Evaluation Report on the European Joint Action Project RD-ACTION (Promoting Implementation of Recommendations on Policy, Information and Data for Rare Diseases) (Grant No. 677024)

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RD ACTION Evaluation Report (2018)

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1. Introduction

Rare diseases (RD) – although numerous (almost 6000 RD have been described to date) and heterogeneic in nature – share a variety of specific problems, like poor recognition leading to diagnostic delay and inappropriate management including adapted social services, poor health outcomes, social burden, limited knowledge on natural history and pathophysiology resulting in an insufficient development of new therapies. These issues make a global, multi-stakeholder approach building shared strategies necessary. The RD-Action project was therefore set up to meet the diverse challenges of RD at a European level, the wide geographic coverage being key to its anticipated success.

The general objectives of RD-Action were to:

- Support the further development and sustainability of the Orphanet database, the biggest global repository of information on RD;
- Contribute to solutions to ensure an appropriate codification of RD in health information systems;
- Continue implementation of the priorities identified in Council Recommendation 2009/C151/02 and the Commission Communication COM 2008 679 on RD, with a view to ensuring the sustainability of the recommended priority actions and to support the work of the Commission Expert Group on Rare Diseases (CEGRD). [Of note, the mandate of the CEGRD ended during the course of RD-Action, a direct replacement has not been installed so far.]

RD-Action was designed to expand and consolidate the achievements of the previous two Joint Actions on RD supported by the European Commission, the "Joint Action Orphanet" and the "EUCERD[1] Joint Action (EJA)". Its main goal was to help member states to implement the measures recommended by the CEGRD and to produce the data necessary to do so. In order to achieve a more holistic approach, the project design followed a transversal structure. It thereby integrated previously independent activities into an overarching project structure with several different work packages to substantially increase networking between the different areas, provide better links between partially synergistic projects, and avoid duplication of parallel efforts.

The individual work packages were:

- WP1 – Coordination
- WP2 – Dissemination
- WP3 – Evaluation
- WP4 – Orphanet, the European database for rare disease
- WP5 – Steering, maintaining and promoting the adoption of Orpha codes across MS
- WP6 – Policy Development for RD and Integration with other relevant initiatives

[1] EUCERD: European Union Committee of Experts on Rare Diseases, the official follow-up committee to the Rare Diseases Task Force (RDTF), established by the Commission Decision 2009/872/EC and composed of a variety of stakeholders including health ministry representatives from all European Member States, representatives from patient organisations and experts from previous or ongoing projects in the RD field. The EUCERD was later followed by the Commission Expert Group on Rare Diseases (CEGRD).

Eventually the project was expected to promote the transfer of European recommendations into national policies, as well as the channelling of information from individual member states to the CEGRD, and thus to the European Commission.

The present report – which is prepared in the frame of work package 3 – sums up the outcomes of the different work packages, in particular with respect to the indicators that were already specified in the grant agreement. In some instances, additional indicators are defined and evaluated. An overview is given about the results and achievements of each work package, and statements on the possible impact for the rare disease field, as well as a further outlook are provided.

2. Methodology

2.1. Structure of the report

The report follows the structure of the project, treating each work package in a separate section. A brief description of the respective work package is followed by a list of the specific objectives and the concrete tasks (as stated in the grant agreement). For each task, one or more sets of indicators (process – output – outcome, and, in some instances, impact; again as proposed in the grant) is shown in table format. The evaluation of each indicator is shown on the right hand side of the table, and a short verbal description of the results is given below. Conclusions and/or a short discussion of the expected impact, as well as a brief outlook on possible next steps and/or future plans complete each section.

2.2. Data retrieval

In a first step, all information available on both the external and internal RD-Action project website was downloaded, sorted according to the work packages, and analyzed for any information and/or figures necessary for the evaluation of each task. This was complemented by screening other project and institutional websites of RD-Action participants for any additional information suited to support the evaluation of the project. Furthermore, the three RD-Action technical reports were analyzed in detail. Partners of the Joint action were asked directly to provide any missing information.

2.3. Indicators

Indicators used include process, output, outcome, and – in some instances – impact indicators. These types of indicators are defined as follows:

- Process indicators

  Process indicators directly describe the processes that lead or contribute to certain outcomes. They are usually no guarantee that the desired outcome will actually be achieved, but they can show that the activity is headed in the right direction (or else help to make corrections at an early stage).

- Output indicators

  Output indicators measure the product, the direct result of an activity. They can therefore be seen as a gauge of process performance, i. e. of the effectiveness of an operation. They still tell us nothing about the usefulness of an activity.

- Outcome indicators

  Outcome indicators are a means to describe the changes that are achieved by certain measures. They are therefore more direct indicators of the effects and benefits of a project.

- Impact indicators

  Impact indicators describe the intended ultimate (short-term or long-term) effect of a measure. They are usually the result of not a single one, but the sum of the outcomes of a project. Also, it may not be possible to measure these indicators immediately after the measures were taken (which is why most indicator sets do not include impact indicators in this report), but depend on long-term observations.

Most indicators used for RD-Action evaluation were already laid down in the grant agreement. They were designed for the specific objectives, but as some work packages overlap in content (to streamline efforts in common fields, the workload for certain areas was sometimes shared between different work packages), the indicators may be applied to more than one work package in this report. In some areas, the project content may have changed during the duration of the grant, so that indicators were adjusted accordingly. Some indicators / indicator sets were newly created. As mentioned before, direct impact measurement is mostly not possible at this point, so that the assessment of the impact of RD-Action will mainly be carried out in a merely verbal format in this report (see below).

2.4. Indicator sets and color coding in the indicator boxes

For better readability, the indicators laid down in the grant agreement were modified in matters of layout into a box-like format, grouping related process, output, outcome and impact indicators in a combined indicator set and subsequently displaying each set in an individual box. In case a task had to be evaluated by more than one indicator set, the sets used were numbered in ascending order ("Suggested Indicator Set 1", "Suggested Indicator Set 2", etc.). Likewise, all additional indicators defined in work package 3, task 3.1, for the evaluation of selected conferences, workshops and the testing phase of the master file with Orpha codes were transformed into an equivalent indicator set format and are presented as separate indicator boxes (titled "Additional suggested Indicator Set from Grant Agreement WP 3, task 3.1: *[title of the specific task*]"). Finally, all newly introduced indicators were also developed in the same set format and are shown in indicator boxes named "New Indicator Set".

In each indicator box, the related process, output, outcome and impact indicators are listed on the left hand side of the box, while on the corresponding right hand side, the degree of completion of each individual indicator – as basis of the positive or negative evaluation of each element – is indicated with the tags "fulfilled", "partially fulfilled", "fulfilled in some cases", "ongoing", "pending", "not performed", and "not applicable". To further visualize the evaluation results for each indicator at first sight, a color coding system was introduced, highlighting each result in green, blue, or red, respectively.

For this color coding, the following rules were applied:

- Green color:

  The green color generally indicates the complete or predominant fulfillment of an element. Green color coding was used when:

  - The indicator fully met or even exceeded the target (in case the indicator was a preset number that had to be reached);
  - The indicator was predominantly fulfilled with only minor work missing or with a deviation from the target of less than 10% of the target value (when the indicator was a preset number);

- The indicator was partially fulfilled in a repetitive task and the results gained in this limited subset of task elements indicate that for the remaining elements where the task was not applied similar to identical results were to be expected (for instance the satisfaction evaluation in a series of workshops, where all surveys performed in a selection of workshops indicate an overall high degree of satisfaction with the content and the organization of the meetings; such a result was interpolated to the rest of the workshops without a survey, leading to an overall positive evaluation of the overarching task);
- The original task was not fulfilled due to a justifiable reason, but one or more similar tasks were performed instead meeting the same goals as intended with the original indicator and thus being a valid substitute for this element.

- Blue color:

  The blue color generally highlights an indicator that was defined prior to the project in the Grant agreement and that is not (fully) applicable to the original task any more due to a change in the circumstances of the project that was out of the responsibility of all project participants. Blue color coding was thus used when:

  - The indicator aimed at a task linked to a specific key institution or entity that was terminated in the course of the project; as a consequence the original indicator could not be fulfilled anymore (this was for example the case with the termination of the mandate of the CEGRD slightly more than one year after the start of RD-Action);
  - The indicator was a number that could not be reached due to the termination of a key institution or entity in the course of the project (i. e. the termination of the CEGRD);
  - The indicator was a number setting a base target that turned out to be irregularly high when revisited at the end of the project due to misleading technical limitations at the time of the Grant agreement when the indicator was defined;
  - The indicator could not be completed and is still ongoing or pending since external institutions are still reviewing the task results that – in principle – have been delivered by the project partners, thus delaying its finalization until the end of the project and beyond.

- Red color:

  The red color finally flags an indicator that was not fulfilled within the frame of the project due to delays caused by or deliberate decisions made by the project partners, which therefore bear the full responsibility for the deviation from the initially project plan. Red color coding was therefore used when:

  - The indicator-related task was not performed by the Joint Action partners due to different reasons explained in the corresponding chapter evaluating the not successful implementation and finalization of the element in question;
  - The indicator was a number that could not be reached – not even close – during the course of the project;
  - The indicator-related task is still ongoing and the indicator itself is not completed, thus being evaluated as “pending”;
  - The information and confirmation on the completion of the indicator is still in preparation and/or not available at the termination of the project; in these instances, the element was again categorized as “pending”.

2.5. Assessment of the future impact of RD-Action

In a field developing as rapidly and sometimes unpredictably as the rare disease field, it is impossible to define impact indicators on the mid- to long-term effects of certain measures of a project in advance. The cessation of the Commission Expert group on Rare Diseases (CEGRD) during the course of RD-Action without implementation of a follow-up political body is a prime example of this challenging situation. Nevertheless, in some instances, RD-Action outputs have already been adopted and are being developed further, and more results will be used in the near future (in these cases, the information stems from RD-Action partners who are also members of official European committees, or have been invited for preliminary discussions in such committees). The report will highlight these already ongoing or soon to be expected developments in its last chapter providing some insights into possible ways for the continuation of the work initiated and carried out by all the Joint Action participants and turning the attention finally to the legacy of RD-Action.

3. Results

3.1. Work package 1 (Coordination)

Description

The main objective of this work package was to manage the action and to make sure that it would be implemented as planned. It was the responsibility of the coordinating team to establish an effective and efficient governance, and to ensure smooth communication and information exchange among participants. Important tasks were monitoring of all project activities, ensuring quality of the implementation of the project, risk management, and budget management. The coordinating team was supposed to provide day-to-day administrative support to the project partners. Timely communication with the CHAFEA and DG SANTE was also assumed by the coordinator.

The coordinating team was located at Orphanet/INSERM (Institut national de la santé et de la recherche médicale).

Specific objectives

1. Establish an effective and efficient governance.
2. Ensure smooth communication and information exchange amongst Joint Action participants & stakeholders.
3. Monitor the activities & ensure quality of the JA implementation.
4. Provide day to day administrative support to the partners.
5. Ensure all communication with the CHAFEA and the DG SANTE, including timely presentation of all deliverables, technical and financial reports.
6. Ensure risk management.

Tasks

For work package 1, no indicators were suggested in the grant agreement. The following indicators were defined after completion of the RD-Action project.

- **Task 1.1: Organization of the Joint-action kick-off meeting**

New Indicator Set	
o Process Indicator	
▪ Nomination of an organizing and a program committee	**Fulfilled**
▪ Organize conference calls of the program committee members	**Fulfilled**
▪ Organize the Joint-action kick-off meeting	**Fulfilled**
o Output Indicator	
▪ Production and delivery of a meeting report	**Fulfilled**
o Outcome Indicator	
▪ Number of attendants at the kick-off meeting	**64**

The organizing committee for the kick-off meeting was recruited from experienced staff from the coordinating team that had already been in charge of organizing similar – and successful – meetings for EU-funded Orphanet projects in the past. The accompanying program committee included all work package leaders and co-leaders, as well as some staff personnel from selected work packages thus resembling the “Executive Committee” (ExCom) of the Joint Action project. The ExCom developed the agenda of the meeting and assigned certain tasks within the Kick-off meeting to selected members, communicating via several conference calls and Email correspondences in-between.

