EUCERD Core Indicators; • Specific EUROPLAN Indicators; • "Report on rare disease research, its determinants in Europe and the way forward", May 2011, S. Aymé, V. Hivert (eds.). **NB: Full documents of the sources referenced above can be found in Section C**	**The topics for discussion are questions formulated to stimulate the discussion within the Workshop**. The conference organisers, with the help of their Advisor, will **select those questions that are relevant for the discussion in their countries**. As such, **not all listed questions need to be addressed in a mandatory way**. They rather represent a "menu" from which to pick the questions that address the most relevant topics in the country, having considered the level of advancement of the national policy on rare diseases in the country.

B. Guidelines for discussion

RESOURCES	TOPICS for DISCUSSION
B.1 Mapping of existing research resources, infrastructures and programmes for RDs	
Council Recommendation on RD 6. Identify ongoing research and research resources in the national and Community frameworks in order to establish the state of the art, assess the research landscape in the area of rare diseases, and improve the coordination of Community, national and regional programmes for rare diseases research. **EUROPLAN recommendations** R 3.1 … Research projects on rare diseases should be made identifiable and traceable within broader national research programs. **Final Report of EUROPLAN I National Conferences** (Area 3, page 38) - "EUROPLAN Conferences were an important opportunity throughout Europe to sketch out and discuss the state of the art of research on rare diseases. From these national 'mappings' it appeared that in most countries there are no dedicated national research programmes or funds for RD research. This is sometimes due to different approaches or traditions in research funding. *For instance, in some countries (Sweden, Denmark, Germany, UK) no thematic approach is adopted, research being funded through bottom-up procedures, whereby the best application gets funded, whatever the theme may be."*	• Evaluation of RD research resources and infrastructures across different disciplines and sources of funds, both public and private. • What is the scope of patient-driven research, i.e. research initiated and/or financed by patients and their associations? • Is there a list or inventory of teams working at national level on RD research? Is it regularly updated? Are research projects on rare diseases identifiable and traceable within broader national research programmes?
B.2 Dedicated RD research programmes and governance of RD research funds	
Council Recommendation on RD Whereas: […] (9) In order to improve the coordination and coherence of national, regional and local	• Does a specific national RD research programme with dedicated funds exist? Is there a scope for such programme? • How are funds allocated? What governance model does exist for handling RD

initiatives addressing rare diseases and cooperation between research centres, relevant national actions in the field of rare diseases could be integrated into plans or strategies for rare diseases.

9. Include in their plans or strategies provisions aimed at fostering research in the field of rare diseases.

EUROPLAN recommendations

R 3.1 Dedicated national research programs for rare diseases (basic, translational, clinical, public health and social research) are established and supported with dedicated funds, preferably for a long period. Research projects on rare diseases should be made identifiable and traceable within broader national research programs.

Final Report of EUROPLAN I National Conferences

(Area 3, page 38-39)

- "It was generally recommended, as Conference conclusions, that RDs be considered as a priority in medical research in the country and ad hoc national research measures be dedicated to RDs. With the exception of Germany, this conclusion concerned both those countries where traditionally a non-thematic approach is adopted and those countries where the absence of dedicated RD funds results rather from limited resources, lack of funds or lack of political willingness."
- As far as the management of RD research is concerned and its sustainability, interesting proposals concern the establishment of a body to be created at national level which steers and advises on RD research, develops public private partnerships with industry and associations, create close links with centres of expertise and acts as a one-stop shop for all information on RD research and/or potential incubator for enterprises (see, by way of example, the "Foundation for scientific cooperation", supported in France by the Second NP, or the proposed extended role of the Spanish CIBERER, Centre for Biomedical Network Research on RD). A centralised database on research projects and research teams would be also handled at central level. Such a system of central coordination would also favour the establishment of a continuous funding scheme (and not only based on call for proposals)."

(**The Fondation Maladies Rares (France) :** *http://fondation-maladiesrares.org/*

research and related funds?

- Is the creation of a "RD research centre", such as the French "Fondation Maladies Rares", embedded in the healthcare/research system a viable option, acting as a one-stop shop for RD research projects? Please consider possible centralised activities such as:
  - centralised database of research projects on RD;
  - identification of priority and needs in the area of RD research;
  - centralisation of funding sources for RD research projects;
  - continuous funding schemes for RD research projects;
  - incubator for SMEs;
  - promotion of public-private partnerships with industry.

"The creation of the Foundation is a measure delineated in the Research axe of the second French Rare Disease Plan (2011-2014). The Foundation groups France's rare disease research into one cooperative structure that will operate with a sustained source of funding to bring a new synergy to fundamental, clinical and translational research. Founding bodies include the French Association Against the Myopathies - a major-league player in France's rare disease field and organisers of the country's famously successful Telethon; national medical and health research organisation INSERM; the Conference of General Directors of the University Hospitals and the Conference of Presidents of the University. The Foundation will be administrated by a Council composed of representatives from each of the founding member strands and will include experienced researchers and members of academia. Furthermore, the Foundation will benefit from the guidance of a Scientific Committee composed of leading medical specialists and scientists in the field." From OrphaNews: http://www.orpha.net/actor/EuropaNews/2012/120314.html)	
B.3 Sustainability of research programmes on RD	
Council Recommendation on RD Whereas: […] (22) The development of research and healthcare infrastructures in the field of rare diseases requires longlasting projects and therefore an appropriate financial effort to ensure their sustainability in the long term. This effort would notably maximise the synergy with the projects developed under the second community health programme, the seventh framework programme for research and development and the successors of these programmes. **Final Report of EUROPLAN I National Conferences** (Area 3, page 38) - "It was equally stressed in basically all countries that it is crucial to support dedicated RD research programmes with appropriate funding, in order to ensure the longevity of research projects and their sustainability. Dedicated programmes would also help optimise scattered resources by improving knowledge on existing research activities and better coordinating them. - Although the majority of Conferences clearly called for public funding, proposals were made to also consider private-public partnerships. In Bulgaria, it was proposed to create an industry-based fund, earmarking 5% of drugs' marketing	• How to ensure, through appropriate funding mechanisms, structural and long-term sustainability of research projects and research infrastructures in the field of RDs? (*See again the above mentioned Fondation Maladies Rare*) • Are there specific programmes to fund RD research, from basic and translational research? Do they enable long term research by providing the assurance of long-term sustainability of the projects they fund? • Do national measures allow the reporting of research funded at the national level on RD? • How are research programmes assessed? What mechanisms, in particular, do allow for the continuity and reiteration of successful initiatives and projects? • What specific solutions should be devised in respect of **public health and social research**, often neglected yet essential to optimise the provision of patient care and services for patients beyond healthcare? • How are research infrastructures supported at national level? Has the possibility of recurring to EU Structural Funds (notably EDRF) for infrastructural projects been explored? • Consider whether a combination of private and public funding is possible. How to

