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RARE-Bestpractices: a platform for sharing best practices for the management of rare diseases

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ABSTRACT

Over the last decade the European Union (EU) has been coordinating actions addressing various aspects of rare diseases and has funded several cross-border research projects. Recently the EU has initiated the biggest rare disease international collaborative effort by launching the International Rare Diseases Research Consortium (IRDiRC).

RARE-Bestpractices is one of the more than 100 collaborative research projects on rare diseases funded under the Seventh Framework Programme for Research and Technological Development (FP7/2007-2013) [1].

As a wide, open and inclusive network, RARE-Bestpractices will build on the knowledge of the experts in rare disease research area and experts in guideline development and health technology assessment area, brought together, for the first time, from academic institutions, agencies, organizations, patient advocacy groups, governmental bodies.

The project aims at building a platform to collect and exchange information on best practices for the management of rare diseases; to identify relevant research needs; to promote the development of high quality guidelines; and to contribute in making patients, health professionals and policy makers "informed guideline users". Besides, RARE-Bestpractices will intend to define the extent to which conclusions from cost-effectiveness analyses for pharmaceuticals are accounted for and implemented in guidelines across a range of countries.

KEYWORDS

rare diseases, practice guidelines as topic, orphan drug production

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WWW.RAREBESTPRACTICES.EU

BACKGROUND

Rare diseases are characterized by a low prevalence in the population although they are not actually rare since in aggregate approximately afflict millions of people of all ages in European countries and globally. In addition they are extremely diverse, as regard origin, severity and organ involved, with a high phenotypic variability within the same disease [2,3].

Despite rare diseases are highly diverse, the obstacles encountered by all countries in delivering the best quality of evidence based care and treatment to the patients affected are common. These obstacles include difficulties in attracting funding and commitment for basic and clinical research and in translating basic science discoveries into appropriate clinical studies that will affect health care practice and health care systems [4,5]. In addition knowledge creation has suffered from a disease-specific approach and a lack of coordination of research initiatives.

To respond to these challenges the European Union has promoted actions to improve research and health services for rare disease patients in European member states [6,7,8,9,10]. In essence these actions has supported innovative strategies to combine effort in sharing resources and infrastructures and making an efficient use of the knowledge available on rare diseases.

THE PROJECT

RARE-Bestpractices project intends to respond to the need of what has been defined a "rare diseases knowledge common" [11] by developing a comprehensive system of publicly-accessible resources to facilitating communication and cooperation in the field of guidelines development, health technology assessment activities, and horizon scanning procedures.

RARE-Bestpractices addresses critical international challenges, such as the appropriate ways for timely translating clinical research results into benefits for rare disease patients, by offering high quality information to health professionals, to patients and their families. It also aims at promoting and supporting a consistent level of healthcare services in European countries.

The project is funded by the Seventh Framework Programme (FP7/2007-2013) of the European Union and will last four years (2013-2016). The National Centre for Rare Diseases (CNMR) of the Istituto Superiore di Sanità acts as a coordinator, bringing together a team of highly qualified experts in the area of rare disease management and epidemiology, guidelines, systematic reviews, health technology assessments, horizon scanning, and health policies coming from 9 countries and 15 organizations across Europe (*Table 1*). The consortium participants are assisted in their work by an external Advisory Board which is composed of experts from major organizations in the field of rare diseases and guideline development.

Table 1. Project participants

Italy	Istituto Superiore di Sanità (Coordinator) Consiglio Nazionale delle Ricerche Associazione per la Ricerca sull'Efficacia dell' Assistenza Sanitaria Centro Cochrane Italiano
Belgium	The European Academy of Paediatrics
Bulgaria	Bulgarian Association for Promotion of Education and Science
France	EURORDIS, European Organisation for Rare Diseases
Germany	University of Freiburg
Spain	Fundación Canaria de Investigación y Salud Institute of Rare Diseases Research, Instituto de Salud Carlos III
Sweden	Karolinska Institutet
The Netherlands	Universiteit Maastricht
United Kingdom	Healthcare Improvement Scotland Jamarau London School of Economics and Political Science University of Newcastle Upon Tyne

Specific project objectives are the followings:

• reach consensus on the methodology to develop guidelines on rare diseases

• build a comprehensive public database of trustworthy guidelines to help professionals, patients, policy makers with the best and most up to date information on rare diseases

• build a comprehensive public database of research recommendations to identify and prioritize rare disease research needs

• define to what extent conclusions from cost-effectiveness analyses for pharmaceuticals are accounted for and implemented in best practice guidelines across a range of countries

• set up training activities targeted at key stakeholders to spread expertise and knowledge in the field of guidelines on rare diseases

• support IRDiRC (International Rare Diseases Research Consortium, www.irdirc.eu) activities as regards both the translation of research results into patient oriented strategies and the identification of research needs.