The RD-Action kick-off meeting itself was held in Luxemburg on September 16, 2015. A meeting report was published on the RD-Action internal website. Attendance at the meeting was high (participating members of the general assembly: 32; designated collaborating partners: 5; collaborating partners: 6; observers: 21).

- **Task 1.2: Monitoring of the activities and overall quality of the project**

New Indicator Set	
o Process Indicator	
▪ Organize conference calls for participants on a regular basis	**Fulfilled**
o Output Indicator	
▪ Produce and distribute the minutes of the conference calls	**Fulfilled**
o Outcome Indicator	
▪ Number of progress reports from work package representatives during the conference calls	**75**

Between June 15, 2015, and June 14, 2018, 17 conference calls for the RD-Action Executive committee (composed of leaders and/or further representatives of each work package were organized. During each call, work package leaders (or their representatives) were supposed to report on the current status of their work package in a structured manner (13 status reports each were delivered from work packages 1, 2, 4, 5, and 6; 10 from work package 3). Minute reports were prepared for each call and published/archived on the internal website.

- **Task 1.3: Ensure communication and information exchange amongst Joint action participants**

New Indicator Set 1	
o Process Indicator	
▪ Publish an internal RD-Action newsletter on a regular basis	**Fulfilled**
o Output Indicator	
▪ Archive of the newsletter editions	**Fulfilled**
o Outcome Indicator	
▪ Number of newsletters published	**14**
▪ Satisfaction with the newsletter assessed in the partners' survey	**Fulfilled**

Fourteen issues of the internal RD-Action newsletter "RD-ACTIONews" were sent to the members of the Joint Action consortium between November 2015 and July 2018. The newsletter mainly contained information on activities and achievements within the different work packages, as well as meetings in the frame of RD-Action. The archive containing all issues of the newsletter is accessible to all partners. Satisfaction with the newsletter was assessed in the year one partners' survey. Of 23 respondents, 43.48% / 47.83% were very satisfied, or satisfied, respectively, with the RD-ACTIONews newsletter. 43.48% stated that they read the entire newsletter, 39.13% only the sections that interested them. Overall, 52.17% were very satisfied with the content of the newsletter (somewhat satisfied: 26.09%).

New Indicator Set 2	
o Process Indicator	
▪ Nomination of an organizing and a program committee	**Fulfilled**
▪ Organize conference calls of the program committee members	**Fulfilled**
▪ Organize annual meetings for RD-Action participants	**Fulfilled**
o Output Indicator	
▪ Production and distribution of meeting reports	**Fulfilled**
o Outcome Indicator	
▪ Satisfaction assessed in participants' surveys	**Fulfilled**

Four meetings were held in the frame of RD-Action: 1) the kick-off meeting in Luxemburg on September 16, 2015; 2) the annual meeting in Paris on October 26 and 27, 2016; 3) the annual meeting in Paris on October 10 and 11, 2017; and the final meeting in Paris on June 28, 2018. The meetings comprised a general part, as well as work package dedicated sessions. The local organizing team and the program committee already established for the kick-off meeting (see Task 1.1) continued their work providing either the full administrative and logistical support for all meetings or discussing and elaborating the details of each meeting agenda, followed by the assignment of general, as well as work package-specific tasks to the committee members. For direct communication, several conference calls ahead of each meeting were organized, followed by further exchanges in written via Email. Meeting reports were published on the internal RD-Action website. Participants' satisfaction with the meetings was assessed in surveys (overall satisfaction rate 89.5% in 2015; 100% in 2017 and 2018).

New Indicator Set 3	
o Process Indicator	
▪ Set up an internal project website for RD-Action	**Fulfilled**
o Output Indicator	
▪ RD-Action website online	**Fulfilled**
o Outcome Indicator	
▪ Satisfaction with the website assessed in the partners' survey	**Fulfilled**

RD-Action extranet was set up as an internal homepage dedicated to the Joint action partners. It provided a wide range of tools and documents per work package which were updated regularly by the coordinating team and/or work package leaders. Certain restricted areas were reserved for the different joint actions committees or working groups. Satisfaction with the website was assessed in the year one partners' survey. Of 23 respondents, 39.13% were very satisfied with the internal webpage (47.83% satisfied). Most partners used it about once a month (52.17% of respondents), mainly to access the RD-ACTIONews newsletter (69.57%), access other documents (65.22%), access links to work package progress reports (52.17%), and access Executive committee reports (30.43%). Less frequent motivations to use the website were to access the grant agreement or consortium agreement, or to access the tracking table (17.39% each).

- **Task 1.4: Intermediary for all communication with the CHAFEA and the DG SANTE**

No specific indicators were defined for this task. All communication with the Commission Services and the CHAFEA were coordinated and performed by the coordinating team. This included – inter alia – a close exchange between the coordinating team and all RD-Action partners, as well as close communication between the coordinating team and the CHAFEA regarding the four amendments of the contract in the course of the project.

Summary and conclusions

With their longstanding experience in the leadership of a large consortium spanning many countries with very different prerequisites, the coordinating team of the Joint Action was predestined and well prepared for this task. To provide optimum conditions for the functioning of the partnership, a common webpage was set up, and a successful kick-off meeting organized at the beginning of the project. To ensure smooth communication and information exchange at all times, regular conference calls were held, where work package leaders or representatives reported about the status and progress of their work. In addition, a bi-monthly internal newsletter was sent out within the Joint action consortium. The editorial board of the newsletter was composed of members of the RD-Action Executive committee. A total of four annual meetings (including the kick-off and the final meeting) guaranteed effective personal communication between the cross-linked work packages.

Overall, organization of the coordination proved very effective and was positively evaluated by the consortium members, as assessed by two partners' surveys. According to the results, the majority of partners were very satisfied or satisfied by the support given by the coordinating team (84.6% in year one partners' survey, 92.6% final partners' survey). The success was mainly made possible by the aforementioned, longstanding experience of the coordinating team and by the use of well-tried communication structures. Not only was the project completed successfully, but also were close ties established between the project partners and cooperations in the rare disease field generally strengthened.

3.2. Work package 2 (Dissemination)

Description

The overarching goal of work package 2 was to disseminate rare disease-related information and improve the two-way information flow between national and European institutions. The work package aimed to ensure the appropriation of the EU-level regulatory framework and Joint action activities at national level, and to facilitate the integration of EU developments into the national systems by the local authorities and other institutions and stakeholders. In this context, the diverse national and local situations would have to be taken into account. On the other hand, emerging national initiatives should be shared with EU policy makers and amongst stakeholders.

Maximum inclusion of all stakeholders in all dissemination activities was the pivotal principle of this work package. Therefore, the first steps of this part of the project were a detailed analysis of all relevant stakeholders involved, and the elaboration of a dissemination plan (deliverable D2.1) for the Joint action which included a detailed description of the "what, why, to whom, when, and how" of the dissemination activities. For each component of this work package, the dissemination plan encompassed the identification of end users, dissemination partners, communication tools, correlation to other work package deliverables, evaluation of the plan, and timing. All subsequent dissemination activities (see below, specific objectives) followed the structure laid out in this plan.

The main purposes of dissemination were to raise awareness, inform / educate, engage (i. e. get input/ feedback from the community and encourage mobilisation of stakeholders), and promote (i. e. "sell" outputs and results of RD-Action). A wide variety of dissemination methods and tools were used to achieve this, including media channels, formal materials, conferences, workshops, and face-to-face meetings to share information amongst all relevant stakeholders.

Specific objectives

1. Set up and maintain the Joint Action dissemination tools.
2. Produce a twice-monthly newsletter of the rare disease community, Orphanews.
3. Hold the European Conference on Rare Diseases and Orphan Medicinal Products in May 2016, in Edinburgh.
4. Support the national workshops aimed at disseminating at national level the Joint Action activities and the Recommendations produced and adopted by the EUCERD and the Commission Expert Group on Rare Diseases (CEGRD).
5. Support national authorities for sustainable and resilient health systems.

Tasks

- **Task 2.1: To set up and maintain the Joint Action dissemination tools**

  For this task, two indicator sets were suggested in the project proposal to evaluate its effects and performance. Some of the indicators are shared with work package 6. The original indicator sets are accompanied by further indicators developed in the frame of this evaluation report.

New Indicator Set 1	
o Process Indicator	
▪ Perform a stakeholder analysis for information dissemination in the frame of RD-Action	**Fulfilled**
o Output Indicator	
▪ List of key stakeholders to be addressed in the frame of RD-Action	**Fulfilled**

A stakeholder analysis was carried out in order to better target key stakeholders and recognize the messages that are important for the different audiences, as well as to prioritize stakeholders, and to identify which messages and tools are best to reach them.

The following target groups were identified:

- Partners of RD-Action
- Members of the CEGRD
- National and local competent authorities
- EU decision makers
- Patients advocacy and support groups representing the patients and their families
- Health professionals
- Industry
- Academia, learned societies, and researchers
- Regulators
- HTA (health technology assessment) bodies / reimbursement authorities (stratification into European, national, regional, and local levels)

For each target group, the specific interest in RD-Action, the dissemination purpose, and the channels of dissemination were defined. This information was summarized in a table and published as an annex to the dissemination plan (see below).

New Indicator Set 2	
o Process Indicator	
▪ Develop a dissemination plan for RD-Action	**Fulfilled**
o Output Indicator	
▪ RD-Action dissemination plan (deliverable D2.1) published on website	**Fulfilled**

The RD-Action dissemination plan was developed as described in the introduction to this section. The plan included the dissemination rules of the Joint Action, the stakeholder analysis, and a dissemination chart in table format as annexes. It was sent out to all partners and published on the RD-Action website.

Suggested Indicator Set 1	
o Process Indicator	
▪ Present the State of the Art of RD activities in Europe	**Fulfilled**
o Output Indicator	
▪ An ongoing, electronic State-of-the-Art resource on policies for RD across the EU MS (with an annual summary report)	**Fulfilled**
o Outcome Indicators	
▪ Web-stats on the number of visitors to the online resource	**Not performed**
▪ Number of downloads of the SoA annual summary (maintain current level of 15,000 per year)	**Not performed**

This indicator set partially overlaps with work package 6, which was responsible for the preparation of the State-of-the-Art report.

Since 2016, the production of the "Resource on the State of the Art of Rare Disease Activities in Europe" has been in the hands of RD-Action (previously, this had been a task of the EUCERD Joint Action). The resource comprises an Overview report, summarizing (amongst others) key European rare disease policy-related documents; the status quo in Europe regarding national plans and strategies; highlights on transversal topics such as registries, genetic testing, research; and rare disease policy frameworks of non-European countries. In addition, country-specific data relating to rare disease activities at the national level in member states are being collected continuously (also after the end of the RD-Action funding period) using an online question bank. All these resources are freely accessible to the general public on the RD-Action website (web-stats were not available at the time of the preparation of this evaluation report). The next formal update of country-specific data will take place in fall 2018 (i.e. post RD-Action).

