RB-REP.05

Final Publishable Summary Report

Platform for sharing best practices for management of rare diseases

(*RARE-Bestpractices*)

Author(s)
RARE-Bestpractices partners

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1. Executive Summary

The specificities of rare diseases (RD), including the limited number of patients, the large number of RD and their diversity as regard origin and clinical manifestations, result in challenges which make research progress and knowledge creation in RD more difficult.

Stemmed from the demand for an increased and shared knowledge on RD, the 4-year EU-funded project **RARE-Bestpractices – Platform for sharing best practices for the management of rare diseases** (www.rarebestpractices.eu) worked to create a sustainable networking platform for collecting, evaluating and spreading best practices to improve the management of RD patients and promoting a consistent level of healthcare services in European countries.

A collaborating network was set up with experts in the area of guidelines, systematic reviews, health technology assessment, health policy, RD epidemiology and public health coming from 9 countries across Europe. The main results are:

- **Agree upon methodology for production of guidelines on clinical management of RDs** – (a) Common methodological quality standards for developing Best Practices (BP) guidelines on RD were developed. In summary, it was concluded that both the Guideline Development Checklist (GDC) (cebgrade.mcmaster.ca/guidecheck.html) and the GRADE methodology for creating guidelines are appropriate for guideline development in the field of RD; (b) the quality standards for evaluating existing guidelines based on the AGREE II instrument have been found appropriate for RD; (c) two pilot guidelines have been successfully developed for two highly relevant RD: Catastrophic antiphospholipid syndrome (CAPS) and Sickle cell disease (SCD) with the latter also "translated" in a version suitable to patients and families.
- **Collection of BP and research recommendations on RD** – (a) Existing health care guidelines and research recommendations on RD were systematically collected - two databases were build: RareGUIDELINE (http://rbpguidelines.eu/) and RareGAP (http://rbpresearch.eu/). The RareGUIDELINE collection presently displays 143 quality appraised guidelines across 31 RD. RareGAP has been conceived to identify where there is a need for further research on RD and counts, to date, 77 research recommendations. (b) A set of principles for engagement with RD patients, carers, families and organisations to be used as guidance for researchers, policy makers and healthcare providers were developed.
- **RD technologies and value assessment** - Value assessment criteria for orphan drugs (OD) across 8 EU Member States were identified and synthesised. Considerable variation in the general methodology of value assessment emerged with an impact on time taken to assess a drug following Market Access (MA) across agencies and significant variation in the gap between MA approval and Health Technology Assessment (HTA) recommendation.
- **Platform infrastructure** - A website was designed to provide links to the project resources and tools and to disseminate information about project activities.
- **Dissemination** – (a) A new scientific international peer-reviewed open access journal was created to provide an advanced forum on important aspects of public health, health policy, clinical research and evidence synthesis. To date 10 issues and 4 supplements were published. (b) Two editions of the International Course "Health care guidelines on rare diseases. Quality assessment" were delivered to promote guideline quality standards and RARE-Bestpractices' outputs across European Member States and to support the ERN and Centres of Expertise that were being set up in the development of

their capacity to produce and use health care guidelines on RD. (c) Training tools were produced to assist in RD guideline development and appraisal.

- **Collaboration with the International Rare Diseases Research Consortium (IRDiRC)** - RARE-Bestpractices partners actively participated in the IRDiRC activities providing important input and working to strengthen a proactive partnership.
- **Scientific coordination, networking** - Two training courses for health care guidelines developers have been organized by AREAS-CCI: one focused on treatments of RD the other on diagnosis of RD.

Key potential impacts of RARE-Bestpractices results can be seen on (a) the methodology for developing and appraising BP for RD, and for engaging patients, carers, families and organisations in evidence translation activities (**impact on methods**); (b) Value assessment criteria for orphan drugs, identification of research gap in RD field (**impact on policies**); (c) the availability of tools such as the two databases, the collaborating online community, the training courses and tools, the newly released guidelines for two rare conditions, the scientific open access peer reviewed journal on RD and Orphan Drugs (**impact on the stakeholders' capacity of action in the field of RD**).

2. List of acronyms and abbreviations

AGREE	Appraisal of Guidelines for REsearch & Evaluation
BP	Best practice(s)
CAPS	Catastrophic antiphospholipid syndrome
CEA	Cost-effectiveness analysis
EBM	Evidence Based Medicine
EPIRARE	European Platform for Rare Diseases Registries
EU	European Union
EU MS	European Member States
EUCERD	European Union Committee of Experts on Rare Diseases
ERN	European Reference Network(s)
EtD	Evidence to decision framework(s)
G-I-N	Guidelines International network
GDC	Guideline Development Checklist
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HTA	Health Technology Assessment(s)
ICORD	International Conference on Rare Diseases and Orphan Drugs
IRDiRC	International Rare Diseases Research Consortium
MA	Marketing Authorisation
MEAs	Managed Entry Agreements
OD	Orphan drug(s)
RCT	Randomized controlled trial(s)
RD	Rare Disease(s)
RSA	Risk Sharing Agreement(s)
SCD	Sickle cell disease
WP	Work Package(s)

3. Summary description of project context and objectives

Rare diseases (RD) are characterized by low prevalence and extreme diversity as regard origin and clinical manifestations. Many RD are life-threatening or fatal, most of them are chronic and seriously debilitating. Collectively they affect millions of people of all ages worldwide.

The small number of people affected with any particular RD as well as the large number of RD result in challenges which complicate research progress and knowledge creation in all countries. These challenges include difficulties in attracting public and private funding for basic and clinical research, in setting up appropriate studies for translating research findings into practice, in coordinating research initiatives. For patients this means late diagnosis, as well as late, inadequate or even harmful treatment, and low quality of care.

The aim of **RARE-Bestpractices** (www.rarebestpractices.eu) - **Platform for sharing best practices for the management of rare diseases** was to create a networking platform for collecting, evaluating and spreading best practices (BP) to improve the management of RD patients and promote a consistent level of healthcare services in European countries. RARE-Bestpractices is a project funded by the EU Seventh Framework Programme during the four-year period 2013-2016 and coordinated by the Istituto Superiore di Sanità – National Centre for Rare Diseases (Italy). The project has built on the knowledge of a team of experts in the area of guidelines, systematic reviews, health technology assessment (HTA), health policy, RD epidemiology and public health coming from 9 countries across Europe (Table 1).

Table 1: RARE-Bestpractices Consortium

No	Name	Short Name	Country
1	Istituto Superiore di Sanità - National Centre for Rare Diseases	ISS	Italy
2	Jamarau	-	United Kingdom
3	Karolinska Institutet	KI	Sweden
4	Healthcare Improvement Scotland	HIS	United Kingdom
5	London School of Economics and Political Science	LSE	United Kingdom
6	National Research Council	CNR	Italy
7	European Organisation for Rare Diseases	EURORDIS	France
8	Associazione per la Ricerca sull'Efficacia dell'Assistenza Sanitaria Centro Cochrane Italiano	AREAS-CCI	Italy
9	Universitaetsklinikum Freiburg	UKLFR	Germany
10	Bulgarian Association for Promotion of Education and Science	BAPES	Bulgaria
11	Servicio Canario de La Salud	SCS	Spain
12	Universiteit Maastricht - Institute for Public Health Genomics	UM	The Netherlands
13	Newcastle University Upon Tyne	UNEW	United Kingdom
14	The European Academy of Paediatrics	EAP	Belgium
15	Instituto de Salud Carlos III	ISCIII	Spain

The objectives of RARE-Bestpractices were to:

- reach consensus on common methodological quality standards for developing health care guidelines on RD
- build a comprehensive public database of systematically identified and critically appraised guidelines to help professionals, patients, policy makers with the best and most up-to-date information on RD
- build a comprehensive public database of research recommendations to identify RD 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 RD
- support the activities of the International Rare Diseases Research Consortium (IRDiRC http://www.irdirc.eu) as regard both the translation of research results into patient-oriented strategies and the identification of research needs.

The work has been organized into eight work packages (WP) to allow an efficient coordination of the project activities (Figure 1).

Core activities

WP3, WP4 and WP5 included the core research activities dealing respectively with setting the quality standards for the development of RD guidelines, collecting existing guidelines and research recommendations on RD, evaluating orphan drug (OD) appraisals to explore processes and best practices in a range of countries.

Technical infrastructure of the platform

WP2 supported WP3, WP4, WP5 and WP6 activities and outputs by developing the platform technical infrastructure.