funds. Similarly, in Italy, a fund is available each year for independent research, which results from the legal requirement upon the pharmaceutical industry to pay their trade association (AIFA) 5% of money committed to their advertising campaigns."	engage private actors to fund RD research? What **public private partnership (PPP)** models are proposed? What type of research initiatives are better supported by PPP e.g. patients' registries? • Are there programmes to involve other private actors, different from the pharmaceutical industry, as for instance bank foundations?
B.4 Needs and priorities for research in the field of RDs	
Council Recommendation on RD 7. Identify needs and priorities for basic, clinical, translational and social research in the field of rare diseases and modes of fostering them, and promote interdisciplinary co-operative approaches to be complementarily addressed through national and Community programmes. **EUROPLAN recommendations** R 3.3 National networks are promoted to foster research on rare diseases. Special attention is given to clinical and translational research in order to facilitate the application of new knowledge into rare disease treatment. Compilation and updating of a directory of teams carrying out research on rare diseases should be endorsed when feasible. **Final Report of EUROPLAN I National Conferences** (Area 3, page 39) - Research on RDs should range from basic to clinical research, with most conferences insisting on how crucial it is to develop further translational research. - Moreover, RD research has to be carried out with a multidisciplinary approach, involving professionals from different backgrounds, as it was pointed out in most Conferences. - Many Conferences (Italy, Denmark, Sweden, Romania, France, Spain, Germany...) highlighted the importance of public health and socio-economic research. Research into quality of life, living conditions, etc. is extremely important not only for public health planning, but also for provision of services which help to provide an answer to the needs of patients in their daily life and to empower them.	• Is an assessment of needs and priorities for basic, clinical and translational research, as well as priorities for social research, been carried out in your country? • How to best prioritise research needs in the country? Not everybody should do everything. How to make active choices aiming to provide good funding to good projects instead that little funding to many projects and not to duplicate efforts? • How to make sure that **translational research** and the development of RD therapeutic solutions are ensured a prominent place in national prioritisation? • How to improve awareness on the need for **research into quality of life, living conditions and social research on RDs** in general? How to ensure that funds are devoted to this type of research?

B.5 Fostering interest and participation of national laboratories and researchers, patients and patient organisations in RD research projects	
Council Recommendation on RD 8. Foster the participation of national researchers in research projects on rare diseases funded at all appropriate levels, including the Community level. **EUROPLAN recommendations** (Par. 56, page 39) "Overall, interdisciplinary approaches to research are necessary to generate new effective therapies for diseases which often affect several organs and or systems. An effective causal therapy is often not available and can only be developed if the disease pathogenesis is understood. This has already been possible for a number of rare diseases. Networking of the different expertise relevant to rare diseases is therefore particularly important and it should be proactively promoted." R 3.2 Specific provisions are included in the National Plans or Strategies to promote appropriate collaborations between Centres of Expertise and/or other structures of the health system and health and research authorities in order to improve knowledge on different aspects of rare diseases. R 3.7 Specific programs are launched for funding and/or recruitment of young scientists on rare diseases research projects. **Final Report of EUROPLAN I National Conferences** (Area 3, page 39-40) - "National Centres of Expertise are important for researchers and patients. A good infrastructure in healthcare where patients meet, gives significant possibilities to research. Currently, a major obstacle for research is the separation between research and care. - The centres should have an independent board that cooperates with patient organisations. Patients are good resources as well, also as mediators to facilitate contacts among their primary care physicians, specialised clinics and researchers. Patient organisations can give strong inputs on questions to be addressed and prioritising them. - Mechanisms could be established to allow 1) researchers to fully integrate within clinical services; and 2) clinicians to devote time to research without compromising care.	• What measures need to be adapted to foster **multi-centre studies** (both national and translational)? • What **national networks** are necessary to support in order to promote RD research especially clinical and translational research? • How to make the link between basic and translational research and **Centres of Expertise**? • What solutions could be devised in Centres of Expertise to "allow 1) researchers to fully integrate within clinical services; and 2) clinicians to devote time to research without compromising care" (from the Final Report EUROPLAN I Conferences)? • What mechanisms need to be put in place to facilitate the set-up of **clinical trials for small populations** run by academics in centres of expertise? • "Overall, interdisciplinary approaches to research are necessary to generate new effective therapies for diseases which often affect several organs and or systems." (EUROPLAN Recommendations). How to best promote **interdisciplinary approaches** to research? • What specific programmes target the recruitment of **young scientists** on RD research? Are specific PhD programs on RDs proposed to students? Are young researchers encouraged to enter the RD field via visible incentives to be foreseen? • How to 'institutionalise' the participation of patients in research, especially in Centres of Expertise? • How to strengthen the exchanges among **patient organisations**? How to promote the direct contact between researchers and patients (e.g. open labs day dedicated to patients and patients organisations)? • What other **collaborative modes** are supported at national level? • Are different model of research collaboration supported for instance "charity networking" or cooperation among non-public non-industry players, such as charities and patient groups? How to support these actors, especially in the translational part of research where they usually lack means to translate excellent