Suggested Indicator Set 2	
o Process Indicator	
▪ Facilitate sharing of experiences on how to implement RD Recommendations and Policy outputs at national level	**Fulfilled**
o Output Indicator	
▪ Set-up forums on SoA resource dedicated to thematic areas, making accessible the key resources and enabling online discussions via interested stakeholders	**Not performed**
o Outcome Indicators	
▪ Number of visitors to these subject-specific pages	**Not performed**
▪ Number of countries visiting these pages	**Not performed**

To facilitate sharing of experiences on how to implement rare disease recommendations and policy outputs at national level can be seen as one of the central tasks of work package 2. In particular, this was achieved via the EUROPLAN meetings, which were designed to assist member states in the implementation of their rare disease national plans (see Task 2.4). However, the idea to set up online forums to facilitate sharing of national experiences was eventually abandoned (or at least not followed up any further within the scope of RD-Action). This was due to a combination of factors:

- Firstly, it took a lot longer than planned to establish the new format for the SoA country reports (agreeing the questionnaire, creating the survey, but – most significantly – creating the Data-Contributing-Committees and encouraging them to commence operations).
- Secondly, the expiration of the Commission Expert Group on Rare Diseases hampered the creation of these planned fora, as there was no authoritative body to advise / agree to participate.
- Thirdly, the development and implementation of the ERNs became a greater priority than anticipated, and the work package 6 team's focus of necessity moved much more in this direction, limiting the time and resources to initiate virtual fora for SoA stakeholders.
- Fourth, in the absence of an Expert Group, word spread of EC plans to create a Steering Group to identify and expand good practices. The exact scope and purpose of such a Steering Group was not clear, however, and thus plans for the SoA forums were deferred, to avoid possible duplication (which was a possibility mid-project, if the Steering Group was going to address rare disease issues in Member States.)
- Finally, in the absence of an Expert Group for rare diseases, and no dedicated EC policy officer to oversee European RD activities, it was difficult to engage DG SANTE colleagues in discussions on the future and sustainability of the SoA resource: this persuaded the work package 6 team not to proceed with the plans to create virtual fora under the RD-ACTION lifespan, as there was no clear route to sustain this resource. (Of Note, the Newcastle team agreed to continue the country collection following the end of RD-ACTION funding, for as long as possible, but could not commit to sustaining this new dimension to the resource)

- **Task 2.2: To produce the Orphanews newsletter**

Suggested Indicator Set	
o Process Indicator	
▪ Ensure an efficient information flow between the European level and the MS level	**Fulfilled**
o Output Indicator	
▪ Publication of 20 Orphanews issues per year	**Fulfilled**
o Outcome Indicator	
▪ Number of Orphanews subscribers increased compared to 15,700 subscribers in 2014	**12,800**
▪ Satisfaction of Orphanews readers	**Fulfilled**

OrphaNews is a freely available, bi-monthly electronic newsletter presenting an overview of scientific and political news about rare diseases and orphan drugs. As the communication tool not only of Orphanet, but of RD-Action in general, it is specifically intended for the rare disease community. With 15,700 subscribers in 2014, it reaches a broad public audience. At first glance, the number of subscribers seems to have decreased by about 15% by the end of the Joint Action, however, the mere comparison of these figures results in a misleading conclusion since the IT tools, the editorial software and the software for the delivery of the newsletter to subscribers – the latter also used inter alia to calculate user frequencies –, have been changed completely between 2014, the time before the start of the Joint Action, and 2018, when RD-Action came to an end. To cite the annual report comprising the third project period (to be published soon): "At the start of 2017, the OrphaNews newsletter also underwent a complete makeover. A new front and back office have improved the look and feel of the newsletter, ease publication processes, and also allow for the implementation of new functionalities. Navigation has been improved through the construction of distinct sections, articles can be shared more easily, and the design is responsive on a range of different mobile devices. Users can now search the archives using an in-house thesaurus of terms, making it easier to find information concerning a certain subject or disease". In addition, the new software allowed for the first time to detect and subsequently exclude inactive users and error mails from the subscription list, delivering the OrphanNews newsletter only to active and functioning mailboxes. As a side effect, new frequency calculations thus included only active users, omitting any inactive or (meanwhile) incorrect mailboxes. In other words, the difference between the total number of subscribers in 2014 and in 2018 at the end of the Joint Action is primarily based on the detection and omission of inactive subscribers. Due to this significant change in the tools and methodology, the outcome indicator measuring the number of subscribers is not fully applicable any more. However, looking at the latest figure as such that still resembles a significant audience for a newsletter in the rare diseases field, it is highly probable to assume that the number of active subscribers at least did not change over the years. Between June 2015 and June 2018, 54 issues of the newsletter were published. The satisfaction of Orphanews readers is assessed on a regular basis in the frame of the annual Orphanet online user satisfaction survey. The results of the 2017 survey showed that 82% of Orphanet users knew the newsletter, and 80% of those familiar with this service rated it "very useful" or "useful" for their own use.

- **Task 2.3: To hold the reference European Conference on Rare Diseases and Orphan Medicinal Products in 2016**

Suggested Indicator Set	
o Process Indicator	
▪ Facilitate the dissemination of knowledge and information and allow input between all the stakeholders	**Fulfilled**
o Output Indicator	
▪ Organization of the European Conference on Rare Diseases involving patients, healthcare professionals, researchers, policy-makers, industry	**Fulfilled**
o Outcome Indicators	
▪ Number of participants (800)	**757**
▪ Satisfaction survey of the participants	**Fulfilled**

Additional suggested Indicator Set from grant agreement WP 3, task 3.1: Organization of the European Conference on Rare Diseases and Orphan Medicinal Products (ECRD) in 2016	
o Process Indicators	
▪ Nomination of a program and an organizing committee	**Fulfilled**
▪ Meetings and conference calls of these committees	**Fulfilled**
▪ Development of a conference website and of other information tools like stakeholder-tailored flyers	**Fulfilled**
▪ Range of different themes and topics of the ECRD including accompanying satellite meetings and tutorials	**Fulfilled**
▪ Coverage of the different stakeholders participating in the program committee and the conference	**Fulfilled**
o Output Indicators	
▪ Number of invited lectures	**75**
▪ Number of oral presentations and posters selected from submitted abstracts	**200 posters**
▪ Production of further information material like newsletters or an online conference report	**Fulfilled**
o Outcome Indicators	
▪ Number of participants by stakeholder groups	**Fulfilled**
▪ On-site participant satisfactory surveys for each session	**Not performed**
o Impact Indicators	
▪ Degree of dissemination of the final conference report	**Information pending**
▪ Coverage of the conference in classical and social media	**Information pending**

The altogether eighth European Conference on Rare Diseases and Orphan Medicinal Products (ECRD) took place in Edinburgh on May 26-28, 2016. This conference series is organized as a biennial event, bringing together all stakeholders, and covering all aspects within the rare disease field. The organization was carried out in a highly professional manner with a dedicated program committee composed of representatives of the different stakeholder groups and in charge of developing and shaping of the conference program, as well as an event-experienced organizing committee responsible for the administrative and logistic tasks.

A broad range of information materials was provided on the ECRD website. In numbers, there were 757 participants (46% patients organizations, 31% academics/health care professionals/ government workers/policy makers/payers/regulators, 20% pharmaceutical industry/ERTC members/consultants/investors, and 3% medical students/post graduate trainees) from 48 countries, >120 session chairs, speakers, and panelists, 28 sessions, and 200 posters. An evaluation questionnaire was made available and returned by 310 attendees (41% response rate). When asked to what extent ECRD 2016 met their expectations, 29% answered “5 / very high” (49% “4 / high”). When asked how much participants learned that would be useful for them in their work, 17% answered “5 – very much” (44% “4 – much”). When asked to what extent they agreed with the following statement: “In the sessions I attended at ECRD 2016, I learnt/heard information that has helped me to refine my thinking on that particular topic”, 23% answered “5 – very high” (44% “4 – high”). 70% said they ‘strongly agreed’ or ‘agreed’ that they had the opportunity to meet new people who would have value to them in their work. An

executive summary of the conference was prepared for broad distribution after the meeting (the summary is still available online on the ECRD website). Other forms of dissemination / media coverage included for example the presence in classical and social media (like the EURORDIS Facebook page and a conference-related Twitter account [ECRD#2016]). A detailed list on the degree of dissemination of the final conference report, as well as the media coverage of the conference is still in preparation and will be added to the public version of this report on the RD-Action website as soon as it is available.

- **Task 2.4: To support national and European integration through national workshops**

Suggested Indicator Set 1	
o Process Indicator	
▪ Ensure an efficient information flow between the European level and the MS level	**Fulfilled**
o Output Indicator	
▪ Involvement in approximately 20 national conferences on implementation of European RD policy for RD in MS during the JA	**Fulfilled**
o Outcome Indicator	
▪ Conference reports each detailing number of participants and the stakeholder group to which they belong (e.g. patient, clinician, policy-maker etc.)	**Fulfilled**

Suggested Indicator Set 2	
o Process Indicator	
▪ Provide tailored support to MS in implementing national policies relating to RD	**Fulfilled**
o Output Indicator	
▪ Evidenced during the national conferences themselves	**Fulfilled**
o Outcome Indicator	
▪ Number of final reports (20)	**19**

EUROPLAN national conferences / workshops are intended to promote the implementation of national plans for rare diseases and facilitate the integration of EU rare disease policies and recommendations into the national systems. They are jointly organized in each country by the respective national alliance of rare disease patients' organizations and EURORDIS. Within RD-Action, 19 conferences or round tables were organized (Belgium organized two round tables). Reports of all events including detailed information on the set-up, as well as a synthesis and recommendations, were made publicly accessible on the RD-Action website.

Of note, compared to the national conferences / workshops promoted and supported in the frame of previous European projects on RD (EUROPAN: 2008 – 2011; EUCERD Joint Action: 2012 – 2015), where all events followed a common structure and a common set of topics deriving from the seven key areas of the Council Recommendation 2009/C 151/02, the conferences / workshops in RD-Action were designed and organized in a far more flexible manner in order to enable each country to focus on their most pressing policy priorities and needs.

- **Task 2.5: Promote sustainable health systems for rare diseases**

Suggested Indicator Set	
o Process Indicator	
▪ To support national authorities to quantify the burden of RDs and available resources for sustainable and resilient health systems	**Fulfilled**
o Output Indicators	
▪ Set-up a workshop to share the analysis of the context (epidemiological, political and health situation) within M12	**Fulfilled**
▪ Set-up a workshop to develop common knowledge on equity and resilience of health systems for RD within M24	**Fulfilled**
▪ Set up a conference to disseminate tools and recommendations on sustainability of implementations RD policy priorities at M36	**Fulfilled**
▪ Policy briefs produced to support national authorities for sustainable health systems for RD	**Fulfilled**
o Outcome Indicators	
▪ Shared analysis of the context (epidemiological, political and health situation) to be presented in the workshop report	**Fulfilled**
▪ Increased knowledge on sustainability of RD-policies assessed by questionnaires after working sessions	**Fulfilled**
▪ Number and satisfaction of attendees to the conference on sustainability by means of survey during and/or after the meeting	**Partially fulfilled**
▪ Establishment of a network for sustainable health systems for RD	**Fulfilled**

Additional suggested Indicator Set from grant agreement WP 3, task 3.1: Organization of a Conference on sustainable health systems for RD	
o Process Indicators	
▪ Defined steps for the overall preparation of the conference including nomination of a conference committee	**Fulfilled**
▪ Implementation of preparatory steps including literature review, analyses, preparatory workshop, eventually establishment of specific working groups	**Fulfilled**
o Output Indicators	
▪ One analysis on epidemiological data on RD	**Not performed**
▪ One review on sustainable health systems	**Fulfilled**
o Outcome Indicators	
▪ Number of participants by stakeholder groups	**Fulfilled**
o Impact Indicators	
▪ Degree and quality of the dissemination of the conference conclusions	**Pending**

The overarching goal of this task was to support national authorities to quantify the burden of rare diseases and available resources for sustainable and resilient health systems, taking into account principles of equity, quality and efficiency. To this end, as a preparatory step, a literature and current data review was performed in order to identify and understand mechanisms that influence the sustainability, equity and resilience of health systems for rare diseases (Ann Ist Super Sanita 53(2): 170-175 (2017)). The further strategy was to address the topic in altogether three workshops, the first of which, titled “Health systems resilience for rare diseases”, was held on June 14, 2016, in Rome. Fifteen participants from eight different countries attended; six working groups for the identified fields of priority were set up during the workshop. The second workshop on this topic took place on September 12-13, 2017, also in Rome, running under the same title as the first workshop, but this time aiming to develop a common knowledge on equity and resilience of health systems for RD. Detailed reports for both events were prepared and published on the RD-Action intranet. The final workshop, “Health systems sustainability and resilience for rare diseases”, took place on June 27, 2018, in Paris (report not yet available; there were 28 participants: 1 representative of health authorities, 4 representatives of patient organizations, 18 experts/ scientists (of these, 7 were representatives of an ERN), 1 representative of the European Commission, 1 from a European Institution, and 3 members of the National Institution of Health). Outputs of this task (beside the aforementioned published review) include six policy briefs presented by the authors at the final workshop, which are presently being revised based on the inputs of the RD-Action partners. Importantly, a European network to reduce health inequalities and to promote measures for sustainability of national strategies for rare diseases was successfully established in the frame of the project.