WORK PLAN

The project has been organized into eight work packages (WP) to allow an efficient coordination of the project activities.

WP3, WP4 and WP5 include the core research activities. They are responsible for setting the quality standards for the development of rare disease guidelines (WP3), for collecting existing guidelines and research recommendations on rare diseases (WP4), for evaluating orphan drug appraisals in a range of countries to map out existing processes and best practices (WP5).

The external communication of the project results and the interaction with other projects/networks/organizations are managed by WP6, which is also responsible for the publication of a periodic science journal. A dedicated WP (WP 7) is working to establish collaboration with the IRDiRC.

WP2 is in charge of designing a flexible technical infrastructure which includes the project web site (www.rarebestpractices.eu), two databases (populated by WP4), and the web community, to support the project activities and the interaction among consortium participants and external stakeholders.

The transversal WP1 (coordination) and WP8 (management) deal with ensuring a smooth execution of project activities. WP1 is also responsible for the organization of the training courses.

EXPECTED RESULTS

A transparent and rigorous methodology for the development of guidelines on rare diseases will be defined. Two brainstorming workshops have been foreseen (in Rome and Freiburg) with the aim of identifying issues specific to the development of recommendations for rare diseases and exploring how GRADE[1] meets such issues. GRADE is a widely adopted approach to synthesizing and presenting evidence, to grading evidence and to making recommendations in health care. A further workshop will be organized to discuss on aspects of the guideline production process not considered by GRADE. In addition to the consortium participants, patient representatives, invited experts in the field and external advisors (e.g. the GRADE working group) are particularly involved in the process. The agreed methodology will be applied and tested by developing a real guideline. Any criticisms will be discussed among partners to improve the methodology.

On the basis of the agreed methodology, training activities will be organised to promote the development of high quality guidelines for rare diseases and their use across Europe. Such initiatives will be targeted to key stakeholders, primarily guidelines developers of Centres of Expertise and European Reference Networks. A plan will be discussed among partners to define aspects such as training format, skills and expertise to involve in running the courses (to be sought within and outside the network), and methods to assess the training value.

Finding updated high quality guidelines on rare diseases is not simple. Currently existing databases and websites often include very heterogeneous documents. This is the consideration leading to the idea of creating a database which will make accessible a collection of rare disease guidelines including an evaluation judgment about quality in development for each item. The aim is to provide health professionals, patients and their families, and policy makers with high quality and up to date information about the management of rare diseases.

A second specific database will collect rare disease research recommendations, i.e. unanswered research questions that might emerge during the guideline or health technology assessment development. Reflecting the research needs, they may be crucial in orienting the research agenda. Mechanisms to prioritize research recommendations will be identified and applied within the database to promote future research. Partners and key stakeholders will be involved to inform the collection development criteria for both databases trough a preliminary information needs analysis.

In the mainstream debate about the appropriate processes to determine the value for money of new technologies, orphan drug assessment requires particular considerations for a number of reasons including high price, limited evidence available, no therapeutic options.

RARE-Bestpractices will map out the current processes for the appraisal of orphan drugs to investigate divergences in coverage decisions which result in unequal access to treatments for patients across countries. A selection of orphan drugs approved between 2006 and 2012 in a number of European countries will be identified to understand how appraisals were conducted, the critical factors leading to positive and negative recommendations, and how do assessments feed into clinical practice guidelines. Best practices based on the evidence collected will be identified across member states by benchmarking with individual practices on a per-case basis.

Finally, RARE-Bestpractices will enhance interaction among stakeholders through the publication of a new international open access, online, peer-reviewed journal focussing on important aspects of public health, health policy and clinical research on rare diseases. The journal *RARE DISEASES AND ORPHAN DRUGS. An International journal of public health* (RARE Journal, www.rarejournal.org) will be published three times per year, with no publishing fees for readers and authors and will make available high-quality articles from epidemiology, public health, health economics, social sciences, ethics and law.

[1] *Grading of Recommendations Assessment, Development and Evaluation*, http://www.gradeworkinggroup.org

DISCUSSION

RARE-Bestpractices will contribute to establishing a wide community of stakeholders interested in producing, acquiring, and sharing knowledge and reliable information on the management of rare diseases.