- By establishing translational centres, clinical and basic science could be connected with social sciences and political sciences in order to optimise the provision of both patient care and services which go beyond healthcare."	initial research into therapies?
B.6 RD research infrastructures and registries	
Council Recommendation on RD 5. Consider supporting at all appropriate levels, including the Community level, on the one hand, specific disease information networks and, on the other hand, for epidemiological purposes, registries and databases, whilst being aware of an independent governance. 8. Foster the participation of national researchers in research projects on rare centres of expertise and networks at national and international level. **EUCERD Recommendations on RD Patient Registration and Data Collection** http://www.eucerd.eu/?page_id=13 1. RD patient registries and data collections need to be internationally interoperable as much as possible and the procedures to collect and exchange data need to be harmonised and consistent, to allow pooling of data when it is necessary to reach sufficient statistically significant numbers for clinical research and public health purposes. […] 2. All sources of data should be considered as sources of information for RD registries and data collections, to speed up the acquisition of knowledge and the development of clinical research. […] 2.4 Collection of data on RD should be delineated in the National RD plan/strategy. 2.5 A system to allow the collection of data directly reported by patients should be included along with systems for data reported by clinicians. […] 3. Collected data should be utilised for public health and research purposes. 3.2 RD data collected should, where possible, facilitate clinical and epidemiological research and the monitoring of care provision and therapeutic interventions, including off-label use of approved drugs and existing medications.	• Is there a policy for RD data collection and RD patient registration laid down in the National Plan or Strategy for RD? • What rules do ensure that **quality standards** of registries are consistently high? • What measures do ensure the **interoperability** of different RD registries and the harmonisation of procedures to collect data and thus facilitate pooling of data for research purposes (as well as public health purposes)? • How to stimulate the harmonisation of procedures and technical tools, in particular the development of minimum data sets, for both registries and biorepositories? • How to engage with **international initiatives** such as those promoted by the **IRDiRC** (see below) in favour of harmonisation and interoperability of RD registries and thus promoting the creation and functioning of registries with larger geographical scope? • What initiatives and incentives are or should be in place to encourage researchers and clinicians to actively participate in the collection of data? • What measures could promote the involvement of patients as well as other stakeholders in the design, analysis and governance of RD registries? • What system could ensure that **data directly reported by patients** are included along with data reported by clinicians? • Is the National Plan or Strategy on RD also facilitating **access and sharing of data** to control how data is shared and published in the public domain? • How to motivate the sharing and open access to pre-competitive resources such as databases, biobanks or knowledge bases for the sake of maximising the scarce knowledge existing? • What mechanisms do ensure the **long-term sustainability of RD patient registries** and other RD research infrastructures in your country? (*see also above,*

3.3 RD data collected should, where possible, be used to provide information for multi-centre and multi-national clinical trial feasibility studies. 3.4 Pooling of data across data collections and other resources, including internationally, should be encouraged to reach a critical mass for data analysis. According to the governance/oversight criteria, data should be made accessible to groups with legitimate questions such as researchers and policy/decision makers. 3.5 Access and sharing of data should be defined to control how data is shared and published in the public domain and this should be facilitated through the national RD plan/strategy. 4. Patient registries and data collections should adhere to good practice guidelines in the field. Specific to the current and future specificities of RD registries: 4.1 Involvement of stakeholders such as patients, policymakers, researchers and clinicians (and industry, where appropriate) in the design, analysis and governance of registries is important to address the complexity and scarcity of knowledge on RD. […] 6. Patient registries and data collections should be sustainable for the foreseeable timespan of the registries' utility. 6.1 Local, regional, national and European structures contributing to or overseeing data collection should all be supported financially to carry out this role in a sustainable way so that financial responsibility for registries is shared proportionately between stakeholders, MS and the EC and defined in the appropriate funding programmes. 6.2 Public-private partnerships for RD registries should be considered where applicable as a long-term model for optimisation of resources, sustainability and co-creation of knowledge. 6.3 All registries and data collections should have in place an exit strategy in its work plan, including contingency planning for the data in the event that the registry is terminated. There should also be a procedure outlined for succession planning for registry continuation. **EUROPLAN Recommendations** R 3.5 Specific technological platforms and infrastructures for rare disease research, including clinical research, are established and supported and the creation of public-private partnership is explored.	*B.3*) In particular: ○ Do RD patient registries usually envisage exit strategies in their work plans? What provisions are necessary to make sure that this occurs on a regular basis? ○ How do different stakeholders share the financial responsibilities for the long-term sustainability of research infrastructure, such as RD patient registries? ○ Are public-private partnerships considered as an option and if yes, how do they work and how are they regulated? • Please explore the feasibility of a common central resource or platform for creating or reconfiguring registries and describing the content of existing registries and databases with the potential to collect data on all RD. • Discussion are ongoing on the creation of a **European Platform for Rare Disease Registration**, supported by the European Commission and aimed to provide common services and tools for the existing (and future) rare diseases registries in the European Union. What contribution you country could provide? How a European Platform may help optimise national resources devoted to rare disease regisitration?