While a survey on the satisfaction of attendees to the last conference/workshop on sustainability of health systems – organized very close to the ending of RD-Action – was not performed any more due to the fact that in the remaining project time all available resources had to be concentrated on the finalization of the last documents of this task, satisfaction surveys were performed for the first two workshops mentioned above. In the first workshop in 2016, all participants were highly satisfied with the duration of the conference, the documentation provided and the fact that they were actively involved in the individual sessions (each item 100% positive replies). In addition, all participants felt that their expectations were met by the workshop and that this event might also be interesting for their colleagues (both 100%). Therefore, participants claimed that they would be interested to increase their knowledge on the topics presented at the conference (100% satisfaction). Minor reservations applied to the question whether participants will be able to make practical use of what was taught in the workshop; here, 22% of the respondents claimed they were not sure whether this would be possible for them, while 78% stated they would be able to use the results in the future. In the second workshop in 2017, participants again were highly satisfied with the content of the workshop, the number and competence of the speakers and the overall organization of the conference (“strongly agree” 80-90% for each item, “agree” for the remaining 10-20%). High satisfaction rates were also noted for the effectiveness of the teaching method, the quality and extent of the teaching materials, and the time allotted for individual and group exercises (“strongly agree” 40-60%, “agree” 10-30% and “not applicable” for the remaining 30-40% for each item). Therefore, all participants declared that the workshop increased their knowledge on the topic (“strongly agree” 80%, “agree” 20%).

Summary and conclusions

Dissemination in the frame of RD-Action posed a particular challenge because of the huge amount of materials and information generated in the course of the project, and because of the diversity of stakeholders involved. One of the key issues to be addressed at the beginning was to identify the different interest groups, to define the best channels of information to reach them, and last but not least, decide on the timing of information dissemination. This challenge was met by elaborating a very detailed and well-structured dissemination plan, which relied on a preceding stakeholder analysis and took into account the timeline of the RD-Action project as a whole. Thus, it was possible to keep a comprehensive view on the various activities, and act accordingly. Dissemination strategies included a wide variety of methods, some of which in particular deserve to be mentioned here; for example, the organization of the ECRD congress with almost 800 participants, which has become probably the most important meeting in the rare disease field worldwide. Another huge effort was the organization of the EUROPLAN workshop series in member states, which was of tremendous support in the implementation of rare disease policies within national (health) systems. Other initiatives, like comparatively smaller meetings addressing specific audiences, as well as long-standing services like the Orphanews newsletter, or the Report on the State of the Art of Rare Disease Activities in Europe, are completing the picture.

3.3. Work package 3 (Evaluation)

Description

One main objective of this work package was to evaluate the action activities with respect to process adherence, output, outcome, and impact. Specific indicators for most of the tasks were already suggested in the RD-Action grant agreement. Evaluation was to be performed according to these indicators, and a final report elaborated for further use. Of note, some tasks were highlighted in particular in the grant agreement, like all conferences and workshops organized in the frame of RD-Action, but also the coding activities. However, evaluation was to span all parts of the project, in order to sum up the achievements, to justify the expenses, and to provide a solid foundation for further activities.

The second pillar of work package 3 was to set up a sustainability plan for databasing activities after the end of the Joint Action. To this end, Orphanet, the European database for rare diseases, was to be evaluated externally, on the one hand by French institutions (focusing on the structure, content, and functioning of the database), and on the other hand by representatives of different stakeholders in each member state to assess their needs regarding the database. Based on the results, a sustainability plan was to be developed, supporting the transformation of Orphanet from a temporarily funded project to a permanent European infrastructure.

Specific objectives

1. Measure the indicators per WP, internally.
2. Evaluate Orphanet in view of its long-term sustainability.

Additional specific objective, as provided in the original project proposal

3. Make Orphanet, the European database for RD sustainable (Objective 6, shared between work packages 3 and 4).

Tasks

- **Task 3.1: Evaluation of the Joint action achievements**

New Indicator Set	
o Process Indicator	
▪ Measure indicators per work package	**Fulfilled**
o Output Indicator	
▪ Production of a report on the RD-Action evaluation	**Fulfilled**
o Outcome Indicators	
▪ Evaluation report published	**Fulfilled**

All indicators suggested in the RD-Action grant agreement were considered and measured. In some instances, additional indicators were defined. Results were wrapped up in the present report, which will be published on the RD-Action page thus being accessible for the general public.

- **Task 3.2: Evaluation of the European database for rare diseases, Orphanet**

New Indicator Set	
o Process Indicator	
▪ Prepare a questionnaire for evaluation of Orphanet with specific focus on stakeholders' needs	**Fulfilled**
▪ Conduct online survey among representatives of the different stakeholders in member states	**Fulfilled**
o Output Indicator	
▪ Production of a report on the results of the stakeholder survey	**Fulfilled**
o Outcome Indicators	
▪ Report distributed within the RD-Action consortium and presented to relevant authorities	**Fulfilled**

An online questionnaire was developed focusing on the needs of stakeholders with regard to the Orphanet database. The questionnaire was sent specifically to previously identified representatives of the different stakeholders in member states. This included Ministries of Health / Social Affairs / Science (or equivalent governmental authorities), as well as the national umbrella organizations of the pharmaceutical industry and rare disease patients' organizations. Apart from that, the questionnaire could also be sent out to other institutions of specific national interest within the rare disease field. The results of the survey were presented in the "Report on the systematic, European-wide Institutional Stakeholder Survey on Orphanet in 2017", which was made public on the RD-Action webpage and can be used to address relevant authorities from this point.

In addition to the stakeholder survey in the frame of RD-Action, an internal evaluation of Orphanet was carried out by two different French institutions: the Haut Conseil en Santé Publique (HCSP) and the Haut conseil de l'évaluation de la recherche et de l'enseignement supérieur (HCERES). This evaluation, which served in parallel as an evaluation in the context of the evaluation of the 2nd French National Plan for Rare Diseases focused on the structure, content, and functioning of the database. The evaluation reports are publicly available on the website of the French Ministry of Health (https://solidarites-sante.gouv.fr/soins-et-maladies/prises-en-charge-specialisees/maladies-rares/article/les-maladies-rares). In addition, Orphanet was evaluated another time by the Inserm in 2017-2018. The report regarding this this evaluation has not been released yet. Of note, no indicators were defined for this sub-task.

- **Task 3.3: Develop a sustainability plan for the Orphanet core activities fitting the needs of European member states, including RD nomenclature and classification**

Suggested Indicator Set 1	
o Process Indicator	
▪ Elaboration of information material explaining the different modules of the Orphanet database specifically designed for the MS authorities to allow informed decision on all parts of Orphanet	**Fulfilled**
o Output Indicator	
▪ Information material distributed by M18	**Fulfilled**
o Outcome Indicators	
▪ All MS interviewed and feedback retrieved	**Not performed**
▪ Number of MS committed to participate in the elaboration of the sustainability plan	**Ongoing**

To achieve a more de-centralized structure of the different Orphanet activities (i. e. to be able to distribute activities more evenly among all consortium partners), a modular representation chart was elaborated during the first year of RD-Action and presented to the consortium. The model describes the actions of Orphanet in three layers: 1) core activities which should be maintained by the coordinating team, 2) shared-core activities where consortium members can agree to participate in knowledge production on a voluntary basis, and 3) national activities involving all national Orphanet teams. This model has also been used in the frame of the aforementioned stakeholder survey to ask each member state which Orphanet activities it could imagine to (co-)finance, working towards a sustainable financing model for the database. This modular representation will be presented to member states authorities to support the decision process for a concrete sustainability plan.

As outlined in the next paragraph, the elaboration of the sustainability plan is still ongoing at the end of RD-Action, a draft document is currently reviewed by the European Commission / Commission Services. After completion of this review, Member States will be again involved in the further drafting process, therefore, a final number of MS participating in the elaboration of the plan can't be provided at this stage and the corresponding outcome indicator had to be defined as "ongoing".

Suggested Indicator Set 2	
o Process Indicator	
▪ Elaboration of a sustainability plan based on the evaluation conclusions	**Fulfilled**
o Output Indicator	
▪ Sustainability plan proposal by M24	**Fulfilled**
o Outcome Indicator	
▪ Adoption of a sustainability plan by participating MS and EC	**Pending**

A sustainability plan for Orphanet was elaborated based on the evaluation results, and on the modular model (see also previous paragraph). In this plan, priority domains and key objectives were identified, together with respective action plans. In addition, several possible funding strategies were developed and explained providing the basis for the upcoming discussion and decision process between the European Commission and the Member States. These efforts should eventually lead to a robust and ultimate solution for the long-term financing of Orphanet. The draft of the sustainability plan is currently reviewed by the Commission Services. After this step, it is planned to adapt the document every six months in response to achievements and new challenges.

Summary and conclusions

Work package 3 comprised not only the evaluation of the whole Joint action RD-Action itself – which was carried out in the form of the measurement of mostly pre-defined process-, output-, outcome-, and impact indicators and is being presented in this report –, but also the development of a specific external evaluation plan for the Orphanet database. While Orphanet has carried out annual user satisfaction surveys for many years (where a window pops up once the user opens the Orphanet website), a survey among stakeholders who may not even know the database yet, but could still be relevant decision-makers when it comes to allocation of national financial support, had never been performed. The survey included introductions to the different services Orphanet provides. Subsequently, participants were asked if their institution would be willing to take over part of the funding for the respective service. While the overall outcome was positive and satisfaction with, or interest in, the database was generally high, the question of a sustainable funding system for Orphanet remained open until the end of RD-Action.

Taking into account the results of the evaluation, and relying on a specifically developed modular representation chart, which showed how the different tasks within Orphanet could be shared among partners, so that member states could take over more responsibilities in the contribution of knowledge, but maybe also of funding, a sustainability plan for Orphanet was developed. The draft version of this plan is currently under review by the Commission Services. After receiving and incorporating the Commissions comments, it will be updated every six months depending on new developments, and finalized after an agreement among the member states. The ultimate goal of this task was to establish and strengthen Orphanet as a permanent European infrastructure.

As a first step in this direction and based on an initiative of the French Health Authorities, the coordinator of RD-Action was recently invited to participate at a high-level meeting of several French institutions (with representatives from the Ministry of Health, the Ministry of Research and the Inserm) in order to prepare a French proposal regarding the long-term development and perspective of Orphanet for the Steering Group on Health Promotion, Disease Prevention and Management of Non-Communicable Diseases. The Steering Group constitutes a high level advisory body to the European Commission and is composed of representatives of each European Member State and EEA Members. This proposal was finally presented to the Steering Group on May 18, 2018, in Paris and the RD-Action coordinator had the opportunity to briefly explain the basic structure and broad content of Orphanet as the most comprehensive database for any information on RD worldwide, as well as the funding needs to sustain its operation.

Of note, from the middle of 2018 onwards, Orphanet will – for the first time – receive a direct, non-competitive grant from the Consumers, Health, Agriculture and Food Executive Agency (CHAFEA).

3.4. Work package 4 (Orphanet, the European database for rare diseases)

Description

The main objective of this work package was to support the evolution of the Orphanet database of rare diseases into a sustainable European infrastructure. Plans for a new IT infrastructure included the transition from a relational database to a more flexible knowledge base, in order to be able to share the IT development efforts with the consortium partners in the future. Orphanet core activities should increasingly be delegated to participating countries, shifting the organization towards a more decentralized and open structure. A community-driven editing process of the database involving expert groups and individual experts, patient representatives, and users in general was to be developed. Also, transparency and traceability should be increased. Thanks to these evolutions, the sustainability plan developed in work package 3 would be facilitated by increasing the database ownership by consortium partners.

Specific objectives

1. Coordinate the activities of the Orphanet consortium (26 associated partners in this JA and 14 collaborating partners).

2. Maintain, update and expand the rare diseases database: the inventory and classification of RD and its alignments with other terminologies (i.e. ICD10, SNOMED CT); links between rare diseases, phenotypes and genes, including cross-references with other resources (i.e. OMIM, HPO); the professional encyclopedia of RD by providing a definition for all RD to be included in the content model of ICD11 and SNOMED CT, as well as in the Orphanet Rare Diseases Ontology (ORDO) and by producing new and updated abstracts and disseminating new content produced by others.

3. Develop the necessary tools to track changes of the Orpha nomenclature, classifications and scientific database content, including an interactive platform allowing for managing input from the community.

4. Provide a directory of expert services in every MS, including centers of expertise, clinical laboratories, patient registries, mutation databases, biobanks, research infrastructures, patient organizations, European reference networks when set up.

5. Provide overarching database data management, quality control and IT support, including training MS teams.

6. Produce reports (Orphanet Report Series) intended to provide compiled pieces of information required for supporting CEGRD activities.