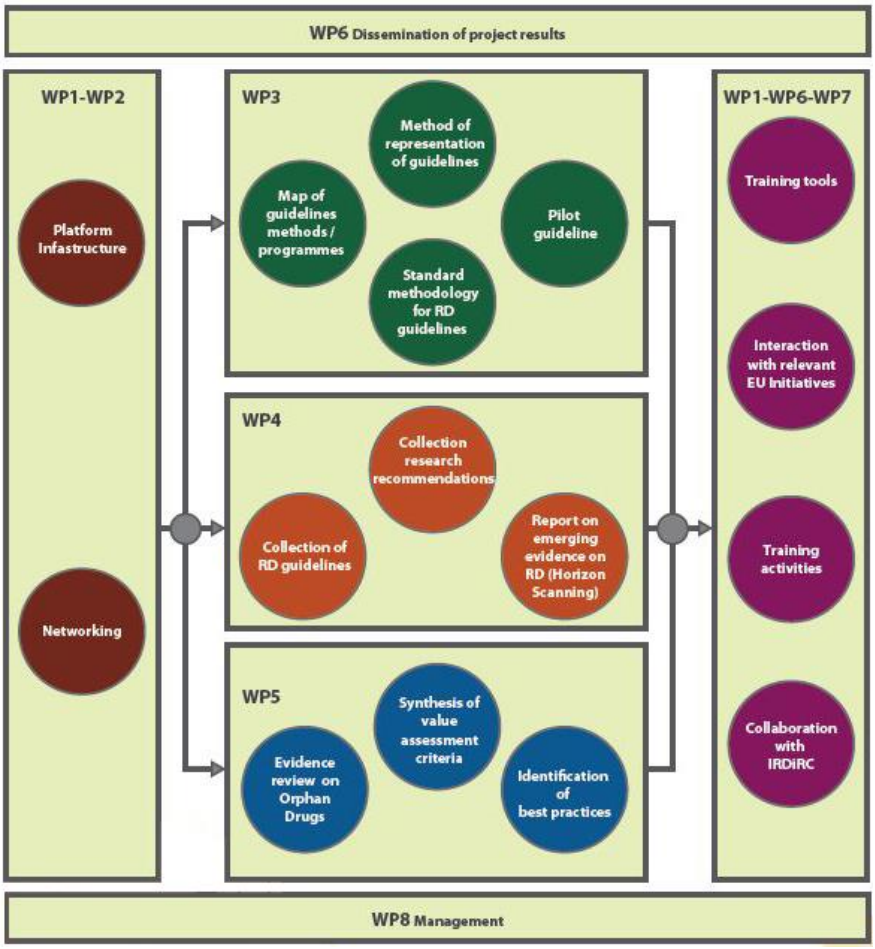
Dissemination and collaboration with IRDiRC

WP6 aimed at building awareness around the project and disseminating the results, also through training tools and courses for RD guideline users. In addition, resources of WP6 were dedicated to the foundation and management of a new open access journal which promotes analysis and discussion on improving health and health care on RD. WP7 worked for establishing collaboration with IRDiRC.

Coordination and management

WP1 (scientific coordination) and WP8 (management) focused on ensuring a smooth execution of project activities. In addition, WP1 was responsible for the delivery of training initiatives directed to RD guideline developers.

Figure 1: RARE-Bestpractices structure



4. Main S&T results/foregrounds

Agree upon methodology for production of guidelines on clinical management of RDs (WP3, Lead: KI)

Analyse the state of art of BP guidelines European Member States

A survey was conducted by AREAS-CCI to gather information on existing or planned programs, processes and resources allocated in developing, disseminating, implementing BP guidelines on RD in the European Member States (EU MS). The survey was launched in October 2013 and closed in April 2014.

The results indicated the EU MS participating in the survey (19 of 28 EU MS; 68%) have so far dedicated scarce resources on the development, dissemination and implementation of BP guidelines on RD. In the majority of the EU MS the initiatives are sporadic and fragmented and led by scientific societies, patient associations or interested groups of clinicians.

The survey indicates that EU MS should devote more resources to the development and implementation of guideline on RD also taking into account that the Centres of Expertise are now required of being capable of producing guidelines to participate in the European Reference Networks.

Devoting resources for initiatives dedicated to the harmonisation of the processes used by guideline developers on the rare diseases is also a priority alongside efforts in disseminating, implementing and evaluating the effectiveness of the guideline produced.

Common methodological quality standards for developing BP guidelines on RD

The common methodological quality standards for developing BP guidelines on RD were developed jointly by the Consortium partners under the leadership of UKLFR and KI.

During the first 18 months, work focused on exploring challenges in developing recommendations included in RD guidelines. Two workshops were organized to explore issues specific to RD. The first workshop was held in Rome in February 2013. A paper summarising this preparatory work was published in the Rare Diseases and Orphan Drugs: An International Journal of Public Health.[1] An additional paper describing the results of the first workshop, was published in the peer reviewed journal Rare Diseases.[2]

A second, two-day workshop was held at UKLFR in Freiburg in October 2013 to explore and discuss a series of prepared mock guidelines (the guidelines simulated and diseases tested included haemophilia, cystic fibrosis, paroxysmal nocturnal hemoglobinuria, Catastrophic Antiphospholipid Antibody Syndrome, primary biliary cirrhosis, avian influenza, and multiple sclerosis). During the workshop the use of the Guideline Development Checklist (GDC) (cebgrade.mcmaster.ca/guidecheck.html) and the use of the GRADE methodology for creating RD guidelines were assessed. Consortium participants, patient representatives, invited experts in the field and external advisors (e.g. members of the GRADE working group) were involved in this workshop. Formal note taking and note checking revealed that the items on the GDC fulfil the need of guideline developers in RD. The checklist is a

"consider but must not do all" approach to considering items and steps in guideline development, including those in RD.

In summary, based on findings of these two workshops it was concluded that both the GDC and the GRADE methodology are appropriate for guideline development in the field of RD and its use should be piloted in real guidelines. In particular, the work on the GRADE evidence to decision frameworks (EtD), tested as part of this task, was judged to accommodate RD very well. The EtD frameworks have been published by the GRADE Working Group in the meantime.[3, 4] Furthermore, the quality standards for evaluating an existing guideline based on the AGREE II instrument (see WP4) have been found appropriate for RD and were suggested for evaluation of completed guidelines.

The work conducted as part of Task 3.2 led to the development of a draft report describing methodological quality standards for BP guidelines on RD.

The report was only finalized after completion of the 2 pilot guidelines (see paragraph below) to allow for incorporation of adjustments based on the experience from the pilot guidelines. Based on the experience gained during the development of the pilot guideline on Catastrophic Antiphospholipid Antibody Syndrome (CAPS) sections on the use of expert-based evidence as well as the use of data from an international patient registry were added.

The pilot guideline on Sickle Cell Disease (SCD) was based on data from randomized controlled trials (RCT) and observational studies allowed applying the widely-used GRADE methodology without further adjustments. Due to the availability of existing systematic reviews for key questions addressed in the SCD guideline, the GRADE-Adolopment process was successfully applied as part of the development of the SCD pilot guidelines and the report on common methodological quality standards accordingly expanded.

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Pilot guidelines

In task 3.3 of WP3 the agreed methodological quality standards were to be applied and tested in the production a real pilot guideline.

Two pilot guidelines – based on the methodological quality standards for guidelines on RD - have been successfully developed for two highly relevant RD: CAPS and SCD. These

topics were selected to allow the development of the pilot guidelines in different scenarios both for the frequency of the diseases and the available evidence to inform guidelines. CAPS is extremely rare and RCTs are not available. SCD is a more common RD and RCT and observational studies are available for key clinical questions. Therefore, the development of guidelines for the selected diseases allowed to capture the spectrum of possible challenges in the development of RD guidelines.

Key experts on these RDs, e.g. from the American Society of Hematology as well as methodologists and patient representatives were involved in the guideline development projects.

The preparatory work for the two pilot guidelines was facilitated through the use of the GDC.

The multi-disciplinary panel that was created for development of the pilot guideline on CAPS convened in Barcelona on 27 April 2016. The pilot guideline on CAPS made use of the GRADE methodology, in particular the Evidence to Decision (EtD frameworks which are implemented in the software GRADEpro Guideline Development Tool. In addition, and specific to the CAPS pilot guideline, systematically elicited expert-based evidence was used to inform the deliberations of the panel. Evidence was complemented by data from an international patient registry. A full day meeting (followed by an online 2-hour meeting) allowed formulation of 7 therapeutic and 3 diagnostic recommendations.

The panel responsible for the development of the SCD pilot guideline met in Freiburg on 16-17 June 2016. The pilot guideline on SCD was based on comprehensive systematic reviews including evidence from various study designs such as RCT and observational studies. In addition, due to the availability of pre-existing systematic reviews, adaptation methodology, i.e. the GRADE-Adolopment framework, was successfully applied. Based on the in-person meeting in Freiburg and some online-discussion and voting with facilitation of the software package GRADEpro GDT (www.guidelinedevelopment.org) six recommendations were produced. The recommendations address the use of blood transfusions and the management of related iron overload in patients with SCD, while the other 7 recommendations deal with hydroxyurea in the management of SCD patients.

Both guidelines are currently being submitted to peer-reviewed journals for publication.

Patient version of the pilot guideline on the SCD

The recommendations included in the SCD pilot guideline were “translated” in a version suitable to patients and families as part of task 3.5 of WP3.

The booklet including the patient version of the recommendations was developed by EURORDIS with the support of the RARE-Bestpractices project partners SCS and UKLFR. The McMaster University (Canada) also supported this initiative. The Association Pour l'Information et la Prévention de la Drépanocytose - the French patient organisation for information and prevention of SCD - has been involved in the development and proof-reading of the booklet. The Scottish Intercollegiate Guidelines Network of HIS also contributed by providing methodological support and access to its tools [1]. Patient representatives and panel experts involved in the production of the pilot guideline reviewed the booklet prior to publication.