Final Report of EUROPLAN I Conferences (Area 3, page 40-41) - "The creation of patient registries was consistently supported by EUROPLAN Conferences. It should be a primary objective and a basic requirement to develop RD research. Moreover, it is necessary that such registries be of high level quality: their structure needs to be clarified and their funding in the long-term ensured. - Clearer definition of rules and regulations concerning the storage of data, quality standards to ensure trustworthiness, the development of uniform data structures and software platforms were recommendations which emerged in more than one Conference. - To complement the general recommendation that research and care should be better coupled together, it was proposed to introduce the obligation to document the treatment progress and to register such data in clinical registries. - Ideas such as the creation of a "registry of registries" (Germany) or an "epidemiological platform" (France) were also considered carefully. Such centrally-managed infrastructures would describe the contents of existing databases, registries and cohorts, whether private or public.	
B.7 EU and international collaboration on research on RD	
Council Recommendation on RD Whereas: […] (7) Rare diseases were one of the priorities of the Community's sixth framework programme for research and development (6) and continue to be a priority for action in its seventh framework programme for research and development (7), as developing new diagnostics and treatments for rare disorders, as well as performing epidemiological research on those disorders, require multi-country approaches in order to increase the number of patients for each study. (13) […] ERNs could also serve as research and knowledge centres, treating patients from other Member States and ensuring the availability of subsequent treatment facilities where necessary. 8. Foster the participation of national researchers in research projects on rare	• How to foster and support the participation of national researchers and laboratories, patients and patients organisations in EU-wide projects? • Does your country plan to join **E-RARE** (for those who are not still partners) as the key programme supporting collaborative RD research at European level? • Does your national research agency support the International Research consortium for Rare Disease Research (**IRDiRC**)? • What support is provided for collaborative research on RD through **European Reference Networks** (**ERNs**)? What national legislative measures do need to be put in place in order to support the development of ERNs as a catalyser of supranational collaborative RD research? (see also Theme 4)?

diseases funded at all appropriate levels, including the Community level. 10. Facilitate, together with the Commission, the development of research cooperation with third countries active in research on rare diseases and more generally with regard to the exchange of information and the sharing of expertise. **EUROPLAN Recommendations** R 3.4 Proper initiatives are developed to foster participation in cooperative international research initiatives on rare diseases, including the EU framework program and E-RARE. The national funding of these initiatives should be increased considerably. R 3.6 Multi-centre national and trans-national studies are promoted, in order to reach a critical mass of patients for clinical trials and to exploit international expertise. **Cross Border Heath Care Directive – DIRECTIVE 2011/24/EU of 9 March 2011 on the application of patients' rights in cross-border healthcare** **http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2011:088:0045:0065:EN:PDF** Article 12 - European Reference Networks 2. European reference networks shall have at least three of the following objectives: […] (e) to reinforce research, epidemiological surveillance like registries and provide training for health professionals; 4. For the purposes of paragraph 1, the Commission shall: (a) adopt a list of specific criteria and conditions that the European reference networks must fulfil and the conditions and criteria required from healthcare providers wishing to join the European reference network. These criteria and conditions shall ensure, inter alia, that European reference networks: […] (iv) make a contribution to research; (vi) collaborate closely with other centres of expertise and networks at national and international level.	

C. Background documents

C.1 Council Recommendation of 8 June 2009 on an action in the field of rare diseases (2009/C 151/02)

Whereas:
[…]

(7) Rare diseases were one of the priorities of the Community's sixth framework programme for research and development (6) and continue to be a priority for action in its seventh framework programme for research and development (7), as developing new diagnostics and treatments for rare disorders, as well as performing epidemiological research on those disorders, require multi-country approaches in order to increase the number of patients for each study.

(9) In order to improve the coordination and coherence of national, regional and local initiatives addressing rare diseases and cooperation between research centres, relevant national actions in the field of rare diseases could be integrated into plans or strategies for rare diseases.

(13) […] ERNs could also serve as research and knowledge centres, treating patients from other Member States and ensuring the availability of subsequent treatment facilities where necessary.

(22) The development of research and healthcare infrastructures in the field of rare diseases requires longlasting projects and therefore an appropriate financial effort to ensure their sustainability in the long term. This effort would notably maximise the synergy with the projects developed under the second community health programme, the seventh framework programme for research and development and the successors of these programmes.

(The Council of the EU) hereby recommends that Member States:
[…]

II. ADEQUATE DEFINITION, CODIFICATION AND INVENTORYING OF RARE DISEASES

5. Consider supporting at all appropriate levels, including the Community level, on the one hand, specific disease information networks and, on the other hand, for epidemiological purposes, registries and databases, whilst being aware of an independent governance.

III. RESEARCH ON RARE DISEASES

6. Identify ongoing research and research resources in the national and Community frameworks in order to establish the state of the art, assess the research landscape in the area of rare diseases, and improve the coordination of Community, national and regional programmes for rare diseases research.

7. Identify needs and priorities for basic, clinical, translational and social research in the field of rare diseases and modes of fostering them, and promote interdisciplinary co-operative approaches to be complementarily addressed through national and Community programmes.

8. Foster the participation of national researchers in research projects on rare diseases funded at all appropriate levels, including the Community level.

9. Include in their plans or strategies provisions aimed at fostering research in the field of rare diseases.

10. Facilitate, together with the Commission, the development of research cooperation with third countries active in research on rare diseases and more generally with regard to the exchange of information and the sharing of expertise."

http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2009:151:0007:0010:EN:PDF

C.2 EUROPLAN Recommendations

EUROPLAN recommendations on Area 2: Adequate definition, coding and inventorying of rare diseases

R 2.8 International, national and regional registries for specific rare diseases or groups of rare diseases are promoted and supported for research and public health purposes, including those held by academic researchers.

2.10 Participation of existing national registries in European/International registries is fostered.

R 2.11 Instruments are identified for combining EU and national funding for registries.

EUROPLAN recommendations on Area 3: Research on rare diseases

R 3.1 Dedicated national research programs for rare diseases (basic, translational, clinical, public health and social research) are established and supported with dedicated funds, preferably for a long period. Research projects on rare diseases should be made identifiable and traceable within broader national research programs.

R 3.2 Specific provisions are included in the National Plans or Strategies to promote appropriate collaborations between Centres of Expertise and/or other structures of the health system and health and research authorities in order to improve knowledge on different aspects of rare diseases.

R 3.3 National networks are promoted to foster research on rare diseases. Special attention is given to clinical and translational research in order to facilitate the application of new knowledge into rare disease treatment. Compilation and updating of a directory of teams carrying out research on rare diseases should be endorsed when feasible.