Additional specific objectives, as provided in the original project proposal

7. Make Orphanet, the European database for RD sustainable (Objective 6; shared between work packages 3 and 4).

8. Support the work of CEGRD and the (first potential and later) approved ERNs (Objective 8; (shared between work packages 4 and 6).

Tasks

- **Task 4.1: Coordination of the Orphanet consortium**

  No indicators were defined for this task.

- **Task 4.2: Maintain and expand the rare diseases database**

Suggested Indicator Set 1	
o Process Indicator	
▪ Creation of newly described RD, and new categories and subtypes to improve RD classification	**Fulfilled**
o Output Indicator	
▪ Around 500 created entries per year	**Fulfilled**
o Outcome Indicators	
▪ Common to all sets of indicators in this task, see Indicator Set 9 (last box)	

Suggested Indicator Set 2	
o Process Indicator	
▪ Inclusion of RD in ICD11	**Fulfilled**
o Output Indicator	
▪ Around 6000 RD transmitted for inclusion in the ICD11 at M36	**5589**
o Outcome Indicators	
▪ Common to all sets of indicators in this task, see Indicator Set 9 (last box)	

Suggested Indicator Set 3	
o Process Indicator	
▪ Alignment of Orphanet entries with ICD10, OMIM, SNOMED CT, UMLS, and MedDRA	**Fulfilled**
o Output Indicators	
▪ Around 6000 RD aligned with ICD10	**7067**
▪ Updated alignments with OMIM, SNOMED CT, UMLS, and MedDRA completely processed	**Fulfilled**
o Outcome Indicators	
▪ Common to all sets of indicators in this task, see Indicator Set 9 (last box)	

Suggested Indicator Set 4	
o Process Indicator	
▪ Inclusion of RD in SNOMED CT	**Fulfilled**
o Output Indicator	
▪ Around 6000 RD transmitted for inclusion in SNOMED CT at M36	**5813**
o Outcome Indicators	
▪ Common to all sets of indicators in this task, see Indicator Set 9 (last box)	

Suggested Indicator Set 5	
o Process Indicator	
▪ Production of definitions for RD	**Fulfilled**
o Output Indicator	
▪ Around 6000 definitions produced by M36	**99,9%**
o Outcome Indicators	
▪ Common to all sets of indicators in this task, see Indicator Set 9 (last box)	

Suggested Indicator Set 6	
o Process Indicator	
▪ Update of existing abstracts and production of those lacking	**Fulfilled**
o Output Indicator	
▪ 500 new or updated texts produced per year	**Fulfilled**
o Outcome Indicators	
▪ Common to all sets of indicators in this task, see Indicator Set 9 (last box)	

Suggested Indicator Set 7	
o Process Indicator	
▪ Annotation with epidemiological data	**Fulfilled**
o Output Indicator	
▪ Around 6000 RD with at least one epidemiological data (prevalence, incidence, birth prevalence or number of case/families) at M36	**5910**
o Outcome Indicators	
▪ Common to all sets of indicators in this task, see Indicator Set 9 (last box)	

Suggested Indicator Set 8	
o Process Indicator	
▪ Annotation with genes	**Fulfilled**
o Output Indicator	
▪ 450 new gene-diseases links/year	**Fulfilled**
o Outcome Indicators	
▪ Common to all sets of indicators in this task, see Indicator Set 9 (last box)	

Suggested Indicator Set 9	
o Process Indicator	
▪ Production of crossreferences with genetic databases (HGNC, OMIM, UniProtKB, Reactome, ensembl, IUPHAR)	**Fulfilled**
o Output Indicators	
▪ All the genes included in the database cross-referenced at least with HGNC	**Fulfilled**
▪ Exhaustivity for the other cross-references	**Fulfilled**
o Outcome Indicators (**common to all nine indicator sets in this task**)	
▪ Increase in the number of visits of the website according to the baseline of 3,660,000 visits in 2014	**7,030,281 (01-08/2018)**
▪ Satisfaction and utility according to the end users (assessed through online survey and proactive surveys)	**Fulfilled**
▪ Number of downloads of the relevant category: increase compared to data presented in the 2014 activity report	**Fulfilled**

Maintaining and continuously expanding the database content is the core task of Orphanet.

The figures obtained at the end of RD-Action clearly show that this task was fulfilled practically to perfection: In all categories, the targets were reached or even exceeded, in some cases to a very high degree. The outcome indicators are of particularly high relevance in this case, as they reflect the satisfaction of the users with the database. The drastic increase in the number of website visits from 3,660,000 visits in 2014 to 9,385,686 visits between the beginning of June 2017 and the end of May 2018 (the time period constituting the last Orphanet project period of RD-Action) or – as an alternative example – to 7,030,281 visits in the first 8 month of 2018 (from the beginning of January to the beginning of September 2018) convincingly demonstrate the continued increase in database access and the extraordinary appreciation for the content of Orphanet that users have developed over the past years. This is also very well reflected in the regular online surveys that are carried out by the central Orphanet team almost since the beginning of the database. In its last iteration in the frame of RD-Action, satisfaction and utility were assessed per category (list of diseases and classifications: 97%; texts on diseases: 96%; epidemiological data: 93%; directories of expert resources: 84.8% satisfaction / utility), showing a significant increase in all areas as compared to 2014. The same was true for the number of downloads (number of downloads of “inventory of rare diseases and cross-referencing” and “classifications”: 63% increase as compared to 2014; encyclopedia: 90%; genes annotations: 100%; expert resources: 80%; a decrease was only seen in the category “epidemiology data” due to on demand status change).

- **Task 4.3: Develop the necessary tools to track changes of the Orpha nomenclature, classifications and scientific database content, including an interactive platform allowing for managing a community-driven curation and edition process**

Suggested Indicator Set 1	
o Process Indicator	
▪ Web-based knowledge management services	**Fulfilled**
o Output Indicator	
▪ Web service fully functional at M36	**Fulfilled**
o Outcome Indicator	
▪ Number of external curators (superior to 32 active expert groups or individual experts assigned to a group of disorders – at least 1 per classification)	**44 (sometimes not 1 per classification)**

Suggested Indicator Set 2	
o Process Indicator	
▪ Publication of procedures and data sources and updates history	**Fulfilled**
o Output Indicators	
▪ Sources available on Orphadata Versions and differentials available in Orphadata	**Fulfilled**
▪ Procedures published in the website orpha.net	**Fulfilled**
o Outcome Indicator	
▪ Number of downloads of procedures documents (no baseline available)	**16588**

Regarding traceability of data in Orphanet, sources are now available for download on the Orphadata site. The date of the last update of each dataset appears on the website. Procedures on data production and maintenance are available as well, with additional documents being produced continuously. To regulate the workflow for updating the scientific content of the database, a web-based curation platform has been developed together with the Garvan Institute in Australia. Currently, 44 external curators are registered for the new platform, however, in some areas Orphanet does not have one expert group or individual expert per classification right now. This is – at least in part – related to the fact that in the ultimate stage of the platform all expert groups or individual experts should be recruited from the knowledge base provided by the recently established European Reference Networks (ERNs) for Rare Diseases, which are intended to link experts for all groups of RD across Europe in well defined thematic networks. While both, the new curation platform and the establishment and initial operationalisation of ERNs developed relatively in parallel, both systems, and in particular ERNs, need some more time to mature before all disease groups are fully covered by experts and the networks are fully operational.

Of note, while working on the new curation platform, Orphanet continued its collaboration with expert reviewers identified by the central team through their publications and their activity related to a given disease / group of diseases. For maximum transparency, the names of all

experts that contributed to the content of the database, as well as the diseases covered by each expert, were published in special annual reports in the frame of the Orphanet report series. The documents for the past three years are:

- Expert reviewers for Orphanet in 2015: http://www.orpha.net/orphacom/cahiers/docs/GB/Expert_reviewers_2015.pdf
- Expert reviewers for Orphanet in 2016: http://www.orpha.net/orphacom/cahiers/docs/GB/Expert_reviewers_2016.pdf
- Expert reviewers for Orphanet in 2017: https://www.orpha.net/orphacom/cahiers/docs/GB/Expert_reviewers_2017.pdf

- **Task 4.4: Provide a directory of expert services in every MS, including centers of expertise, clinical laboratories, patient registries, mutation registries, biobanks, patient organizations, European reference networks when set up**

Suggested Indicator Set	
o Process Indicator	
▪ Expansion, update and quality control of directory of expert resources in each participating MS	**Fulfilled**
o Output Indicators	
▪ Exhaustivity of the representation of expert resources in each country	**Not performed**
▪ Annual mailing to the professionals database for updating expert resources	**Fulfilled**
▪ Dates of last updates displayed in the Orphanet website	**Fulfilled**
▪ Post-release quality assessment by MS scientific advisory boards once a year	**Partially fulfilled**
o Outcome Indicators	
▪ See Task 4.2, Suggested Indicator Set 9 (above)	

The directory of expert resources in partnering countries was maintained and expanded on a regular basis according to the Orphanet standard operating procedures, including annual mailing to all professionals listed in the database to obtain updates. The date of the last update is shown under each dataset on the website. Scientific advisory boards are not established in each country, as local post-release quality assessment is organized individually.

Estimates on the exhaustivity of the representation of expert resources in each country are not yet available, the work on this indicator is still ongoing. As an intermediate step, however, a set of calculations describing the proportional coverage of all rare diseases per expert resource per country has been developed for the following areas/resources:

- Patient organisations (excluding patient alliances)
- Expert centres (medical patient management)
- Diagnostic tests
- Research projects

- Clinical trials
- Registries
- Biobanks

As one would expect in a still developing field, for most expert resources, the percentage of rare diseases coverage varies considerably between the different Member States, ranging from coverage rates as low as 0-10% in some and values as high as 80-100% in other Member States. However, overall proportional coverage rates also vary significantly between the different expert resources. When looking at these resources in more detail, four different coverage settings can be identified:

- Resource areas with a high level of rare diseases coverage across Member States.

  This setting is particularly true for the category “Expert centres”, where a majority of countries participating in Orphanet have reached coverage levels of 60-80% or even 80-100% proportional coverage.

- Resource areas with an intermediate level of rare diseases coverage across Member States.

  This is the case for the resource category “Patient organisations”, where more than half of the countries achieve coverage rates of around 50% and more, i. e. up to 80-100%, proportional coverage, while the rest of the Member States present mainly with very low coverage rates.

- Resource areas with a wide variety of rare diseases coverage across Member States.

  Prime examples for this setting are the resources “Diagnostic tests” and “Research projects”, where coverage levels are distributed relatively evenly between the different countries, ranging from 0-10% up to 60-80% (diagnostic tests) and 80-100% (research projects) proportional coverage, respectively, and where a clear majority of Member States only reaches coverage rates below 50%.

- Resource areas with a low level of rare diseases coverage in all Member States.

  This is the characteristic setting for the categories “Clinical trials”, “Registries” and “Biobanks”, where in all countries coverage levels do not exceed 0-10% proportional coverage.

Further information on the detailed proportional coverage rates per resource area and Member States can be found in the slides from the Orphanet work package presentation at the final RD-Action meeting in Paris on June 27, 2018, provided in the internal area of the RD-Action website (http://www.rd-action.eu/extranet/2018-final-meeting/), that were used to present these findings to the project partners.

- **Task 4.5: Provide overarching database data management, quality control and IT support, including training MS teams.**

  No specific indicators were defined for this task.

  During RD-Action, quality control for all the country data in Orphanet was executed following the same standard procedures that were applied in the years before the Joint Action, including an internal data review by the central team to check data integrity and comparability across partner countries and to identify any incorrect and/or incomplete data entries. These divergencies were collected and published in Quality Assurance Reports (QAR), internal quality documents send on a regular basis to all Orphanet members indicating in detail which inaccurate individual datasets need to be completed and/or corrected in each country. Entries in subsequent QARs are only deleted if the requested changes were fulfilled by the partner. During RD-Action, altogether 10 QARs were issued.

  In addition, Orphanet teams from all Member States received regular trainings during the course of RD-Action, including 2 annual training meetings for information scientists in Paris, as foreseen in the grant agreement, and at least two virtual training sessions per year organized as tele-conferences.