The partnership intends to offer a response to the challenges of improving quality and consistency of best practices for rare diseases, complying with the European Union directive which encourages European member states to provide high-quality and quantitatively adequate healthcare to citizens as well as to produce "good practices guidelines" [9].

The benefits of well developed guidelines in supporting health related decision are widely recognized [12]. They are particular helpful for the rare diseases community, for which identifying and disseminating the most scientifically sound healthcare practices requires more effort than for common conditions.

RARE-Bestpractices will address this matter by ensuring that patients and their families, health professionals, policy makers have access to "trustworthy" guidelines on rare diseases.

This will be provided by developing a methodology which explores issues specific for rare diseases, assessing the use of GRADE approach [13] in creating guidelines for rare diseases and drawing on existing initiatives in the field of "standards for guidelines" [12,14-16].

In addition, a comprehensive information system including resources to facilitate communication and cooperation in the field of guidelines on rare diseases (collection of guidelines, training tools, etc.) will be made publicly available.

Through these initiatives, the RARE-Bestpractices consortium intends to promote the development of high quality guidelines and to contribute in making patients, health professionals and policy makers "an informed guideline user".

As a wide, open and inclusive network, RARE-Bestpractices will build on the knowledge of the experts in rare diseases research area and experts in guidelines and health technology assessment area, brought together, for the first time, from academic institutions, agencies, organizations, patient representatives, governmental bodies. This will maximize the dissemination of the outputs of the project ensuring uptake of its innovative findings by the rare disease community, including rare disease national plans, Centres of Expertise and European Reference Networks in compliance with European Union legislation.

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REFERENCES

1. European Commission. 2013. Rare Diseases. How Europe is meeting the challenges. Available from http://ec.europa.eu/research/health/pdf/rare-diseases-how-europe-meeting-challenges_en.pdf
2. Aymé S., Rodwell C., eds., "2013 Report on the State of the Art of Rare Disease Activities in Europe", July 2013. Available from http://www.eucerd.eu/upload/file/Reports/2013ReportStateofArtRDActivities.pdf
3. Eurodis Factsheet "What is a rare disease". Available from http://www.eurordis.org/sites/default/files/publications/Fact_Sheet_RD.pdf
4. Taruscio D, Capozzoli F, Frank C. Rare diseases and orphan drugs. Annali Dell Istituto Superiore Di Sanità. 2011;47(1):83-93
5. Griggs RC, Batshaw M, Dunkle M, Gopal-Srivastava R, Kaye E, Krischer J, *et al*. Clinical research for rare disease: Opportunities, challenges, and solutions. Molecular Genetics and Metabolism. 2009;96(1):20-6.
6. European Parliament and the Council. Regulation (EC) 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products. Official Journal 2000; L 18:1-5. 22/1.
7. Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions on Rare Diseases: Europe's challenges (COM(2008)679 final)
8. European Council. Recommendation of 8 June 2009 on European action in the field of rare diseases. Official Journal C151: 7-10.
9. Directive 2011/24/EU of the European Parliament and of the Council of 9 March 2011on the application of patients' rights in cross-border healthcare. L 88/45.
10. Abbott A. Rare-disease project has global ambitions. Nature. 2011;472(7341):17.
11. IOM (Institute of Medicine). 2010. Rare Diseases and Orphan Products: Accelerating Research and Development. Washington, DC: The National Academies Press
12. Graham R, Mancher M, Miller Wolman D, Greenfield S, Steinberg E, eds. Clinical practice guidelines we can trust. National Academies Press, 2011
13. Terracciano L, Brozek J, Compalati E, Schunemann H. GRADE system: new paradigm. Current Opinion in Allergy and Clinical Immunology. 2010;10(4):377-83.
14. Brouwers MC, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G, *et al*. Development of the AGREE II, part 1: performance, usefulness and areas for improvement. Canadian Medical Association Journal. 2010;182(10):1045-52.
15. Brouwers MC, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G, *et al*. Development of the AGREE II, part 2: assessment of validity of items and tools to support application. Canadian Medical Association Journal. 2010;182(10):E472-E8.
16. Brouwers MC, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G, *et al*. The Global Rating Scale complements the AGREE II in advancing the quality of practice guidelines. Journal of Clinical Epidemiology. 2012;65(5):526-34.

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Methodology for production of best practice guidelines for rare diseases

Brief title: Methodology for guideline production

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