The booklet is composed of several sections explaining what is SCD, what are the causes and the main manifestations of the disease. Then, it expands on the diagnosis means. Furthermore, it describes the current available therapeutic options and gives answer to questions important to patients such as the relation with SCD and pregnancy. It ends by a

glossary which will help the patient community to better understand the disease, the appropriate management of the disease and to better interact with the community.

The booklet will be publicly available at Project Website once the professional version of the guideline will be made public as a scientific publication.

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Collection of BP and research recommendations on RD (WP4, Lead: HIS)

The activities of WP4 focused on collecting existing health care guidelines and research recommendations on RD. Whilst WP2 developed the database infrastructure to host the information, WP4 identified and organised the information. The collections are accessible through the databases RAREGUIDELINE (http://rbpguidelines.eu/) and RAREGAP (http://rbpresearch.eu/).

RAREGUIDELINE

The RAREGUIDELINE collection provides a comprehensive set of systematically identified and quality appraised health care guidelines on RD published within the last 10 years.

In developing a procedure for the collation of RD guidelines WP4 worked through four stages as described below:

Stage 1 – Topic selection

Several methods were used to identify conditions which should be priorities for inclusion in the guidelines collection. Firstly, there were the conditions used to develop and test the search methods for guideline retrieval. These were a purposive sample of high, medium and low prevalence RD. Secondly, RARE-Bestpractices partner organisations and Advisory Board members were invited to nominate disease topics of particular relevance or importance within their respective areas of expertise. Finally, key organisations were invited to submit topics e.g. the project partner EAP and The Council of European Rare Disease Federations. A list of 44 topics was drawn up to form the initial model collection (Table 2).

Table 2: List of topics identified for initial inclusion in RAREGUIDELINE

1.	Addison's disease	23.	Herpes simplex encephalitis
2.	Alstom Disease ^^	24.	Klinefelter's syndrome
3.	Anal atresia ^^	25.	Joint hypermobility syndrome
4.	Aniridia	26.	Huntington's disease*
5.	Bardet Biedl Disease	27.	Long QT syndrome
6.	Biliary atresia	28.	Lichen sclerosus
7.	Brucellosis (human)	29.	Hirschsprung's disease
8.	Carcinoid syndrome	30.	Lyme disease
9.	Catastrophic antiphospholipid syndrome	31.	Mitochondrial disease (multiple disorder)
10.	Coarctation of the aorta in the newborn	32.	Multiple myeloma
11.	Congenital anaemias	33.	Myasthenia gravis
12.	Congenital cataract ^^	34.	Noonan syndrome
13.	Congenital myasthenias ^^	35.	Osteosarcoma
14.	Costello syndrome*	36.	Paroxysmal nocturnal haemoglobinuria
15.	Cushing's syndrome	37.	Phaeochromocytoma
16.	Cushing's disease	38.	Phenylketonuria
17.	Cystic fibrosis	39.	Porphyrias
18.	Duchenne Muscular Dystrophy	40.	Progressive Subnuclear Palsy^^
19.	Epidermolysis bullosa	41.	Turner syndrome*
20.	Gaucher's disease	42.	Spinal muscular atrophy

21.	Giant cell arteritis	43.	Waldenström Macroglobulinemia
22.	Hereditary Spastic Paraplegia (Strümpell-Lorrain disease)	44.	Wolfram Disease
*conditions selected for testing search methods ^^ conditions where no guidelines were identified by systematic search			

Stage 2 – Document identification

WP4 developed a search protocol outlining a minimum set of resources to be searched for each disease topic. The protocol was designed to be relatively straightforward and require minimal knowledge or experience of literature searching. It was intended to be systematic but not exhaustive and focused on resources not requiring member subscription. This development work has been published in a peer-reviewed article.[1]

Stage 3 – Inclusion criteria

Criteria were devised defining which documents could be included in the collection (Table 3). The main criteria were whether the document included recommendations for practice.

Table 3: List of inclusion and exclusion criteria

	Inclusion	**Exclusion**
Document type	Any document produced by a stakeholder group which is described as a guideline, consensus statement, or best practice statement **AND** contains recommendations* for practice.	Patient information documents. Local (e.g. hospital) care protocols or pathways. Publications produced by individual authors who are not part of a guideline development group.
Year	Published within 10 years	
Language	English, French, Spanish, Dutch, Italian, German	
Topic	Directly relating to the named condition. Guidelines on single interventions for the named condition.	Generic symptom management e.g. dementia management. Reviews of single interventions which do not contain recommendations.
Format	PDF, web document, print document, journal article, eBook	Text books

** Genetic testing documents may not include recommendations as such. Any testing protocol described as best practice or consensus should be included in the first instance.*

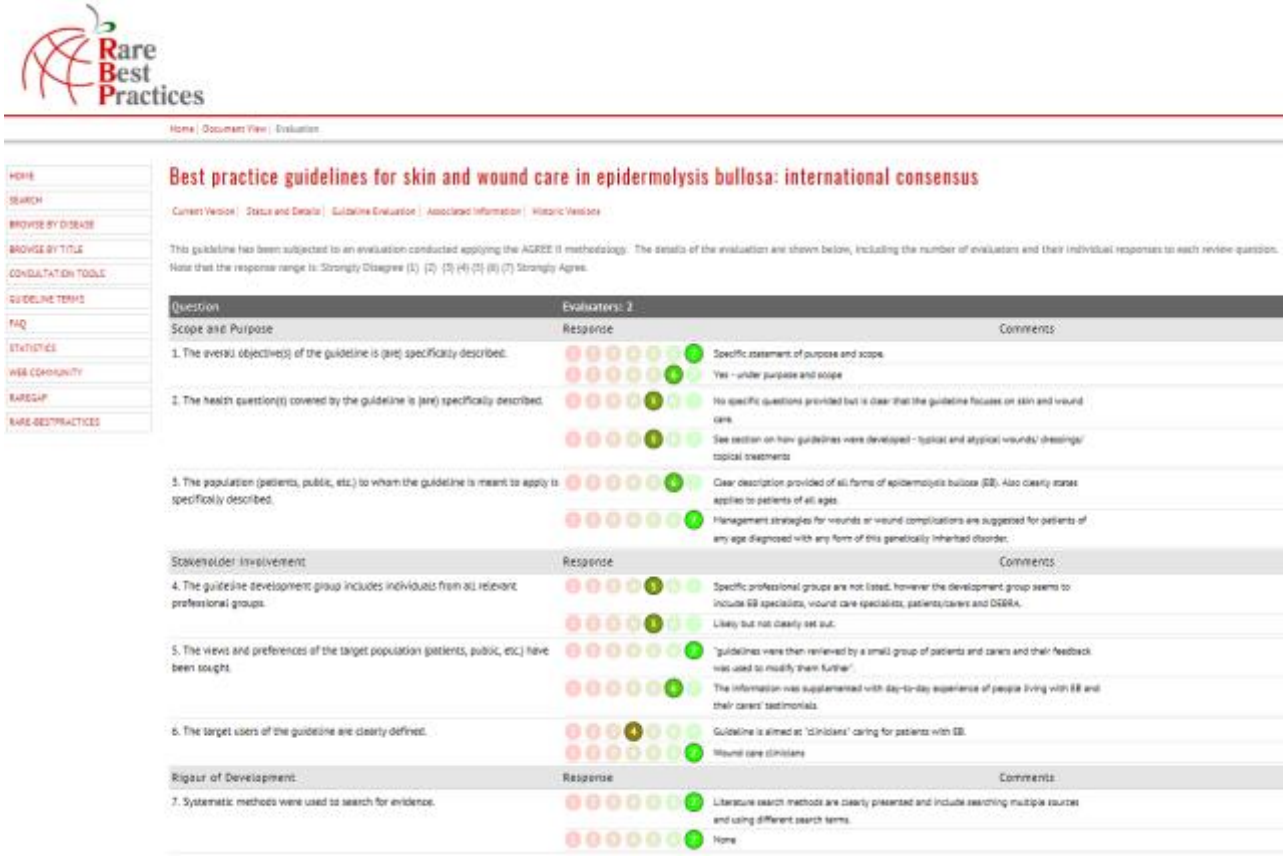
Stage 4 – Quality appraisal

WP4 hosted an international workshop to test out an existing tool – the Appraisal of Guidelines for Research & Evaluation (AGREE II, http://www.agreetrust.org/) instrument - for evaluating the methodological quality of RD guidelines. The AGREE II instrument is an internationally recognised assessment tool which consists of 23 items arranged into six quality domains. The tool was found to be applicable to RD guidelines although some additional guidance was developed to help those appraising guidelines consider aspects which were particularly relevant to RD for example the likelihood of a low volume of published evidence. The workshop findings are published in a peer-reviewed journal article.[2]

For each guideline identified for inclusion in the collection partners completed at least two quality appraisals. For users of the database this means that they can quickly check the

methodological quality of the documents they are accessing, by means of visual representation of AGREE II measures (Figure 2).

Figure 2: Screenshot of an appraised guideline



There are around 250 quality appraised guidelines in the RAREGUIDELINE model collection; six major European languages are represented.

This work represents a collaboration of and contribution from a great many organisational and individual partners across the world who identified and appraised guidelines including RARE-Bestpractices consortium members Jenny Harbour, Ali McAllister, Karen Ritchie, Lorna Thompson (HIS), Paola Laricchiuta, Cristina Morciano (ISS), Pedro Serrano Aguilar, Tasmania del Pino Sedeño, Mar Trujillo Martin (SCS), Carlo Leo, Pierpaolo Mincarone (CNR), Manuel Posada (ISCIII), Liesbeth Siderius (EAP), Ingrid Töws (UKLFR). The full list of contributors is detailed in the database webpage http://www.rbpguidelines.eu/contributions.