- **Task 4.6: Produce reports (Orphanet Report Series) intended to provide compiled pieces of information required for supporting CEGRD activities.**

Suggested Indicator Set	
o Process Indicator	
▪ Production of data to support policy analyses and decisions	**Fulfilled**
o Output Indicators	
▪ Publication of compiled data (Orphanet Report Series) on specific areas (publication rates depending on the topic)	**Fulfilled**
▪ At least 13 different ORS	**8**
o Outcome Indicators	
▪ Number of downloads of the ORS (2014 baseline: 2,250,000)	**655,551**
▪ Satisfaction assessed through the online satisfaction survey and proactive surveys	**Fulfilled**

Orphanet reports are a series of texts covering topics relevant to all rare diseases and have been issued for many years. The number of reports stayed the same as compared to 2014 (eight reports published in year 3 of RD-Action), a fact mainly related to the decreased and finally suspended demand of the policy work package (WP6) after the termination of the CEGRD. For this reason, the output indicator of at least 13 different ORS is not applicable any more on the project.

Surprisingly, the number of downloads of the ORS decreased significantly by almost 71%. While this might in part be explained by the facts that (1) the Orphanet database uses different IT tools in 2018 compared to 2014 capable of detecting and eliminating robot requests far better than before (similar to the changes described for the OrphaNews newsletter under Task 2.2), thus probably leading to an overestimation of the ORS downloads in previous years

before the switch in the IT systems, and (2) the years 2014 and 2015 represent the two years with the by far highest download numbers in the past 8 years (with 2.250.172 and 2.515.722 downloads, respectively), therefore constituting a misleading baseline when compared to the other 7 years in the time period 2010 to 2016, there still remains a very relevant decrease in demand for which the reasons are unknown at present and that needs to be addressed by the Orphanet consortium.

Interestingly, despite the decrease in demand, satisfaction with the ORS was higher than in 2014 (83.8%).

Summary and conclusions

During the three years of RD-Action funding, the infrastructure of the Orphanet database has been developed further and extended tremendously. This includes the IT infrastructure, where an entirely new external manual curation platform has been established which enables users to submit their demands for modifications, and allows for the assignment of a rare disease to a specific expert. This opens new possibilities for the editing processes of the database, supporting the retrieval of most accurate, up-to-date scientific data. On the other hand, steps guaranteeing much higher transparency and traceability of data have been taken, and quality management has been improved systematically (of note, Orphanet had already been at a very high level in all these areas before, especially given the enormous scope of the database). All these actions and measures helped further to the foundation to make Orphanet a sustainable European infrastructure.

3.5. Work package 5 (Steering, maintaining and promoting the adoption of Orphacodes across MS)

Description

The aim of this work package was to develop a toolset assisting member states in the implementation of Orpha codes in their health systems to allow for standardized and interoperable coding of rare diseases. This included setting up a steering committee of representatives from different member states to be able to learn from local experiences already in place, and to define strategies and necessary steps. The cornerstones of this work package were the development of a file containing all necessary Orpha codes ("master file") for common use for all European countries, as well as the definition of guidelines addressing quality of codification and coherence of exploitation at the European level.

Of note, the current project was not meant to address local implementation of the Orpha coding, but to provide guidance and common standards in order to make sure data are exploitable and comparable at EU level.

The work package was led by the DIMDI (German Institute of Medical Documentation and Information).

Specific objectives

1. Define the common objectives for coding RD in MS, the common level of granularity to be used and guide the implementation.
2. Define a codification resource aimed at having consistency across MS coding for RD.
3. Tune the codification resource after having tested it in a subset of coding groups through pre-existing tools.

Tasks

- **Task 5.1: To define and set the necessary strategy and tools to implement the Orpha codes in the European countries**

Suggested Indicator Set	
o Process Indicator	
▪ Complete review of current coding systems actually in place in member states and actual plans	**Fulfilled**
o Output Indicator	
▪ Review document of existing technical implementations for RD coding of MS by M12	**Fulfilled**
o Outcome Indicator	
▪ Review paper published for all Consortium partners (e.g. at RD-ACTION workspace) and results presented at Consortium meeting	**Fulfilled**

An online survey on the current coding situation in member states was carried out addressing defined expert institutions in the participating countries. The results were wrapped up in a review document of existing technical implementations for rare disease coding in member states (Deliverable D5.1). The paper was published on the generally accessible public part of the RD-Action website.

- **Task 5.2: Specification of the required resources for coding RD consistently across Europe**

Suggested Indicator Set 1	
o Process Indicator	
▪ Production of guidelines on how and why to code with Orpha codes in health systems in order to generate standardized and comparable data all over member states	**Fulfilled**
o Output Indicator	
▪ Standard procedures and guide for the coding with Orpha codes by M24	**Fulfilled**
o Outcome Indicator	
▪ Guidelines published for all consortium partners (e. g. EU workspace)	**Fulfilled**

The paper “Standard procedure and guide for the coding with Orpha codes” (Deliverable D5.2), containing international rules and guidelines for coding rare diseases, was produced and published on the RD-Action website.

Suggested Indicator Set 2	
o Process Indicator	
▪ Elaboration of a coding file allowing for good quality and consistency coding across MS	**Fulfilled**
o Output Indicator	
▪ An European integrated master file by M24	**Fulfilled**
o Outcome Indicator	
▪ Draft coding file published for all Consortium partners (e. g. at RD-ACTION workspace)	**Fulfilled**

A beta-version of the file containing all necessary Orpha codes ("master file") for common use for all European countries was produced and published on the RD-Action website.

- **Task 5.3: Promoting the Orpha codes across MS by sharing coding tools and testing the master resource**

Suggested Indicator Set	
o Process Indicator	
▪ Testing of coding file and guidelines in existing coding tools	**Fulfilled**
o Output Indicators	
▪ Test results and a refined file and guidelines by M36	**Fulfilled**
▪ Number of single RD entities registered using the master file	**2,378**
▪ Number of more specific codings	**21,638**
▪ Ratio of correct and incorrect coding entries	**100% correct**
o Outcome Indicator	
▪ Final coding file Version 1 published for all Consortium partners (e. g. at Orphanet-website and / or RD-ACTION workspace)	**Fulfilled**

Testing of the master file containing the Orpha codes was a pivotal part of the project in order to evaluate the compatibility with and easy integration into existing health information and coding systems, and to check the applicability of the guidelines. Field testing of the coding file and the guidelines was performed in two phases (a retrospective and a prospective one). Phase 1 included 51,883 patients from the French rare disease registry and 46,331 patients from the Veneto region registry (Italy). In phase 2, 41,284 patients were included. Results were presented at different stages of testing at the annual RD-Action meeting in 2017, at the final meeting in 2018, and at the final codification workshop in Venice in June 2018 (see below). Using the coding file, 2,378 single rare disease entities were registered. Orpha codes clearly demonstrated a better ability to describe rare disease patients. The number of more specific codings was 21,638 (as compared to the use of ICD-10; Orpha codes: 40,382 specific codings, ICD-10: 18,744). Only 902 patients (2% of the entire cohort) were left without a specific Orpha code. In other words, the percentage of rare disease patients described by specific codes was 98% using Orpha codes, versus 45% using ICD-10. Of note, all the coding

entries were correct. After completion of testing, the final version of the coding file was published on the RD-Action website.

Additional suggested Indicator Set from grant agreement WP 3, task 3.1: Organization of a workshop addressing the information about the strategies and tools to implement the Orpha codes in the European countries	
o Output Indicators	
▪ Information material provided in the workshop intended for the distribution within the Member States	**Not performed**
▪ Workshop report	**Pending**
o Outcome Indicators	
▪ Number of participants	**33**
▪ Number of Member States represented	**6**
▪ Online user satisfactory survey for all participants	**Not performed**
o Impact Indicator	
▪ Decisions on the further implementation of Orpha codes in individual Member States	**Ongoing**

A final codification workshop was held on June 20-21, 2018, in Venice. Participants came from six different countries (France, Germany, Italy, Ireland, Portugal, and Spain). In addition, Orphanet, the WHO, and the JRC (Joint Research Centre) of the EC were represented. The total number of participants was 33. The workshop was organized in order to inform the participants about the work carried out in the frame of work package 5 of the RD-Action, in particular presenting and receiving feedback on the results of the Orpha code testing activity (task 5.3). Furthermore, the future perspectives regarding the use of Orpha codes to record rare disease patients were discussed. An online user satisfaction survey was not performed; a workshop report is currently in progress, but will be published at a somewhat later date (as it was not a milestone or a deliverable of RD-Action).

Data on concrete decisions to implement Orpha codes in individual member states are not available to date, as the preparation and testing of the tools has only been completed just now. However, of note, the recently approved RDcode project will support four member states (Malta, Spain, Czech Republic, Romania) in adopting Orpha codes to code rare disease patients. This process will be based on the resources developed in this work package.

- **Task 5.4. Plan for next steps needed to address long-term maintenance, and sustainability of the resources and guidelines**

Suggested Indicator Set	
o Process Indicator	
▪ Plan for routine maintenance and update of developed resources	**Fulfilled**
o Output Indicator	
▪ A draft recommendation on how to guarantee long term availability of developed resources by M36	**Fulfilled**
o Outcome Indicator	
▪ Presentation of draft recommendation in paper and at final Consortium meeting and/or to CEGRD for further consideration and decision-making	**Fulfilled**

Draft recommendations for routine maintenance (D5.5) were presented at the final RD-Action meeting (the final version will be published after inclusion of RD-Action partners' comments).

Summary and conclusions

In order to analyze the present status of rare disease coding across member states, a survey was conducted at the beginning of RD-Action work package 5. Responses from 21 member states were taken into account. The results show that only few countries have already implemented strategies to produce statistics on rare diseases at national level. However, many have identified it as a priority, and Orpha codes emerge as the main specific coding system for rare diseases. More than 50% of responding countries are using Orpha codes at a national, regional, or local level; 70% are in the process or already have adopted the RD-Action guidelines for Orpha code implementation (see also http://www.rd-action.eu/workpackage/workpackage-5).

The necessary tools for establishing Orpha codes as a coding system for rare diseases which is compatible with existing health information systems were developed, tested, and refined in the frame of work package 5. This includes a so-called master file that allows for easy cross-linking between Orpha codes and ICD-10, as well as a specification and implementation manual for the file.

Finally, a codification workshop was held before the end of the RD-Action project. The workshop focused on the legacy of work package 5 and the future perspectives of the use of Orpha codes. Starting from the resources developed during RD-Action, the issue of rare disease coding was tackled from the perspectives of all relevant stakeholders involved (WHO, Orphanet, JRC, ERNs).

Taken together, during RD-Action, the starting position of rare disease coding in Europe was evaluated, all necessary tools were prepared to fit the needs of individual member states, as well as to allow for coherent acquisition of epidemiological data on rare diseases. Thus, RD-Action work package 5 paved the way for the next step, which will be the actual local implantation of specific rare disease coding in member states.

3.6. Work package 6 (Policy Development for RD and Integration with other relevant initiatives)

Description

RD-Action work package 6 built on the work previously developed within the EUCERD Joint Action, intended to support the implementation of the European recommendations relating to rare diseases at the member state level. The main objective of this work package, at the outset, was to support the development of policies and recommendations for consideration and adoption by the Expert Group on Rare Diseases (CEGRD) and subsequent delivery to the European Commission. The work package was designed to collaborate with relevant projects and initiatives within the rare disease field and in pertinent related areas to ensure cross talk and integration to support the tasks.

Importantly, the tasks in work package 6 were less strictly defined (as compared to other project parts) in order to be able to react on new developments in a more flexible manner, and to allow for an easier adaptation of work contents. In this context it should be mentioned that the mandate of the CEGRD ended in 2016, so that the main emphasis of the efforts within work package 6 shifted towards the support of the Commission Services and the European Reference Networks (ERNs; this included the Board of Member States on ERN (BoMS) and later also the ERN coordinators). The mission of WP6 thus largely became a) to support the setting-up the ERNs, helping them to become operational, and b) once established, to assist the Networks in addressing shared policy-oriented challenges, by seeking common approaches and generating tools and guidance with the Networks, for the Networks.

Specific objectives

1. Develop and implement a methodology to support the development of policies and recommendations in association with all relevant stakeholders.
2. Provide information and policy support to the Expert Group on Rare Diseases.
3. Produce the Report/Resource on the State of the Art of Rare Diseases Activities in Europe.