R 3.4 Proper initiatives are developed to foster participation in cooperative international research initiatives on rare diseases, including the EU framework program and E-RARE. The national funding of these initiatives should be increased considerably.

R 3.5 Specific technological platforms and infrastructures for rare disease research, including clinical research, are established and supported and the creation of public-private partnership is explored.

R 3.6 Multi-centre national and trans-national studies are promoted, in order to reach a critical mass of patients for clinical trials and to exploit international expertise.

R 3.7 Specific programs are launched for funding and/or recruitment of young scientists on rare diseases research projects.

R 3.8 The assessment of already existing drugs in new combinations and in new indications is supported since it may be a cost-effective way to improve treatment for patients with rare diseases.

http://www.europlanproject.eu/_newsite_986987/_down/results/2008-2011_2.EUROPLANGuidance.pdf

C.3 EUCERD Core Recommendations on Rare Disease Patient Data Registration and Data Collection

http://www.eucerd.eu/wp-content/uploads/2013/06/EUCERD_Recommendations_RDRegistryDataCollection_adopted.pdf

[Background to the Recommendations…]

1. RD patient registries and data collections need to be internationally interoperable as much as possible and the procedures to collect and exchange data need to be harmonised and consistent, to allow pooling of data when it is necessary to reach sufficient statistically significant numbers for clinical research and public health purposes.

1.1 They should use international standards and nomenclature to code the tentative or final RD diagnosis. Either the OMIM code or the Orpha codes are recommended alongside any other coding system in operation in the MS health systems, such as ICD and SNOMED-CT, with a view to establishing a common semantic approach.

1.2 There should be adoption of a minimum common data set across RD that registries should collect, in collaboration with global initiatives, to allow the establishment of national and/or European RD population registries, which have the potential to collect data on all RD patients.

1.3 A minimum common data set should be defined, and supported with a semantic approach and Standard Operating Procedures. Interoperability (via means of mapping) of registry specific data sets towards this common data set should enable comparison across all RD and internationally.

1.4 For disease-specific registries, appropriate core data sets specific to the diseases or disease groups should be adopted. In the future, such disease-specific registries could fall under the remit of RD ERNs. Every effort should be made to incorporate current disease-specific registry initiatives where quality can be assured.

1.5 To avoid duplication and to support Cross-Border Healthcare, the possible benefits of using a global or European RD patient identifier (possibly incorporating the current health identifier) should be investigated to provide a way to link information, samples and research data, and to ensure a quick and secure means of data sharing and protection.

1.6 For countries with regional organisation of healthcare, where multiple registries exist, overlap and duplication between the regional and national registries, should be avoided.

2. All sources of data should be considered as sources of information for RD registries and data collections, to speed up the acquisition of knowledge and the development of clinical research.

2.1 As with all registries, registries for RD should establish clear purposes and objectives of the data collection: the type of data collection should be suited to the need, and the data captured should be appropriate to the proposed use of the data, both in terms of scope and level of detail.

2.2 RD Centres of Expertise, where they exist, should contribute to a registry(ies). Other experts in the field should also contribute to the registry(ies).

2.3 (Electronic) health records from any sector of healthcare delivery are a valuable source for core data collection. Automatic data acquisition from these sources should be envisaged to ease the data collection process.

2.4 Collection of data on RD should be delineated in the National RD plan/strategy.

2.5 A system to allow the collection of data directly reported by patients should be included along with systems for data reported by clinicians.

3. Collected data should be utilised for public health and research purposes.

3.1 RD data collected should be used to support policy development at local, regional, national and international level.

3.2 RD data collected should, where possible, facilitate clinical and epidemiological research and the monitoring of care provision and therapeutic interventions, including off-label use of approved drugs and existing medications.

3.3 RD data collected should, where possible, be used to provide information for multi-centre and multi-national clinical trial feasibility studies.

3.4 Pooling of data across data collections and other resources, including internationally, should be encouraged to reach a critical mass for data analysis. According to the governance/oversight criteria, data should be made accessible to groups with legitimate questions such as researchers and policy/decision makers.

3.5 Access and sharing of data should be defined to control how data is shared and published in the public domain and this should be facilitated through the national RD plan/strategy.

4. Patient registries and data collections should adhere to good practice guidelines in the field.

Specific to the current and future specificities of RD registries:

4.1 Involvement of stakeholders such as patients, policymakers, researchers and clinicians (and industry, where appropriate) in the design, analysis and governance of registries is important to address the complexity and scarcity of knowledge on RD.

4.2 Representatives of all stakeholders should be invited to provide best possible expert support through an advisory board or committee to ensure appropriate information flow and knowledge exchange into and from the registry, and they should define a sustainability and exit strategy for the registry. Where appropriate, representatives from industry should also provide input.

4.3 This multi-stakeholder model for registry governance should apply not only at a national level but also at the European level and/or pan-European Platform repository of RD registries.

4.4 The process for consenting patients for participation in a RD registry should take into account the wider European and international context to ensure that patients are well informed of this dimension and the consent process is in line with the legal requirements at European and International level.

4.5 Patients already in a RD registry may be required to go through an additional consenting step to ensure compatibility with such systems.

4.6 RD registries should have a system to provide regular feedback to registered patients and their clinical teams, recognising their specific role in the success of registries in this field.

5. Existing and future patient registries and data collections should be adaptable to serve regulatory purposes, where required.

5.1 For the monitoring of therapeutic interventions for RD, a strategy between industry, academia and regulators should be agreed to ensure that data collection is expanded as necessary, and in time embedded in disease-specific registries to serve, for example, the requirements for post-marketing surveillance, and to support development of new therapies. Data access needs to be compliant with agreed guidelines established by the registry.

5.2 As quality assurance is crucial, it is a priority for existing RD registries to explore their capacity to adapt to collect data for regulatory purposes.