The resource may be accessed freely by the intended audience of healthcare professionals, patient and carers and researchers and policy makers.

RAREGAP

RAREGAP has been conceived to identify where there is a need for further research on RD by identifying gaps in the current research. A research recommendation (RR) is defined as a statement that describes “the need for further research, and the nature of the further research that would be most desirable”.

WP4 used Cochrane systematic reviews, which are robust reviews of scientific evidence, to access research recommendations relating to rare disease conditions. Cochrane systematic reviews were selected for development of the initial collection because they are recognized as gold standard for methodological quality and allow identification of genuine evidence gaps where investing further research resources would be useful (conversely, low methodological rigour in systematic reviews may result in the identification of false uncertainties).

These recommendations were then formatted for submission to the RAREGAP database by clearly setting out the patient population, the intervention and relevant comparisons and outcomes which would define the research question in a manner that researchers and research funders could use to plan research activities and avoid duplication. There are 77 research recommendations listed and openly accessible in the RAREGAP database.

Principles for engagement with rare disease patients, carers, families and organisations

An additional task undertaken by WP4 was to develop a set of principles for engagement with RD patients, carers, families and organisations to be used as guidance for researchers, policy makers and healthcare providers. Draft principles were developed based on a systematic literature search and discussion with key informants. The principles were then consulted on and amended through input from a range of stakeholders including patients, patient organisations and researchers. Key principles emerging are as below:

- **Consider** patients and patient organisations as co-partners in developing patient engagement strategies at an early stage in any project. Focus on building and maintaining trusting relationships.
- **Recognise** that RD patients, carers and families have very particular expertise to contribute to evidence translation activities and the great value in capturing this given the likelihood that the traditional evidence base for many conditions is limited. Patients should be treated as experts on their disease.
- **Trust** that RD patients, families, carers and organisations are often highly motivated to contribute particularly where encouragement, support, guidance and co-ordination to do so, is provided.
- **Be mindful** when interacting with RD patients' families and carers, of the broader family issues related to the genetic origin of many RD.
- **Undertake** thoughtful targeting of recruitment efforts recognising that umbrella organisations are an important part of the RD network.
- **Appreciate** that RD organisations are often small (and geared largely towards patient support) and respect limitations on their time, resources and expertise.

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RD technologies and value assessment (WP5, Lead: LSE)

Value assessment criteria for orphan drugs across eight EU Member States

Recent evidence suggests that there is significant variation in the outcomes of HTA processes for prescription drugs, including OD, across Europe.

WP5 had three main objectives: (a) To outline the existing national policies for OD with particular emphasis on special considerations made in the HTA process; (b) To determine the criteria used to assess the value of OD in selected European Member States (EU MS) relying on broad evidence-based medicine (EBM) and cost-effectiveness analysis (CEA) criteria in each jurisdiction; and (c) To understand the way clinical practice guidelines are developed for RD and to explore best practices based on the evidence collected.

Methodology

To address the above objectives, processes of EBM and CEA for OD were mapped out in eight EU MS: England, France, Germany, Italy, Poland, Scotland, Spain and Sweden. A case study analysis of 20 orphan drug-indication pairs appraised by the HTA bodies of the above countries between January 2006 and December 2012 was conducted. The list included cancer and non-cancer drugs, as well as ultra-orphan drugs. Prescribing guidelines developed in the eight study countries for the indications in scope were retrieved to investigate how each country's HTA recommendations feed into the prescribing/clinical guidelines. Additional help was required from key informants in a number of instances.

Key findings

a) **HTA processes and national policies for OD across jurisdictions** – There is considerable variation in the general methodology of value assessment as well as the way this applies to ODs across countries. In some cases, prices are based on added clinical benefit (France and Germany), whereas in Sweden, a broad societal perspective is adopted. In Sweden, Spain and Italy, the devolved healthcare systems leave less of a role for HTA, though this is beginning to change or is likely to change in the future with new legislation. England and Scotland have specialized assessment pathways for orphan drugs. In France and Italy fast-track mechanisms exist to help in making new technologies available with no delay. In Germany, additional benefit is considered proven at Marketing Authorisation (MA) if the budget impact for the drug and its indication does not exceed €50 million per annum. Risk Sharing Agreements (RSA) or Managed Entry Agreements (MEAs) are frequently used in England, France, Italy, Poland, Scotland and Sweden.

b) **Regulatory approval and HTA appraisals** – Following an analysis of the 20 drug-indication pairs on a case-by-case basis, it was concluded that there is little uniformity across agencies in the time taken to assess a drug following MA and that significant variation exists in the gap between MA approval and HTA recommendation.

c) **Access and equity implications** – There was an apparent difference in the resulting recommendations, suggesting that the interpretation of clinical data is not uniform across agencies. Also, there is little uniformity in the time taken by each agency to assess a drug subsequent to receiving MA. Given the clear time lapse between MA and HTA recommendations, the diverse criteria for reimbursement and inconsistencies in appraisal outcomes across countries, it is clear that patients across the study countries have different access to OD depending on the setting in which they live.

d) **Requirements for and use of clinical and economic evidence** – A preference for robust Phase III trial data was apparent across all agencies. Most agencies except HAS, IQWiG and AIFA considered cost-effectiveness.

e) **Main reasons for recommendations** – The key driver for NICE was cost-effectiveness with cost implications frequently outweighing evident clinical benefit in instances where the ICER estimate lay outside the "threshold" of £20,000-£30,000 discussed in the literature. Yet, this threshold may not be as rigidly adhered to for OD. Greater weight is placed on other factors, like for example patient need and lack of alternative treatments. TLV in Sweden seems to be more driven by need than cost. SMC emphasised the need for a demonstrated economic case for a drug, and model and clinical trial design are heavily scrutinised.

f) **Clinical practice guidelines developed across the study indications** – As NICE in England uses the criteria of clinical and cost-effectiveness to appraise drugs, its decisions are considered binding and are followed by doctors when making a therapeutic decision. But even if the HTA appraisal is negative, there is always a possibility for patients to have access to ODs in other ways. In France, decisions by HAS may be considered binding for clinical practice. In Germany, AWMF collates guidelines developed by the various national medical scientific professional organizations. In Italy, EMA guidelines are followed centrally and AIFA usually endorses the EMA's position. In Scotland, the Scottish Intercollegiate Guidelines Network (SIGN) develops evidence-based clinical practice guidelines for NHS Scotland. In Sweden, national and regional clinical and prescribing guidelines were identified from a variety of sources, but TLV's decisions are binding.

Conclusions and policy implications

The variations in HTA recommendation outcomes across EU Member States and the often very significant time lapses between the date of MA and the final HTA recommendation, imply variations in access and highlight the importance of establishing specific policies for ODs, in order to ensure fair assessment and equitable access to treatment for RD. Importantly, the prevalence of special considerations in yielding positive recommendations or, even, positive recommendations with restrictions, is very high and, often, context-specific, as research on 20 drug-indication pairs suggests.

HTA processes need to be standardised or at least approximated and international HTA collaboration and communication between HTA agencies and manufacturers need to be intensified and improved upon; that will undoubtedly enhance the efficiency and effectiveness of appraisal procedures across European MS. The greatest challenge is the uniform implementation of recommendations, but this is crucial in ensuring the geographical equity in access.

Platform infrastructure (WP2, Lead: JAMARAU)

The activities of WP2 focussed on the creation and maintenance of the project IT Platform, which comprises of a website and two database applications; RAREGUIDELINE, and RAREGAP.

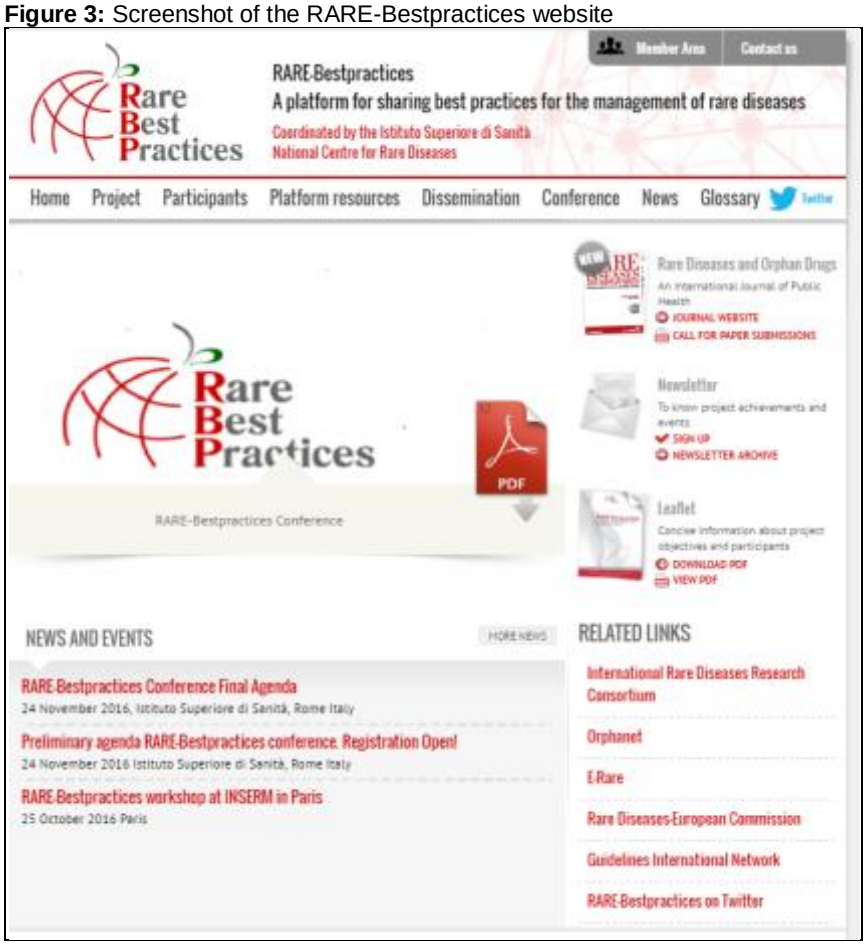
Project website

The website was designed to provide links to the project resources and tools and to disseminate information about project activities. The following sections were developed:

- a public section (see Figure 3) with information on project aim and objectives, links to related websites (e.g. E-RARE 3 project, Orphanet portal), information on project partners, project publications as well as project news and events and external related news and events.