Additional specific objective, as provided in the original project proposal

4. Support the work of CEGRD and the (first potential and later) approved ERNs (Objective 8; (shared between work packages 4 and 6).

Tasks

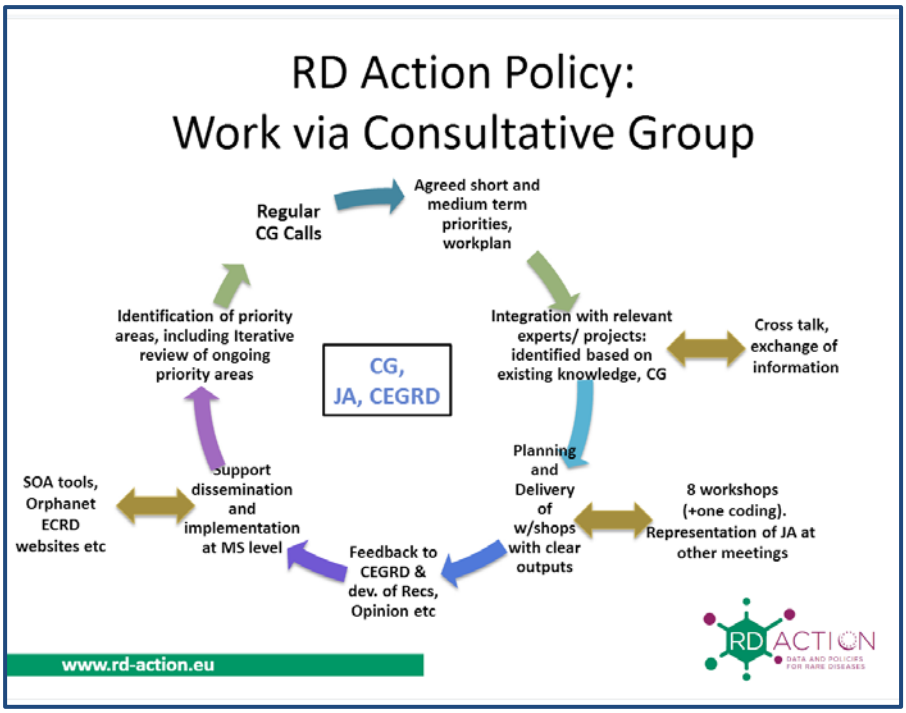
- **Task 6.1: Implement a robust policy methodology to support the work of the Expert Group on Rare Diseases**

Suggested Indicator Set	
o Process Indicator	
▪ Implement a policy methodology to support the work of the Expert Group on Rare Diseases	**Fulfilled**
o Output Indicator	
▪ Methodology published by M12	**Fulfilled**
o Outcome Indicator	
▪ Recommendations, reports and opinion papers disseminated to the CEGRD on a regular basis	**Not applicable**

As was mentioned in the introduction to this section, the CEGRD existed only until the end of 2016. However, comprehensive support was provided for the short period of time between the start of RD-Action and the end of the CEGRD mandate.

To this end, the team of work package 6 developed at the beginning of the project a Methodology for working with the CEGRD, with RD-ACTION Partners, and external partners. Partners who had expressed interest in participating to the Policy work package were invited to constitute a Consultative Group (CG) for work package 6. This body played an important part in the overall methodology of supporting the CEGRD, whilst one existed. A Membership List and Terms of Reference were elaborated and regular CG teleconferences took place from the beginning of RD-ACTION: 16 calls were organised in total across the project.

This CG would support workshop planning and delivery and engage with the CEGRD as per the following Methodology Cycle:



During the RD-ACTION proposal preparation stage, a substantial list of potential thematic priorities (TPs) was suggested for WP6 consideration:

- European Reference Networks (ERNs)
- E-Health and data-sharing
- Registries and Data Platforms
- Centres of Expertise and healthcare pathways
- Integration of rare diseases in Social policies and specialised Social Services
- Genetic Testing/Next Generation Sequencing
- Primary prevention of rare congenital anomalies
- Neonatal screening
- Coordinated approaches to pricing and innovation mechanisms to improve access to rare disease diagnostics and therapies, including HTA.
- Best Practice/guidelines on diagnostics
- Methodology for assessing the socio-economic burden of illness of rare disease.
- Genetic counselling
- Comprehensive information systems (helplines, information points, etc.)
- Implications from funded research (for prevention, treatment and care)

To explore the status quo of each of these TPs and identify meaningful policy gaps for the WP to feasibly address, one-to-one teleconferences were arranged with CG members. All CG members were offered this opportunity, to engage them in the work, and in the end 12 calls took place (between January and February 2016). The calls and discussions with EURORDIS partners –who had in turn organised a major consultation with their National Alliances- resulted in a decision to focus policy-focused activities on ERN support, with a (limited) side-focus on 3 standalone topics, for which support of the CEGRD was crucial. These 3 were socio-economic burden of rare diseases; prevention; and public health indicators for rare diseases.

Before the expiration of the CEGRD, documents were disseminated, including the following:

- Draft workplan for Policy-Related workshops
- Summary of the ERN Matchmaker resource (see next section)
- Draft concept paper on Prevention
- Draft concept paper on Public Health Indicators

Work package 6 did not develop the concept papers further, as from late 2016 onwards there was no body to whom these could be conveyed; furthermore, the Indicators topic evolved into a task relating to common Indicators for ERNs, specifically, and the Consultative Group of work package 6 judged the Prevention topic to be too difficult to advance in the absence of an Expert Group. It should be noted that work package 6 also provided Minutes for the CEGRD meetings, which was not part of the initial plan.

In the absence of the Expert group, many Reports and informal Recommendations were prepared and disseminated instead to DG SANTE, the BoMS, and the ERN community (see Task 6.2)

- **Task 6.2: Provide comprehensive policy support to the Expert Group on Rare Diseases**

Suggested Indicator Set 1	
o Process Indicator	
▪ Drafting, elaboration and revision of recommendations, reports and opinions	**Fulfilled**
o Output Indicator	
▪ Reports, recommendations and policy position papers issued from eight workshops during the JA until M38	**Fulfilled**
o Outcome Indicators	
▪ Satisfaction assessed through post-workshops surveys	**Fulfilled in some cases**
▪ Recommendations, reports and opinion papers disseminated to the CEGRD on a regular basis	**Not applicable**
▪ Number of approved recommendations/updates/reports/ opinions	**10**

Additional suggested Indicator Set from grant agreement WP 3, task 3.1: Organization of workshops on different policy topics	
o Process Indicator	
▪ Defined steps for the overall preparation of the workshops including nomination of corresponding workshop organizing committees	**Fulfilled**
o Outcome Indicators	
▪ Total number of participants per individual workshop	**Fulfilled**
▪ Number of participants by stakeholder groups	**Fulfilled**
▪ Coverage of Member States per individual workshop	**Not applicable**

During the entire RD-Action funding period, seven major workshops dealing directly with ERN-related policy topics were organized, starting in summer 2015 with a workshop in preparation of the first call for ERNs. Its goal was to assist the rare disease community in organizing itself around the 21 broad thematic groupings which had been defined previously by the EUCERD Joint action, thereby ensuring collaborative and non-competitive ERN proposals. Immediate output of this workshop was the so-called “Matchmaker tool”, an online resource designed to assist experts in identifying Healthcare Providers (HCPs) interested in setting up or joining an ERN within the same thematic field. The tool was launched in December 2015; until May 2016, 801 responses were received.

Following this hands-on support to the implementation of ERNs, the mission of work package 6 changed slightly, to focus more on generating policies, guidance and recommendations with the ERNs, for the ERNs. Six major workshops (involving over 350 people in total) were organised and delivered, each dedicated to exploring how ERNs could add value in a given area. Information on each workshop is available via the main home page for RD-ACTION WP6 ERN support (the pages include summaries of participant profiles and participant lists):

- September 27-28, 2016 (Brussels; >55 participants): “Exchanging data for virtual care in the ERN framework” (including a pre-workshop meeting between the BoMS and the applicant network coordinators).
- April 26-27, 2017 (Brussels; 68 participants): “Using standards and embedding good practices to promote interoperable data sharing in ERNs”.
- June 1-2, 2017 (Newcastle; 40 participants): “Indicators and Outcomes for ERNs”.
- December 6-7, 2017 (Rome; 63 participants): “How can ERNs generate, appraise and utilize clinical practice guidelines, to enhance the impact of consensus guidelines in national health systems?”.
- April 12-13, 2018 (Frambu/Norway; 67 participants): “Creating a Sustainable Environment for Holistic & Innovative Care for Rare Diseases & Complex Conditions”.
- May 29-30, 2018 (London; 64 participants): “How ERNs can add value to clinical research in rare diseases and highly specialized domains”.

In addition to these large, ERN-focused workshops, work package 6 organized several additional meetings and workshops, designed to build synergies between the ERNs and the rare disease community on the one hand, and the eHealth field on the other.

The table below presents a summary, with links, to the main outputs submitted to meet this Indicator:

How has RD-ACTION supported the conceptualisation and implementation of ERNs (2015-2018)?	http://www.rd-action.eu/wp-content/uploads/2018/05/Summary-of-RD-ACTION-Support-for-ERNs-2015-18.pdf
Informal FAQs and Discussions on RD ERNs (2015)	http://www.rd-action.eu/wp-content/uploads/2015/12/Informal-FAQs-and-Discussions-on-RD-ERNs-Jan-2016.pdf
Summary of the RD-ACTION 'Matchmaker' for Rare Disease ERN (2016)	http://www.rd-action.eu/wp-content/uploads/2015/12/RD-ACTION-ERN-Matchmaker-Summary-Final.pdf
Summary of disease expertise per ERN (2016)	http://www.rd-action.eu/wp-content/uploads/2015/12/RD-Action-Matchmaker-Summary-of-disease-expertise-recorded-under-each-Thematic-Grouping.pdf
What do Coordinators require from an ERN ICT platform?	http://www.rd-action.eu/wp-content/uploads/2015/12/What-do-Coordinators-require-from-an-ERN-ICT-platform.pdf
Report from the meeting of the 'Task Force on Interoperable data-sharing within the framework of the operations of ERNs' 18.2.16	http://www.rd-action.eu/wp-content/uploads/2016/05/Meeting-Report-Task-Force-on-Interoperable-Data-Sharing-in-the-framework-of-ERNs.pdf
Report: Activities of the Task-Force on Interoperable Data-sharing in the framework of the operations of ERNs – 1st year summary and workplan 2017-2018	http://www.rd-action.eu/wp-content/uploads/2016/05/1st-year-summary-and-next-steps-for-2017.pdf
Presentation: Results of canvassing on ERNs and Research priorities	http://www.rd-action.eu/wp-content/uploads/2015/12/RD-ACTION-presentation-results-of-canvassing-on-ERNs-and-Research-Malta-March-2017.pptx
RD-ACTION WP6 analysis of issues concerning the ERN Platform for clinical patient management and the EU Platform for RD Registration	http://www.rd-action.eu/wp-content/uploads/2015/12/RD-ACTION-analysis-of-the-key-issues-regarding-ERNs-and-Registries-Dec-2016.pdf
Report of Meeting between Applicant Network Coordinators and the ERN Board of Member States 28.9.16	http://www.rd-action.eu/wp-content/uploads/2016/11/Report-of-Meeting-between-Applicant-Network-Coordinators-and-Board-of-Member-States-of-ERNs-28.9.16-Final.pdf
Report: 'Exchanging data for virtual care within the ERN Framework'	http://www.rd-action.eu/wp-content/uploads/2016/12/Report-of-RD-ACTION-Workshop-Exchanging-Data-for-Virtual-Care-within-the-ERN-Framework-1.pdf
Exchanging Data for Virtual Care in ERNs – Highlights and Conclusions	http://www.rd-action.eu/wp-content/uploads/2016/12/Highlights-and-Conclusions.pdf