5.3 There should be an early dialogue on the type of registry required (and what data is required for regulatory purposes), and/or whether a registry exists for the condition targeted, with all stakeholders, in order to optimise the registration of patients and the generation of knowledge for RD for which a therapeutic intervention is being developed. Collection of data regarding off-label use of approved drugs and existing medications should be encouraged.

6. Patient registries and data collections should be sustainable for the foreseeable timespan of the registries' utility.

6.1 Local, regional, national and European structures contributing to or overseeing data collection should all be supported financially to carry out this role in a sustainable way so that financial responsibility for registries is shared proportionately between stakeholders, MS and the EC and defined in the appropriate funding programmes.

6.2 Public-private partnerships for RD registries should be considered where applicable as a long-term model for optimisation of resources, sustainability and co-creation of knowledge.

6.3 All registries and data collections should have in place an exit strategy in its work plan, including contingency planning for the data in the event that the registry is terminated. There should also be a procedure outlined for succession planning for registry continuation.

C.4 EUCERD Recommendations on Quality Criteria for Centres of Expertise for Rare Diseases in Member States

http://www.eucerd.eu/?post_type=document&p=1224

Recommendations relevant to research:

Mission and scope of centres of expertise (CEs) for rare diseases (RD) in Member States (MS)

[…]

13. CEs contribute to research, to improve the understanding of the disease and to optimise diagnosis, care and treatment, including the clinical evaluation of long-term effects of new treatments.

Criteria for designation of CEs for RD in MS

[…]

22. Contribution to state-of-the-art research.
23. Capacity to participate in data collection for clinical research and public health purposes.
24. Capacity to participate in clinical trials, if applicable.

The European dimension of CEs

[…]

42. Networking of CEs is a key element of their contribution to patient diagnosis and care, to ensure that expertise travels rather than patients themselves when appropriate; exchange of data, biological samples, radiological images, other diagnostic materials, and e-tools for tele-expertise are promoted.

C.5 EUCERD Core Indicators

http://www.eucerd.eu/wp-content/uploads/2013/06/EUCERD_Recommendations_Indicators_adopted.pdf

NB: Out of the 21 EUCERD core indicators, please find below selected indicators for this specific theme.

10. Existence of a national policy on rare disease clinical practice guideline development and implementation
11. Type of classification/coding used by the health care system
12. Existence of a national policy on registries or data collection on RD
13. Existence of RD research programmes and/or projects in the country
14. Participation in European and international research initiatives
20. Specific public funds allocated for RD research
21. Public funds specifically allocated for RD research actions/projects per year since the plan

Core Indicators – Definitions and associated answers

INDICATOR	**AREA OF COUNCIL REC.** (2009/ C151/02)	**INDICATOR DESCRIPTION**	**TYPE OF INDICATOR**	***SHORT* ANSWER**	***DETAILED* ANSWER** *(multiple answers are possible, if needed)*
CONTENT INDICATORS					
KNOWLEDGE, CLASSIFICATION/CODING, REGISTRIES AND RESEARCH					
10. Existence of a national policy for developing ,adapting and implementing clinical practice guidelines	2	The indicator checks the existence of a policy for developing, adapting and implementing clinical practice guidelines (CPGs) for diseases/groups of diseases *("Adapting" refers to adaption of supra-nationally based clinical guidelines to the local context)*.The cumulative production of protocols and clinical guidelines is an instrument for equity of access to care by rare disease patients across the European Union.	Process	YES	**YES**, a policy exists for developing CPGs
					YES, a policy exists for adapting CPGs
					YES, a policy exists for implementing CPGs
				NO	
11. Type of classification/coding used by the health care system	2	The adoption and the daily use of an internationally recognised, comprehensive, health care codification system is important for RD management and would encourage the harmonisation of disease nomenclature worldwide. This enables budgetary and management decisions to have a more	Process	*Type of coding system used*	ICD-9
					ICD-10
					OMIM

		solid basis and would constitute one relevant tool for Health Technology Assessment.			SNOMED
					MESH
					ICD-O
					Others
				ORPHA Code is used in addition to national coding system	YES
					NO
12. Existence of a national policy on registry and data collection on RD	2 & 3	This indicator collects information on Member States' support, at all appropriate levels, to rare diseases registries and databases for epidemiological, public health and research purposes, as well as on the role ensured by public authorities for the coordination and sustainability of data collection.	Process	YES	**YES**, for national/centralised registry and data collection
					YES, for regional registry and data collection
				NO	
13. Existence of a RD research programmes/projects in the Country	3	This indicator aims to describe the status of RD research in the country, most notably whether a dedicated programme exists, or whether RD research is carried out by individual projects within the general research programme.	Process	YES	**YES**, specific research PROGRAMME
					YES, specific PROJECTS for RD within general research programme
				NO	
14. Participation in European and international research initiatives	3	Participation of national research agencies in international research initiatives (such as E-RARE – www.e-rare.eu, and IRDiRC – www.irdirc.org) is important to foster research on rare diseases a global level, by pooling resources and coordinating national research programmes to overcome the fragmentation of research on RD.	Process	YES	**YES**, E-RARE
FINANCIAL SUPPORT INDICATORS *(IMPLEMENTATION OF THE PLAN/STRATEGY)*					
20. Specific public funds allocated for RD research	3	This indicator aims to identify the policy decision(s) to allocate a portion of the national research budget specifically to RD research.	Process	YES	
				In progress /in development	
				NO	

21. Public funds specifically allocated for RD research actions/projects per year since the plan started	3	This indicator verifies the total amount of public funds (in EUR) allocated to RD research projects or programmes	Outcomes	*Number*	Value Value available partially: only for funds allocated exclusively to National Plan (N/A for funds allocated in the general budget) N/A: it is incorporated in the general research funds

C.6 EUROPLAN Indicators

http://www.europlanproject.eu/_newsite_986989/Resources/docs/2008-2011_3.EuroplanIndicators.pdf