  In order to ensure a single point of access to the RARE-Bestpractices resources and tools, the website provides links to: the Rare Diseases and Orphan Drugs Journal, RAREGAP (the research recommendation database) and RAREGUIDELINE (the database of critically appraised guidelines), training tools and training activities. Furthermore, the website provides a link to the project newsletter and allows a volunteer subscription to the newsletter in in order to receive more information on the project activities by e-mail.
- A member area which contains confidential project documents for the project management.

Figure 3: Screenshot of the RARE-Bestpractices website



Development of RAREGUIDELINE and RAREGAP database applications

In developing the database applications, WP2 worked through a staged process.

Stage 1 – Consultation and Scoping

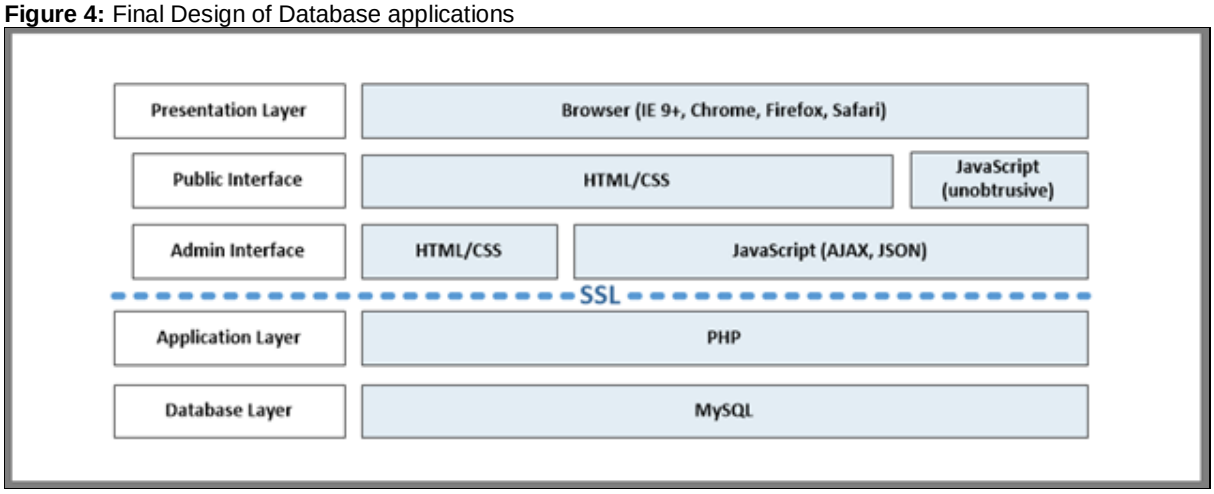
Consultations were undertaken with partners to agree the scope of the database applications and gain an understanding of the outcomes to be targeted for completion within the project. Other stakeholders with an interest in guideline development were consulted through a workshop conducted by HIS.

While the consultations were underway the server and Core System Software were implemented and general content applied.

Stage 2 – Design and Development

Work focused on designing the workflows, processes and validations that drive the database applications. This included research into the best and most effective solutions for achieving the desired outcomes. The final design (Figure 4) comprised a presentation layer (where users view published information), a public interface (the functionality used to generate the public web pages), an administrative interface (used by administrators to create, view and maintain records in the database), an application layer (interprets user requests and feeds back results) and a database layer which stores the information.

Figure 4: Final Design of Database applications



Stage 3 – Implementation and Review

The databases were released (firstly as a prototype to key administrators, then to partners and then publicly). Key staff where provided with training in the use of the databases and given time to familiarise themselves with the functionality, after which a review of the resources was initiated. The review aimed at determining if the databases where fit for purpose and at identifying and evaluating opportunities for further refinement. Work during this phase also comprised compilation of a user manual for each database.

Stage 4 – Refinement

Feedback for modification of the databases was evaluated and refinements prioritised based on importance in terms of the agreed objectives, capacity to implement within the timeframe/with the available information and the degree of value added. Prioritised refinements were coded and the user manuals updated accordingly.

As a result of these efforts WP2 delivered the IT Platform that consists of the information website and the database applications RAREGUIDELINE and RAREGAP. These are freely publicly accessible from the section “Platform resources of the RARE-Bestpractices website as well as from www.rbpguidelines.eu. www.rbpresearch.eu.

In addition to being a repository, RAREGUIDELINE contains a range of consultation tools and resources (e.g. online survey, web community forum) to facilitate discussion between experts in support of future development and review and the expansion of the collection, while RAREGAP provides capacity for funding bodies to identify research that they are willing to fund.

WP2 also supported WP3 and WP4 in the conduct of surveys using the RAREGUIDELINE consultation tools and assisted with the recording of the video tutorials for RAREGUIDELINE and RAREGAP (see WP6).

Dissemination (WP6, Lead: ISS)

Rare Diseases and Orphan Drugs – an International Journal of Public Health

WP6 dissemination, task 6.5. carried out the work for the creation of a new scientific open access journal Rare Diseases and Orphan Drugs – an International Journal of Public Health (RARE Journal, http://rarejournal.org). A working group was established composed of project participants: Domenica Taruscio (project leader, ISS) Cristina Morciano (WP6 dissemination leader, ISS), Rumen Stefanov (task leader), Georgi Iskrov, Tsonka Miteva-Katrandzhieva (BAPES), Holger Schünemann (UKFRL). Experts of publishing issues of the ISS, (Paola De Castro, Director of the ISS Publishing Unit, Federica Napolitani, editorial coordinator, ISS Publishing Unit) were also involved in the working group as Advisory Board.

The objective of the working group was to define the journal proposal and to prepare the journal launch. A checklist of the activities to be carried out and of the critical issues to be addressed for the creation and launch of the journal was developed. Furthermore, the group explored current journal practices such as editorial policy, author guidelines, standard of reporting, publishing platforms, copyright issues, promotional activities, etc. To perform this task the working group has proceeded through meetings, teleconferences and e-mail exchanges. After several consultations with the member of the Consortium the journal structure, policy documents, rules and procedures were approved by all members.

Journal aims and scope

RARE Journal is an international peer-reviewed journal published three times per year, with no publishing fees.

The mission of RARE Journal is to provide an advanced forum on important aspects of public health, health policy, clinical research and evidence synthesis (e.g. HTA, health care guidelines) in ways that will improve health care and outcomes for persons suffering from RD, as well as globally increase RD experience sharing. RARE Journal publishes several types of articles, including original research article, case report, systematic review and meta-analysis, report of health care guidelines, HTA, epidemiological registry report, commentary, letter to Editors, meeting and project reports. The Journal also anticipates special issues dedicated to a specific topic, such as particular rare disease or a group of RD.

RARE Journal serves the international RD community by publishing high-quality articles from epidemiology, public health, health economics, social sciences, ethics and law, with a special accent on RD best practices guidelines, RD research recommendations, and RD epidemiological reports. Specific sections of RARE Journal include: Epidemiology and Clinical Research (rare disease epidemiology, clinical research and methodology), Guidelines, Systematic Reviews, Health Technology Assessment and Horizon Scanning (rare disease guidelines and systematic reviews, health technology assessment and horizon scanning), Prevention (primary prevention, risk factors and screening, quality assurance, genetic testing), Rare Disease Policy (policy and decision-making, health economics, law and ethics, narrative medicine, patients' needs, quality of life), Undiagnosed Rare Diseases.