Recommended Practices for Data Standardisation in the context of the operation of ERNs	http://www.rd-action.eu/wp-content/uploads/2017/05/Recommended-Practices-for-Data-Standardisation-in-the-Context-of-the-operation-of-ERNs-final-2017.pdf
Annotated second version of the proposal on continuous monitoring of ERNs (a record of workshop discussions)	http://www.rd-action.eu/wp-content/uploads/2017/06/Draft-proposal-on-continuous-monitoring-of-ERNs-version-2-20.8.17.pdf
Key conclusions and Recommendations on ERNs and Clinical Practice Guidelines	http://www.rd-action.eu/european-reference-networks-erns/workshop4/
Outline and context for RD-ACTION and INNOVCare workshop on integrated and holistic care for rare diseases	http://www.rd-action.eu/wp-content/uploads/2018/08/Outline-for-Workshop-April-2018-.pdf
Recap of Breakout Session from workshop 'Creating a Sustainable Environment for Holistic & Innovative Care for Rare Diseases & Complex Conditions'	http://www.rd-action.eu/wp-content/uploads/2018/04/Breakout-Sessions-Recap_ALL_INNOVCare-RD-Action_Workshop-Holistic-Care-RD_Norway_12-13-April.pdf
OrphaNews Editorial for Workshop on integrated and holistic care for rare diseases	http://international.orphanews.org/newsletter-en/editorial/nl/id-20-april-2018.html#or_id-20-april-2018
Workshop on ERNs and Clinical Research: Summary of the Workshop Conclusions and Next Steps	http://www.rd-action.eu/european-reference-networks-erns/rd-action-workshop-co-organised-with-ema-and-dg-sante/
Activities of the Task-Force on Interoperable Data-sharing in the framework of the operations of ERNs – 1st year summary and workplan 2017-2018	http://www.rd-action.eu/wp-content/uploads/2016/05/1st-year-summary-and-next-steps-for-2017.pdf
Report from the meeting of the 'Task Force on Interoperable data-sharing within the framework of the operations of ERNs' 18.2.16	http://www.rd-action.eu/wp-content/uploads/2016/05/Meeting-Report-Task-Force-on-Interoperable-Data-Sharing-in-the-framework-of-ERNs.pdf
Report from the workshop of the 'Task-Force on Interoperable data-sharing in the framework of the operations of ERNs' 30.6.16	http://www.rd-action.eu/wp-content/uploads/2016/05/Meeting-Report-30.6.16-Task-Force-on-interoperable-data-sharing-in-the-framework-of-ERNs.pdf

Taken together, numerous reports, recommendations, and policy position papers resulted from all the events (the number stated in the first indicator box takes into account only the most prominent "sample outputs"). All documents were shared with the consortium on the RD-Action website.

Suggested Indicator Set 2	
o Process Indicator	
▪ Disseminating information on RD-Action and the RD field to groups/domains outside the 'traditional' RD sphere, and enabling the integration and engagement of these stakeholders alongside ongoing RD-specific groups and initiatives	**Fulfilled**
o Output Indicator	
▪ Conference Calls and attending meetings and workshops of initiatives from fields including – though not limited to – e-health, chronic diseases, medical education, and social services, and reporting on these integration activities in policy reports to the CEGRD at M18 and M36	**Fulfilled**
o Outcome Indicator	
▪ Number of individual non-RD-specific projects/initiatives the Policy WP has engaged with directly, as reported in the policy reports at M18 and M36 (target is 10 by M36)	**>10**

To combine the experiences of the eHealth field with the knowledge and experience of the rare disease / ERN community, and to formalize collaborations, work package 6 established the "Task-Force on Interoperable data-sharing in the Rare Diseases and eHealth communities" in November 2015. The task force was concepted as a long-standing institution and is chaired by the work package 6 leads. Activities and outputs were made publicly accessible on the RD-Action website.

Through this Task-Force, work package 6 built collaborations with numerous eHealth projects, including the following: EXPAND; JASeHN; eHAction; eSENS; Antilope; VALUeHealth; EHR4CR. Collaborations were also built with communities including data management and interoperability, and rare cancers (e.g. the GO-FAIR Implementation Network, the JA for Rare Cancers (JARC), EXPO-r-Net, etc.).

The communities and initiatives outlined above were introduced to the issues and achievements of the rare disease field through the Task-Force (in the case of eHealth actions), through teleconferences designed to enhance Integration activities, and through attendance of the work package 6 leads at numerous meetings and conferences. During the latter, many presentations were delivered (verbal and poster presentations) to dissemination information and open new avenues for collaboration.

- **Task 6.3: Produce the Report/Resource on the State of the Art of Rare Diseases Activities in Europe**

Suggested Indicator Set 1	
o Process Indicator	
▪ Present the State of the Art of RD activities in Europe (see also WP 2)	**Fulfilled**
o Output Indicator	
▪ An ongoing, electronic State-of the Art resource on policies for RD across the EU MS (with an annual summary report)	**Fulfilled**
o Outcome Indicator	
▪ Number of countries contributing national information each year (28)	**24**

Suggested Indicator Set 2	
o Process Indicator	
▪ Monitor MS developments in implementing national RD activities	**Fulfilled**
o Output Indicator	
▪ Coordinate annual MS completion of the EUCERD Recommendations on Core Indicators and upload to the SoA resource	**Not performed**
o Outcome Indicator	
▪ Number of MS completing the Indicators table each year (28)	**Not performed**

For details on the State of the Art resource and its production please refer to the section on work package 2, task 2.1, suggested indicator set 1. The 2016 summary report featured data from 24 member states; two member states did not provide any information, and the inputs from two member states were too limited to be published. The next summary report will be coming up in fall 2018.

The revised resource on the “State of the Art of Rare Disease Activities in Europe” was presented and disseminated at many events across the project lifespan: between June 2015 and July 2018, the Resource and its components had been promoted to up to 3010 participants. For full details, see Deliverable 2.3, “Dissemination of the Resource on the State of the Art of Rare Disease Activities in Europe”.

Following the formal Autumn update of country-specific data, a summary table relating to the EUCERD Recommendations on Core Indicators will be completed.

Summary and conclusions

Work package 6 continued the tasks of the EUCERD Joint action, in that it 1) worked to support the development of policies and recommendations for consideration and adoption by the CEGRD (until the end of its mandate), and 2) took over the production of the resource on the state of the art of rare disease activities in Europe. However, with the establishment of the ERNs (including all the activities preceding their implementation, as well as the still continuously required assistance in unfolding all their anticipated functions), an entirely new field of activity opened up and eventually absorbed a greater part of the resources of work package 6. Along these lines, RD-Action support of ERNs started right at the beginning of the Joint action in Summer 2015 with a workshop in preparation of the first ERN call, based on which the Matchmaker tool was set up – an application which helped tremendously in bringing interested expert from all over Europe together, thereby contributing significantly to the shaping of the structure of the networks in their present form. Subsequently, countless other meetings (in addition to the major workshops set out the original project plan) were organized with even more numerous outputs including reports, recommendations, and opinion papers supporting the further development of the ERNs in a variety of different aspects.

In addition to the work within the rare disease community in the narrower sense, work package 6 also reached out to relevant partners in other areas – the most prominent example being the eHealth field with the formation of a long-standing, integrative task force –, and so helped to bridge the gap to other experts offering valuable input for the functioning of the ERNs.

4. Conclusions

After three years of working together in this large European cooperative project, the Joint Action RD-Action is now finished. RD-Action was facing the task of bringing two previous Joint Actions (EUCERD JA and JA Orphanet) together – two projects which had in common the dedication to rare diseases, but were otherwise very different in their approaches. The RD-Action consortium managed this challenge outstandingly and took this unique chance to achieve a remarkable consolidation within the rare disease field in Europe, establishing close ties between all partners, building up synergies, and using outputs in a much more efficient, common effort.

Technically, RD-Action is a successful project in that it delivered all its deliverables and milestones on time, and most indicators defined in the original project proposal were fulfilled (if this was not the case, it was in most instances a change in circumstances that prevented it). The performance of the project in terms of fulfilling pre-set indicators was treated exhaustively in this report. The remaining question is obviously about the mid- and long-term impact of the Joint Action. As mentioned at the beginning, impact indicators were only rarely included in the technical evaluation, because objective impact measurement is virtually impossible directly at the end of a project. Nevertheless, a few measures have had specific and immediate impact within the rare disease field (although it must be emphasized that these measures were usually part of long-standing efforts that were merely continued under renewed circumstances) and should be mentioned here in particular (in the order of the corresponding work packages).

ECRD - the European Conference on Rare Diseases & Orphan Medicinal Products

This biennial conference series started in 2001 in Copenhagen with little more than 200 attendants and has since then been growing to what is now one of the most successful conferences worldwide to discuss, share, and distribute information on developments in all areas of rare diseases. The structure is unique in its patient-centered approach, giving not only representatives, but also individual patients a forum and an opportunity to participate. Only on few occasions are patients, experts, and all other stakeholders as close together as in this meeting, rendering it an indispensable resource for all. While the ECRD 2016 was included in RD-Action under the umbrella of the Dissemination work package 2, its continuation does not depend on the continuation of the Joint Action or a succeeding RD project. Further conferences will be organised in a continuous fashion, most probably keeping the biennial cycle, with the ECRD 2018 on May 10-12, 2018, in Vienna being the first iteration outside the RD-Action grant frame.

EUROPLAN conferences

These meetings have proven to be the best forums to discuss and pursue national strategies and/or plans for rare diseases. However, after the end of specific funding by the EU-funded projects Europlan and Europlan 2, these conferences are increasingly difficult to be set up and organised in many Member States, a challenge that the Joint Action already had to face. Since at present no new common funding streams are in sight to support this type of meeting in the different European countries, the organisation of future national conferences will depend largely on the commitment of national rare disease alliances to keep the momentum going. Thus, in this area, the legacy of RD-Action remains open.

Orphanet nomenclature and database

Orphanet, the European database in rare diseases, has brought immense progress for the rare disease field in terms of visibility, transparency, and organization. Orphanet has begun to work on a classification of rare diseases in 2007; the results are the basis for the efforts related to coding and epidemiology of rare diseases (see below). In the frame of RD-Action, Orphanet was able to implement a series of innovations including a participative platform for data curation, a new quality management system, and a new organizational structure, the Orphanet Network, which will ensure collaborative decision making so that procedures can be adapted to national situations more effectively. With regard to the sustainability of Orphanet, a concept with several funding approaches has been developed and will now be treated in the high-level Steering Group on Health Promotion, Disease Prevention and Management of Non-Communicable Diseases. Taken together, some of the efforts in the Joint Action related to Orphanet already unfold their potential, impacting actual discussions and further developments on national, as well as the European level.

Strategy and tools for implementing Orpha codes in Europe

Based on the Orphanet nomenclature, RD-Action work package 5 has developed a strategy, as well as all the necessary tools and guidelines to implement a highly specific coding system for rare diseases in European countries. As all testing and fine-tuning has now been done, the next step will be to put the system to practical use in member states. It is to be expected that this will revolutionize epidemiological data collection (as well as – potentially, depending on the national situation – reimbursement for healthcare services etc.) for rare diseases. In line with this, a follow-up pilot project for the actual implementation of Orpha codes in the health care systems of selected Member States currently not using a (supplementary) Orpha coding has recently been launched by the European Commisssion.

RD-Action support for European Reference Networks (ERN)

Work package 6 has supported the ERNs from the very initial phase of European top-experts organizing themselves around the thematic fields previously proposed by the EUCERD committee, finding the best partners for future cooperation, until the consolidating phase of actually getting the networks operational. RD-Action has contributed major input on several pivotal points, like data sharing and virtual care, clinical practice guidelines, clinical research, and monitoring of ERNs. The workshop series organized during the Joint action produced a number of output papers, some of which are already used in related working groups of the ERN coordinators and the Board of Member States on ERNs in order to further discuss and elaborate the individual topics, issue official recommendations and implement these recommendations in the Networks. As prime example, the document on indicators from the workshop on continuous monitoring of ERNs has been integrated into a related document from the fused working groups on indicators and monitoring of ERNs that has just recently been adopted by the Board of Member States. The indicators defined in this document now constitute the first set of indicators that will soon be used to monitor key operations of all 24 ERNs.

Similar developments in other areas, like for instance clinical guidelines, will follow in the near future.

In conclusion, RD-Action has had huge impact, which will be measurable soon (e. g. how many documents produced in the frame of the project have actually been adopted, how many countries have implemented the coding system etc.). Patients may have seen some benefits directly, as the project promoted participative approaches in many areas (like the ECRD congress, the EUROPLAN meetings, but also the inclusion of patient representatives in ERN workshops). Positive aspects that are not readily quantifiable – but equally important – are strengthening of networking activities and optimal use of (academic and other) resources in a field were general support is still relatively scarce.

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