Area to be explored	Aims	Actions		Indicators	Type of indicator	Answers
Research on Rare Diseases	Support research programmes for RD	Building a research programmes for RD	**3.1.**	**Existing a RD National/Regional research programmes**	Process	• *Specific research programme for RD* • *RD research programme included in the general research programme as a priority* • *Not RD research programme*
			3.2.	**RD research programme monitoring**	Process	• *Not existing, not clearly stated* • *Existing, clearly stated, partly implemented* • *Existing, clearly stated and substantially implemented*
			3.3.	**Number of RD research projects approved by year (if possible yearly starting the year before plan commencement)**	Outcomes	*Percentage of RD projects by the total of projects approved*
			3.4.	**Clinical trials funded by public bodies**	Outcomes	• *Yes, action implemented* • *No actions have been taken* • *Under discussion*
			3.5.	**E-RARE joining**	Process	• *On going* • *In process* • *not considered*

			3.6.	**Including public health and social research, in the field of rare diseases**	Process	• *Yes* • *No* • *Under discussion*
			3.7.	**Research platforms and other infrastructures are also funded by the research programme**	Process	• *Yes* • *No* • *Under discussion*
	Recruitment of young scientists	Existence of national policy in support of the recruitment of young researchers/scientists specifically for rare diseases	**3.8.**	**Number of young scientists recruited every year to work specifically on rare diseases**	Process	• *Number great equal zero*
	Ensure funds for the research programme	Allocate funds for the RD research programme	**3.9.**	**There are specific public funds allocated for RD research**	Process	• *Yes* • *No* • *Under discussion*
			3.10.	**Funds specifically allocated for RD research actions/projects per year since the plan started**	Outcomes	• *Million Euros allocated to RD research projects* • *Percentage of funds allocated for RD projects by the total funds allocated for projects*

C.7 REPORT ON RARE DISEASE RESEARCH, ITS DETERMINANTS IN EUROPE AND THE WAY FORWARD

S. Aymé, V. Hivert (eds.), "Report on rare disease research, its determinants in Europe and the way forward", May 2011.

Full report: ***http://asso.orpha.net/RDPlatform/upload/file/RDPlatform_final_report.pdf***

[…]

Final recommendation and proposals:

4. WHAT COULD BE PROPOSED – ISSUES TO HIGHLIGHT FOR THE FUTURE AND SUGGESTIONS

4.1. Funding of European collaboration and continuity in action

Networks are essential tools in the field of rare diseases for knowledge and data-sharing. Establishing European or global networks of all stakeholders involved in the care, treatment and research of rare diseases is the only way to address healthcare issues. These networks are the only way to achieve the critical mass which is necessary, in terms of resources and expertise, to successfully treat rare diseases. Most EC-funded research projects and networks on rare diseases include as one of their objectives the establishment of international patient registries. Consistent budgets are dedicated to the creation of these databases, whereas no specific instrument is available to maintain them as research tools for future use.

The main issue brought up during the discussions is related to the sustainability of the structures which have already been created thanks to the funding of research projects and networks, such as patient registries, but also biobanks, and technological platforms. Participants at the RDPlatform expert workshop of experts (3 December 2009) proposed potential solutions for the sustainability of these kind of structures once EC funding is over. The budget for maintaining the infrastructure is relatively small in comparison to the budget which is necessary for the initial construction of the network so the EC could be involved in the financing of the coordination and maintenance of these structures though a specific call for proposals. Two possibilities were proposed: 1) The E-RARE instrument could take care of including these kinds of calls in their programme, and it was proposed that lobbying should be carried out so that developing national plans for rare diseases include national participation in the E-Rare project as an efficient means to fund RD research; 2) A new instrument could be created at DG Research to allow for the transposition of a project from a research project to a tool for public health. One other proposal was that some databases could be allocated to learned societies.

4.2. Incentives for clinical trials in the US which do not exist in Europe

The aim of the orphan product development (OPD) grant program is to assist sponsors in defraying the costs of clinical trials incurred in the development of drugs, medical devices, and medical foods for rare diseases and conditions. The program has an annual budget of approximately $ 14 million. Domestic or foreign, public or private, non-profit or for-profit entities (excluding those engaging in lobbying activities), state and local units of government, and non-HHS federal agencies may apply. To be eligible, the clinical investigation of the drug or the device must be conducted under an active investigational new drug application or investigational device exemption, respectively. Applicants may apply for OPD grants electronically via http://www.grants.gov/. Beginning in the 2009 fiscal year, funding levels for these grants will be up to $ 200 000 per year for up to three years for Phase 1 clinical investigation and up to $ 400 000 per year for up to four years for Phase 2 or 3 clinical investigation. Between 2000 and 2006, OOPD received an average of 69 grant applications annually. Of these, about 17 were funded each year. The majority of grantees (76%) were affiliated with universities and medical centres. Approximately 19% of grants were awarded to pharmaceutical companies. A quarter (24%) of grants was for oncologic drugs, 14% for metabolic disorders, and less than 10% for each of a number of other disease categories. To date, OPD grants have supported clinical development of 41 approved orphan drugs and medical devices.

4.3. Expanding knowledge and databases

There is a lot of data that still need to be collected, about prevalence, natural history, biological mechanisms, etc., in order to improve the R&D area. But apart from the generation and collection of new data, some existing data may be compiled and used. For example, the FDA recently proposed the "rare disease repurposing database": the aim is repurpose previously approved products which have already followed the R&D process . The same approach may be used in Europe with data concerning off-label use.

The most accurate tool for data collection would be international registries, but there is often some heterogeneity in the quality of the different sources of data and sometimes one has to face different types of regulations. New approaches would allow for optimal use of heterogeneous sources of data. In this vein, Concept Web Alliance is addressing the challenge associated with the production of an ever increasing amount of data from different types of sources. The main features of this challenge include storage, interoperability and analysis of such massive and disparate data sets.