RARE Journals implemented an online tracking system for authors, editors, reviewers and readers. This enables all stakeholders to easily submit a paper, to follow up the peer review and copy editing process, as well as to be notified for of new issues and publications. To ensure timely review, RARE Journal assembled a strong 28-member Editorial Board of leading international experts in RD, orphan drugs and in the development of health care guidelines, HTA and systematic reviews. Dr Domenica Taruscio (ISS) and Prof Holger

Schünemann (McMaster University) are Editors-in-Chief, supported by Prof Rumen Stefanov (Medical University of Plovdiv) as Managing Editor and Cristina Morciano (ISS) as Work package 6 leader. An Advisory Board was also created to support Editors in ensuring that the policy of the journal is correctly implemented (aim and scope, organization of the editorial process, impact). They provide recommendations and new ideas to the Editors to ensure the quality and credibility of the contents, efficiency of the editorial process, broad diffusion and high impact of the journal. The combination of these activities proved to be very successful. RARE Journal produced 10 issues for the project period, publishing scientific papers from all around the globe – USA, India, UK, France, Italy, Spain, Canada, Tunisia, Ecuador, the Netherlands, Sweden, Czech Republic and Bulgaria. This clearly demonstrated the good potential of the Journal, in particular among low- and middle-income countries, because of its Editorial policy of open access and free-of-charge publications.

Figure 5: Journal cover with Editors and Advisory Board

RARE Journal successfully established partnerships with the EPIRARE (European Platform for Rare Diseases Registries) Project and the International Conference on Rare Diseases and Orphan Drugs (ICORD), publishing the proceedings from scientific events organized by these platforms. EPIRARE was a three-year project co-funded by the European Commission within the EU Program of Community Action in the field of Public Health. This project aimed to define options for the preparation of a legal basis, fields in which effective synergies can be achieved, governance framework and possible options to support the platform either financially or by hosting it in an organization or a Community institution. EPIRARE also assessed the feasibility of a minimum data set common to all RD designed to inform policy-making.

ICORD is an international Society for all individuals actively involved in RD and/or orphan drugs, including health care, research, academic, industry, patient organizations, regulatory authorities, health authorities, and public policy professionals. The mission of ICORD is to improve the welfare of patients with RD and their families world-wide through better

knowledge, research, care, information, education and awareness. One of the main activities of ICORD is the organization of the ICORD annual meetings, which have been successfully arranged ten times all over the world.

Missions of both EPIRARE and ICORD are consistent and coherent with the RARE-Bestpractices Project's objectives and with the RARE Journal's rationale, thus being natural partners for collaboration and dissemination.

Courses for health care guideline users

Two editions of the International Course "Health care guidelines on rare diseases. Quality assessment" were designed and delivered by the Istituto Superiore di Sanità (ISS) with the support of Healthcare Improvement Scotland (HIS) in WP6, task 6.3. Both courses took place at the Istituto Superiore di Sanità in Rome, Italy. The first edition of the course was held on 23-24 February 2015, the second edition on 3-4 December 2015.

These activities were intended to promote guideline quality standards and RARE-Bestpractices' outputs across European Member States and to support the ERN and Centres of Expertise that were being set up in the development of their capacity to produce and use health care guidelines on RD. The courses specifically trained participants to appraise health care guidelines for RD by using the AGREE II instrument, the international tool to assess the quality and reporting of health care guidelines.

The course agenda included an overview of the RARE-Bestpractices project, the state of art of European Reference Networks and related novel scenarios for guideline production, the basic concepts of the development of trustworthy guidelines, a short description of the available methodological standards and tools and an introduction to the RARE-Bestpractices databases. Then, it focused on the AGREE II instrument and its application to RD guidelines. The second day participants had the chance to apply the AGREE II instrument appraising a rare disease guideline and to discuss issues arising in the scoring exercise.

Tutors involved in the courses were methodologists and experts on RD and health policies coming from ISS (Domenica Taruscio, Paola Laricchiuta, Cristina Morciano) HIS (Karen Ritchie), Comprehensive Cancer Centre the Netherlands (Sonja Kersten), University of Glasgow (Michele Hilton Boon). In the first edition of the course from the European Commission participated Enrique Terol who gave a presentation on the health care guidelines in the framework of the constitution of the European Reference Networks.

Nineteen participants, mostly medical doctors and biologists, coming from 7 different countries (Italy, France, Romania, Lithuania, Sweden, Ireland, Slovenia) attended the first edition of the course. The second edition of the course was attended by eighteen participants (medical doctors and other health professionals) coming from 7 different countries (Italy France, UK, Germany, Hungary, Serbia, Australia).

All the course attendees were invited to participate in the RARE-Bestpractices project and to contribute to the development of the collection of RAREGUIDELINE. Coordinated by HIS, they were part of the group of contributors who were involved in the appraisal of the guidelines to be included in the database.

Two questionnaires were administered to the participants at the end of both courses: a pre-post test to measure changes in knowledge; a satisfaction questionnaire to seek feedback on the perceived overall value and quality of delivery of the training. The analysis of the answers to the questionnaires showed that the training courses succeeded in improving the

knowledge of the participants on the covered topics and that participants perceived the courses as a valuable learning experience.

The programmes of both courses are downloadable from the page "RARE-Bestpractices website > Platform resources > training activities.

Health Care Guidelines on rare diseases: quality assessment - 23-24 February 2015 Istituto Superiore di Sanità, Rome Italy: http://www.iss.it/binary/cnmr4/cont/Programme_GL_assessment_2015_01_15.pdf

Health Care Guidelines on rare diseases: quality assessment. Second edition 3-4 December 2015 Istituto Superiore di Sanità, Rome Italy: http://www.iss.it/binary/cnmr4/cont/Programme_GL_assessment_2015_10_12.pdf

Figure 6: Participants and tutors at the first edition of the International Course "Health care guidelines on rare diseases. Quality assessment"

Training tools

Four training tools produced by AREAS-CCI are accessible from the main menu of the home page RARE-Bestpractices website at *Platform Resources / Training Tools* (http://www.rarebestpractices.eu/pagine-28-training_tools):

1. The RARE-Bestpractices Glossary
2. Tutorial of AGREE II instrument on guidelines for RD. Application on a Guideline

3 and 4. Two Video Tutorials explaining what information is available in RareGUIDELINE and RareGAP and how to use the databases

1. The Glossary contains definitions of key terms used in the RARE-Bestpractices and aims to ensure understanding and consistent use of core terminology relating to RD, EBM, health care delivery and decision making tools. The Glossary is the result of a multidisciplinary collaboration of experts of the RARE-Bestpractices consortium. A PDF version contains a preamble and references for each key term along with a description of the methodology used to develop the Glossary. (RB-DEL. 6.6)

2. The tutorial of AGREE II provides a practical example on how the instrument can be applied to assess the quality and the development rigour of clinical guidelines on RD. Three AREAS-CCI authors independently assessed a guideline on “Motor neurone disease: non-invasive ventilation” (www.nice.org.uk/guidance/cg105). The results of the independent assessment were compared and disagreements were resolved by discussion. The final results are reported in a set of 31 slides. (RB-DEL. 6.7)

3 and 4. Two video tutorials explain what information is available in RareGUIDELINE and RareGAP and how to use the databases. The tutorials are developed as video and provide general description of the databases, show how to navigate on them and browse guidelines and research recommendations for RD. AREAS-CCI was in charge of this task with the support of JAMARAU for developing the videos.

Collaboration with the International Rare Diseases Research Consortium (IRDiRC) (WP7, Lead: ISS and BAPES)

RARE-Bestpractices partners actively participated in the activities of **the International Rare Diseases Research Consortium (IRDiRC)** providing important input and working to strengthen a proactive partnership. IRDiRC and RARE-Bestpractices project do share common objectives, namely to promote communication on the management of RD by disseminating trustworthy guidelines globally, to identify and prioritise RD research needs, and to facilitate timely, effective and efficient translation of research results into patient-oriented strategy on the clinical, as well as the public health level.

In the period of 2013-2016, RARE-Bestpractices partners took part in the meetings and teleconferences of IRDiRC's Interdisciplinary Scientific Committee. This ensured the synchronization of RARE-Bestpractices activities to IRDiRC priorities and recommendations. RARE-Bestpractices partners successfully identified IRDiRC Task Forces of particular interest for best practice documents collaboration and dissemination, such as Automatable Discovery and Access (ADA), Patient-Centred Outcome Measures (PCOM), Small Population Clinical Trials (SPCT), Data Mining and Repurposing (DMR) and Participant Unique Identifiers (PUID) Task Forces. These are specific groups, aiming to address the complex rare disease-related issues through comprehensive recommendations for multiple stakeholders. Project partners closely followed IRDiRC's progress in order to create synergies with the RARE-Bestpractices activities and deliverables.

International collaboration and coordination are crucial in the field of RD, as there are very limited amount of expertise and experience available. RARE-Bestpractices Consortium and IRDiRC have established effective communication channels and more importantly strong partnerships. Key RARE-Bestpractices deliverables are now well positioned and integrated within IRDiRC's research network. For example, RAREGUIDELINE and the training activities would help IRDiRC's stakeholders to spread expertise and knowledge in the field of guidelines. RAREGAP is now a highly beneficial tool for IRDiRC's overall obejctives, as institutions and funding agencies could use it to identify gaps in research and structure their calls.

Individual rare disease stakeholders have devoted themselves to rare disease issues for several decades, but these efforts have been fragmented and progress slow. In large this is due to difficulties inherent to this field, such as small numbers of patients and large heterogeneity of RD. Indeed, for many conditions, there are very limited amount of expertise and experience available. International collaboration and coordination have consistently emerged as an efficient way to foster overall progress in this field. The RARE-Bestpractices – IRDiRC partnership is a real-world example how to address this complex issue. This is a long-term commitment of global rare disease stakeholders to ensure RARE-Bestpractices' dissemination and sustainability within IRDiRC's activities beyond 2016.

Scientific coordination, networking (WP1, Lead: ISS)

Courses for health care guideline developers

In WP1, two training courses for health care guidelines developers have been organized by AREAS-CCI. The events were disseminated through the RARE-Bestpractices partners, the RARE-Bestpractices website (http://www.rarebestpractices.eu/), the Cochrane Italy website (http://www.cochrane.it/), the course faculties and other AREAS-CCI contacts, as well as Guidelines International Network (G-I-N), the GRADE working group, and the RARE-Bestpractices Twitter account @RAREBestP.

At the end of each course participants were asked to fill an evaluation form.

The first course "Course for health care guidelines developers on treatments of rare diseases" was held in Milan (Italy) at IRCCS Istituto di Ricerche Farmacologiche Mario Negri on 10-12 February 2016 and provided participants with the opportunity to acquire skills necessary to produce health care guidelines on TREATMENT of RD. The faculty was composed by members of the RARE-Bestpractices consortium (Domenica Taruscio, Joerg J. Meerpohl, Roberto D'Amico, Cinzia Del Giovane, Graziella Filippini, Silvia Minozzi, Vanna Pistotti, Juliette Senecat, Holger Schunemann) and by international experts of guidelines development, implementation and dissemination, as Nancy Santesso from McMaster University (Hamilton, Canada) and Elie Akl, from American University of Beirut (Beirut, Lebanon). Twenty-eight people, coming from Europe and Canada, attended the course. Fifty-seven percent of participants strongly agreed that the knowledge and information gained from participation at the course met their expectations, 69% evaluated the trainers as good communicators and 77% considered the trainers being knowledgeable on the topics. The courses material (multimedia, lectures, exercises, recommended articles) was sent by AREAS-CCI to the attendees.

The second course "Course for health care guidelines developers on diagnosis of rare diseases" was held in Modena (Italy) at the University of Modena and Reggio Emilia on 6-7 June 2016 and provided participants with the opportunity to acquire skills necessary to produce health care guidelines on DIAGNOSIS of RD. The faculty was composed by members of the RARE-Bestpractices consortium (Domenica Taruscio, Paola Laricchiuta Roberto D'Amico, Graziella Filippini, Silvia Minozzi, Holger Schünemann) and by international experts on systematic review and diagnostic test accuracy, Rob Scholten and Lotty Hooft from the University Medical Center Utrecht - Cochrane Netherland.

Nineteen people, coming from Europe, attended the course. Sixty seven percent of participants strongly agreed that the knowledge and information gained from participation at the course met their expectations, 87% evaluated the trainers as good communicators and 80% considered the trainers being knowledgeable on the topics.

The programmes of both courses are downloadable from RARE-Bestpractices website > Platform resources >training activities.

Course for health care guidelines developers on treatments of rare diseases at:

http://www.cochrane.it/sites/cochrane.it/files/public/uploads/programme_gl_febrary2016_newdeadline.pdf

Course for health care guidelines developers on diagnosis of rare diseases at: http://www.cochrane.it/sites/cochrane.it/files/public/uploads/Programme_GL_June2016_1.pdf.

5. Potential impact, the main dissemination activities and exploitation of results

Potential impact

RARE-Bestpractices is offering a response to the challenges of improving quality and consistency of BP for RD, in accordance with (i) the recommendations of 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” (article 12. 3,4 - Directive 2011/24/EU); and (ii) the more recent Commission delegated decision (C(2014)1408 f) which includes “develop and implement clinical guidelines” among the criteria and conditions that ERN must fulfil.
In this section, the impact of RARE-Bestpractices is outlined with reference to methods, policies, and partners and stakeholders.

Impact on Methods

A multitude of approaches in developing, evaluating, disseminating guidelines are utilized across European countries. Moreover, a lack of guidelines for the proper management of patients is currently experienced within the RD community.

The immediate impact of RARE-Bestpractices lies in overcoming the fragmented approaches currently being utilized in the EU. RARE-Bestpractices is offering a methodology which considers issues specific for RD, building on the GRADE approach and other existing initiatives in the field of “standards for guidelines”. The **common methodological quality standards for developing BP guidelines on RD**, developed jointly by the Consortium partners, patient representatives, invited experts and external advisors, consider both the GDC and the GRADE methodology appropriate for guideline development in the field of RD and have been summarised in a report and in a manuscript currently under submission in a peer review journal and that will be made publicly available once published. The method, already tested in the development of two pilot guidelines, can be considered as a useful resource for all the experts involved in the development of guideline on RD. Project partners also explored the utility of recurring to the graphical representation through standardised languages / notations of healthcare processes addressed in clinical practice guideline in order to increase comprehensibility and reduce possible misinterpretations.

Another investigated issue was the **appraisal of the methodological quality of rare disease (RD) guidelines**. In fact, RARE-Bestpractices partners clearly expressed the view that the role of high quality guidelines as tools for healthcare improvement is as relevant to rare as it is to common conditions and that standards should not be lowered for RD. The utility of the internationally adopted *AGREE II* instrument was verified also in the field of RD and, within the Project, some additional specific guidance was developed for those undertaking the appraisals of RD guidelines.

Finally, RARE-Bestpractices partners investigated the **principles for engagement of patients, carers, families and organisations with rare disease**. This methodological contribution is of help for all the researchers, policy makers and healthcare providers to support their efforts in evidence translation activities with the RD patient community.

An expected positive impact of the methodological work performed within RARE-Bestpractices will be on ERNs capacity of developing recommendations/guidelines on RD.

Impact on Policies

An important impact of the project is related to the **Value assessment criteria for orphan drugs**. The analysis performed within the Project suggests a significant variation in the outcomes of HTA processes for prescription of drugs, including OD, across Europe and an often very significant time lapses between the date of MA and the final HTA recommendation. This, of course, implies variations in access and highlight the importance of establishing specific policies for ODs, in order to ensure fair assessment and equitable access to treatment for RD. RARE-Bestpractices highlighted the need of standardise HTA processes or, at least, of supporting international HTA collaboration and communication between HTA agencies and manufacturers.

One of the tools developed within the project (see next section) is the *Rare-Bestpractices Research Recommendation Database* (*RAREGAP*). It is intended for the collection and dissemination of research recommendations specifically related to RD by pointing out records of diagnostic tests, treatments and other aspects of management of rare diseases that are known to be uncertain in their effectiveness or safety. *RAREGAP* will be useful in identifying priority areas for research and preventing unnecessary or accidental duplication of effort. With the aim of promoting the use of this database also beyond the project, a collaboration statement was signed with E-RARE 3, the transnational cooperation on rare disease research funding organizations that works in close collaboration with IRDiRC, EUCERD and EURORDIS also for identifying RD research needs.

Moreover, RARE-Bestpractices worked to strengthen a proactive partnership with **IRDiRC** with whom it shares common objectives, namely to promote communication on the management of RD by disseminating trustworthy guidelines globally, to identify and prioritise RD research needs, and to facilitate timely, effective and efficient translation of research results into patient-oriented strategy on the clinical, as well as the public health level. Key RARE-Bestpractices deliverables are now well positioned and integrated within IRDiRC's research network: *RAREGUIDELINE* and the training activities to spread expertise and knowledge in the field of guidelines, *RAREGAP* to identify gaps in research and structure their calls for funding research initiatives.

In order to ensure maximum impact on policy makers, a workshop was organised with stakeholders involved in the RD field from the European Commission, Health Ministries, ERNs and relevant networks/initiatives to improve awareness on project results.

Impact of developed tools on the partners and other stakeholders' capacity of action in the field of RD

Several tools have been developed within the project which give rise to a **Platform for sharing best practices for management of rare diseases**. The implemented comprehensive system of resources is facilitating the establishment of a community of stakeholders interested in cooperating and sharing knowledge in the field of guidelines on RD.

The **RARE-Bestpractices website** is conceived to be a high-quality information reference point providing both validated informative resources (collection of health care guideline, collection of research recommendations, training tools, methodological quality standards) and news about the project's activities. It will also greatly increase networking opportunities through a **user-friendly work environment** which facilitates cross-talk among different groups of stakeholders. More specifically, the two **databases** will have a great impact on those developing/adopting guidelines, for the research community and, as previously

reported, for the policy makers involved in the assignment of resources for the research. The *RAREGUIDELINE* will help to address the inequality that is potentially exacerbated where higher-prevalence disease guidelines are better resourced, better disseminated and more easily retrieved. *RAREGUIDELINE* will provide non-specialist practitioners with guidance on the management of patients with the included conditions. Moreover, ERNs can use the guidance presented within the database to support their functions and to assess the need for clinical guidelines development. The database tools can facilitate online consultation for guideline creation and should therefore support the development of new, or revised guidelines by groups of stakeholders who are geographically distant. Moreover, the project is enabling the large RD community to access RD guidelines transparently appraised for quality through a single point of access. The enhancement of methodological rigor of health care guidelines will increase the quality of guidelines and ultimately the health care for RD patients in a positive circle.

A great attention has been put during the project to the training in order to assist in RD guideline development and appraisal. **Training courses** have been organized and **Tools** developed. Tools are freely available in the project website.

Two new clinical practice guidelines have been developed recurring to the methodology agreed within the project and will be publicly disseminated for the benefit of the whole community. Two RD have been addressed: Catastrophic antiphospholipid syndrome (CAPS) and Sickle cell disease (SCD). In the latter case a **version intended for patients** and care giver has been developed too.