Such an approach includes the comparison of nomenclatures, ontologisation of concepts, mechanistic approaches, and data mining of patient data from hospitals or from health insurance records.

Some ideas of application have been provided:

• Improving phenotyping: Devise an intelligent web-based tool, the PhenoTyper, that helps people make an adequate, and for others useful, description of the phenotype of the patient. A phenotype description is often a weak part of data available from a patient. Although this is partly the fault of the person creating the description, it certainly is also caused by the fact that proper tools to help this person are not available. Related to this it is often difficult to determine whether some aspects of a phenotype were not present or not checked. The PhenoTyper tool should help to use proper terminology (ontology) during phenotyping, registering any aspect that was checked (or not checked) and automated reporting. Pictures could be shown as examples and to clarify choices available. Example: Question 1-date of visit; Question 2-gender of the patient; Question 3-age of the patient; Question 4- complaints (age at onset). At this point the intelligent software comes in suggesting things to check/questions to ask based on the observations given up to that point. A very simple example; when the complaints include "difficulty climbing stairs", check Gower's sign, …, measure CK-level.

• Repository for standardised molecular phenotyping

4.4. International initiative to be launched

Europe is not the appropriate level for collaboration. An international initiative is required as increasing the number of therapeutic and care options for RD patients requires a better knowledge of pathophysiology and natural history of the RD, so as to help identify potential therapeutic targets, validate biomarkers and define appropriate surrogate end-points to adequately evaluate treatments and therapies. In order to translate research results into the marketing of orphan drugs, it is important that meaningful, validated data are collected and shared internationally. Furthermore, it is essential to strengthen the links between academia and industry, so that industry better capitalises on strong academic research results to translate these into new diagnostic tools and therapies. Patients have an important role to play in this process.

For rare disease research, coordination of efforts is the key to success in order to maximise scarce resources. Worldwide sharing of information, data and samples to boost research is currently hampered by the absence of an exhaustive RD classification, standard terms of reference and common ontologies, as well as harmonised regulatory requirements. Duplication of research efforts must also be avoided, and links between teams working on similar issues must be created.

An International Rare Diseases Research Consortium was recently announced by the EU and by the US. It will stimulate and coordinate basic and clinical research, by promoting the links between existing resources, fostering the molecular and clinical characterisation of RD and encouraging translational/preclinical and clinical research. Priorities for such an international endeavour are: the elaboration of standard terminologies and common ontologies with a view to an adequate classification of diseases; the development of predictive, validated in vitro and in vivo animal models; the identification and validation of biomarkers and surrogate end-points; and the development of new diagnostics and therapies.

4.5. Points for action

4.5.1. On funding processes

• Although there are well-identified sources of funding, both at the EU and national levels, and a clear determination of the European Commission as well as of some countries to support rare disease research, the various initiatives are still not coordinated. The relationships and dialogue between the different Funding Agencies at EC and national level is strongly encouraged, in order to provide a coherent view of the funding opportunities to potential applicants.

• The conclusions from the discussion among experts were that national funding should better aim at supporting emerging projects. E-rare funding (national funding for teams participating in a joint European project) is appropriate to start collaboration at EU level, when EC funding is more for mature projects between partners already involved in joint activities.

• EC support is crucial for networking between experts, organization of consensus meetings, sustainable infrastructures and common tools such as disease registries.

• Extension of funding for already funded projects and avoidance of fractionated funding also have to be taken into consideration.

• National plans have to be designed keeping in mind the field of research and allowing the reporting of funded medical domains at the national level.

• In the process of grant attribution, to be labelled as a project for "rare diseases" may have quite a negative impact compared to projects on common diseases. But the field of rare diseases is a pioneer field in terms of research and deserves to be allowed to live its own life without been systematically assessed in the same way as the other fields. This is why the International Research Initiative is so welcome.

• An International initiative has to be encouraged to allow for a more global collaboration.

4.5.2. To address the specificities of research in the field of rare diseases

• All stakeholders agree that it is crucial to avoid duplicating efforts: therefore it is important to share resources and data, and to establish as much as possible open-access precompetitive platforms, such as databases, knowledge bases, biobanks or collections of animal models.

• Emphasis has to be put on funding projects aimed at elucidating the pathophysiological mechanisms of rare diseases, in terms of genes, gene-environment interactions and cell signalling.

• This field remains of high interest for Industry and interest will increase with the implementation of new technologies such as next generation sequencing. One of the main bottlenecks to resolve for now is to allocate resources to epidemiological research in order to establish prevalence of these diseases in a more accurate manner.

4.5.3. To make the most of data repositories and information technologies

• Development of repositories of data is a major aspect of current changes in the field of rare diseases; the range of applications is wide from exome studies to diseases registries. Attention has to be paid to the harmonisation and homogenisation of practices.

• Initiatives and incentives have to bring clinicians to actively participate in the collection of data. Then guidelines and templates have to be established to enable data collection from different sources.

• Several aspects have to be explored such as repository of the questionnaires, data format, governance rules, agreement, quality assessment by EUCERD for example; in other words, the full package of the registry toolkit.

4.5.4. To ensure that patients and families will benefit from research outcomes

• We recommend that the international efforts be directed toward the identification of clear, specific genotypic and phenotypic criteria for the diagnosis of all diseases, disorders or conditions, whatever their cause, and that these criteria should be available to clinicians across clinical specialties and national healthcare systems, together with the associated resources necessary to operationalise these in everyday clinical practice to secure their application, and that systems be in place to enable the data generated to lead to improvement in the quality and quantity of life of patients and families with rare diseases.

• We recommend that the necessary collaboration between stakeholders across countries and across disciplines be made possible so as to ensure optimal development of new therapies where and when possible. Cross-border regulatory hurdles should be addressed and public-private partnerships for precompetitive resources should be encouraged.