An important impact on the RD community has been achieved through the creation of a new **scientific international peer-reviewed open access journal**: *Rare Diseases and Orphan Drugs – an International Journal of Public Health (RARE Journal, http://rarejournal.org)*. The mission of RARE Journal is to provide an advanced forum on important aspects of public health, health policy, clinical research and evidence synthesis (e.g., HTA, health care guidelines) in ways that will improve health care and outcomes for persons suffering from RD, as well as globally increase RD experience sharing.

Main dissemination activities

Dissemination – in charge of WP6 - was central and continuous throughout the life of the project. A dissemination plan was prepared at the beginning of the project and subsequently updated. The dissemination activities were meant to reach the audiences identified as relevant to the project. The target groups identified were the researcher and health care professional community, the patient community and the policy makers and the stakeholders from relevant initiatives.
RARE-Bestpractices has produced 16 papers either published or currently submitted to peer-reviewed journals for publication, 100 oral presentations, 7 posters, 6 workshops/special sessions, 1 conference, and 18 E-News/web sections or posts.

Published papers are reported:

1. Morciano C, Basevi V, Faralli C, Hilton Boon M, Tonon S, Taruscio D. Policies on Conflicts of Interest in Health Care Guideline Development: A Cross-Sectional Analysis. *Plos One.* 2016;11(11).
2. Morciano C, Laricchiuta P, Taruscio D, Schünemann H. European Reference Networks and Guideline Development and Use: Challenges and Opportunities. Public Health Genomics. 2015;8(5).
3. Pai M, Iorio A, Meerpohl J, et al. Developing methodology for the creation of clinical practice guidelines for rare diseases: A report from RARE-Bestpractices. *Rare Dis*. 2015;3(1):e1058463. doi:10.1080/21675511.2015.1058463.
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The oral and poster presentations were given in several national, European and international events.

The dissemination workshops/special sections organised by RARE-Bestpractices partners include:

- parallel workshop “Patient involvement in best practices guidelines development: improving rare disease care” during the 2014 EURORDIS Membership meeting, Berlin (Germany);
- a workshop on rare disease and ethics group during the 2014 EAP Spring meeting, Rzeszow (Poland);
- the RARE-Bestpractices workshop *AGREEII. How to appraise a rare disease guideline* during the 2015 Congress of the European Academy of Paediatrics, Oslo (Norway);
- the workshop *Good clinical practice in the context of European Reference Networks* during the 2016 EURORDIS Membership Meeting, Edinburg (UK);
- the interdisciplinary session *Early childhood disabilities, rare diseases and guidelines* during the 2016 Congress of the European Academy of Paediatric Societies, Genève (Switzerland);
- the workshop *Developing and using health care guideline for rare diseases* at the French National Institute of Health and Medical Research (Inserm), Paris (France), 25 October 2016.

A final RARE-Bestpractices symposium was held in Rome, 24 November 2016, with the aim of disseminating the project findings and offering a forum for discussing with relevant stakeholders how results could be taken into account in delivering better health decision making and health policies for rare diseases. The event brought together leading experts in the area of evidence synthesis and guideline development to discuss the methodological advancements and knowledge resources developed by the RARE-Bestpractices Consortium and focus on mechanisms for ensuring the production of reliable, relevant, usable evidence in a bid to increase the value of research on rare disease. More than 70 delegate attended the Conference.

An important means of dissemination was the new scientific international peer-reviewed open access journal *Rare Diseases and Orphan Drugs – an International Journal of Public Health (RARE Journal, http://rarejournal.org)*. As previously reported, the mission of RARE Journal is to provide an advanced forum on important aspects of public health, health policy, clinical research and evidence synthesis (e.g. HTA, health care guidelines) in ways that will improve health care and outcomes for persons suffering from RD, as well as globally increase RD experience sharing. To date 10 issues were published (since 2014) and 4 supplements.

Six *newsletters* were published to provide dedicated information about the project results and achievements and are archived in the RARE-Bestpractices website. At the date of December 2016, the subscribers were 266.

A RARE-Bestpractices *Twitter™* account was created in March 2014 and, since then, 143 tweets were sent out. It has 279 followings and 475 followers (last check on February 2017).

Exploitation of results

Project results allowed RARE-Bestpractices partners to build a community characterised by an **effective network of expertise**, the **availability of working methodology** applicable in the field of RD for clinical practice guideline systematic *search*, *appraisal* with respect to methodological quality, *development*, *easy representation* for patients and care-givers, the **availability of specific tools** such as *guidelines repository*, *collection of research needs*, support for *training* of guideline developers and appraisers, *web-community* for remote interaction. Such a platform can be considered as a solid starting point to be exploited in future initiatives such as application for research / coordination calls, consultancy for interested organizations (e.g., Centres of Expertise, Scientific Societies, National Agencies) and hence an added value for both the RARE-Bestpracrtices partnership and, of course, the RD community.

More specifically, out of the project results highlighted in the *Potential impact* paragraph, some can be practically exploited:

- *RARE-Bestpractices Platform in the form of a project Website* – The website may constitute a solid basis for future initiatives (training, funded researches, provision of expert services, etc.) thanks to the developed repository (databases, training tools, project results) and collaborating tools (web community).
- *Best Practices Guidelines Database* – The database content is publicly available. It is intended to meet the needs of multiple stakeholders: Clinicians, patients and policymakers will be able to quickly and easily identify relevant guidelines on specific topics without needing to navigate complex interfaces or conduct difficult searches. Moreover, the value of the collection is increased by the fact that Guidelines have been appraised with respect to their quality using Agree II methodology. Guideline developers will be able to demonstrate the need for a particular guideline to funding bodies by demonstrating gaps in current guideline coverage, scope, or quality as recorded in the database. Researchers will be able to use the database to investigate the translation of evidence into guidelines, for example, or for epidemiological research into guideline coverage and quality.
- *Research Recommendations Database* – The database content is publicly available. It will ensure that RD guideline developers, researchers and patient organisations have access to a well-designed platform for disseminating research recommendations.
- *WEB Community* - The web-community is publicly available and can be exploited to build cooperating networks involved in research / guideline development in the field of RD.

6. Project public website and relevant contact details

For additional information please visit the Project WEB site: www.rarebestpractices.eu

Project Coordinator	Dr. Domenica Taruscio
Coordinating Beneficiary	National Centre for Rare Diseases Istituto Superiore di Sanità Via Giano della Bella , 34 00161 - Rome, Italy
e-mail	rare-bestpractices@iss.it domenica.taruscio@iss.it
phone	+39 06 49904016
fax	+39 06 49904370

7. Document History

Date	Author	Changes
28/09/2016	P. Mincarone	Template preparation
23/12/2016	L. Thompson	Contribution added on Project Databases and principles for engagement with rare disease patients, carers, families and organisations
08/01/2017	G. Iskrov	Contribution added on the rare Journal and on the collaboration with IRDiRC
11/01/2017	G. Filippini	Contribution added on the training courses
12/01/2017	M. Boudes	Contribution added on the Patient version of the SCD guideline
16/01/2017	J. Auld	Contribution added on the Platform
20/01/2017	J. Meerpohl	Contribution added on the Guideline Development Methdology and Pilot Guideline on SCD and CAPS
08/02/2017	V. Tzouma	Contribution added on value assessment criteria for Orphan Drugs
16/02/2017	C. Morciano	Added contribution and made revisions in RARE-Journal paragraph Added contribution and made revision in project IT Platform chapter Revision in Training Courses chapter
20/02/2017	P. Laricchiuta	Project context and objectives added Paragraph order changed
21/02/2017	P. Laricchiuta	All paragraphs revised Paragraph “Courses for health care guideline users” added
24/02/2017	P. Laricchiuta	Paragraph order changed Revisions in all paragraphs
28/02/2017	P. Mincarone	Minor edits
01/03/2017	M. Boudes	Public version of the pilot guideline revised
01/03/2017	K. Ritchie	WP4 results revised
01/03/2017	P. Mincarone	Main dissemination activities section added. Executive summary added (still to be shortened)
04/03/2017	G. Filippini	Paragraphs “Analyse the state of art of BP guidelines” and “Training tools” completed
05/03/2017	J. Auld	Minor edits in the paragraph “Platform infrastructure”
06/03/2017	J. Meerpohl	Minor edits in the paragraph “Pilot guidelines”
07/03/2017	P. Kanavos	Minor edits in the paragraph “RD technologies and value assessment”
07/03/2017	P. Mincarone	Paragraphs “Potential impact” and “Exploitation of results” added.

		Executive summary and List of acronyms and abbreviations updated
08/03/2017	G. Iskrov	Minor edits in the paragraph “Rare Diseases and Orphan Drugs – an International Journal of Public Health”
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13/03/2017	P. Mincarone	Table 4: Communication activities based on inputs from UKLFR
14/03/2017	P. Laricchiuta	Executive summary - Revision of the first paragraph and comment “Summary description of project context and objectives” revision “Impact” comments
17/03/2017	P. Mincarone	Revision of the executive summary and of the Impact paragraph. Minor revisions and formatting all-over the document
02/04/2017	General Assembly	Approval
03/04/2017	Domenica Taruscio	Final Approval