Deliverable N°: D3.2
Title: Report on the State of the art of available PCOMs/PROMs and overlap/gap analysis

Introduction

Report on the State of the art of available PCOMs/PROMs and overlap/gap analysis in the framework of the ERICA WP3 "Patient Centered Research". ERICA WP3 aims to define Rare Diseases' priority areas for future Rare Patient Reported Outcome Measures (PROMs) development, support ERNs in the implementation of PROMs and to create a central repository of PROMs for ERNs. In this deliverable, ERICA WP3 team describes and illustrates objectives, methods and results of the analysis of the PROMs and ObsRO available in the scope of each ERN and its correlated gaps.

Background

A **clinical outcome assessment (COA)** measures patient symptoms, mental state or the effects of a disease on patient functions. A COA can be used to determine whether or not a drug has been proven to provide a treatment benefit (i.e. a benefit compared with other treatments). According to the International Rare Diseases Research Consortium (IRDiRC)[1], Report on Patient-Centered Outcome Measures in the Field of Rare Diseases on February 2016, there are five types of COAs:

Type of COA	Definition
Patient Reported Outcome (PRO)	Measurements based on data provided by patients, or proxies, regarding their health condition
Observer Reported Outcomes (ObsRO)	Measurements based on an observation by someone other than the patient or a health professional who is in a position to regularly observe and report on a specific aspect of the patient's health
Clinician-reported outcomes (ClinRO)	Measurements based on a trained health-care professional's report following observation of a patient's health condition

[1] https://www.irdirc.org/wp-content/uploads/2017/12/PCOM_Post-Workshop_Report_Final.pdf

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Performance Outcomes (PerfO)	Measurements based on a task performed by a patient according to instructions administered by a healthcare professional.
Biomarkers	Physiologic, pathologic or anatomic patient characteristics measured by an automated process or algorithm as an indicator of normal biologic processes, pathologic processes, or biological responses to a therapeutic intervention.

COAs are crucial instruments for rare diseases (RDs) and orphan drugs development. Those measurement tools monitor research (i.e. clinical trials, registries, and clinical patient management) and assess its efficacy and safety for patients together with the evaluation of the diseases' progress (i.e. symptoms, mental or side effects, functions). COAs are scarce in many RDs clinical areas due to the lack of background knowledge about how to develop and validate them and the scattered accessible evidence on those complex conditions. This is especially true for COAs other than biomarkers; namely PRO, ObsRO, ClinRO, PerfO. In addition, it is normally difficult to identify patients' cohorts because of the low incidence of RDs and/or poor presence of patients' associations. Finally, in Europe there is no central repository for RDs COAs. Therefore, healthcare professionals and researchers may not properly exploit available COAs because they might not be aware of their accessibility or even their existence. As a result, there is a general lack of resources leaving experts' centres and healthcare services less able to implement, validate and/or adopt COAs for RDs.

PRO, ObsRO, ClinRO and PerfO instruments gather essential information from patients (besides data gathered through biomarkers) allowing patients and families to take a more active part in health assessment with healthcare professionals, making research more accurate and closer to the patients' experience. In addition, it defines criteria that guarantee the most efficient results as patients are the most accurate reporters of the impact of the disease/treatment on their lives. Accordingly, for the purpose of this report we will consider PRO, ObsRO, ClinRO and PerfO all together as Patient-Centered Outcome Measurement Instruments (PCOMs), most of them being Patient Reported Outcome Measures (PROMs). Nevertheless, we are aware that further efforts and actions are needed to acknowledge these instruments as Patient Centered.

Objectives

The **ERICA work package 3 (WP3)** is dedicated to **Rare Diseases Patient-Centered Research** specifically focused on PCOMs/PROMs. PCOMs/PROMs are crucial axes for improving the lives of people living with RDs, for Orphan Drugs development, and for strengthening the collaboration of healthcare professionals, patients and caregivers during the health assessment process. In addition, the ERICA WP3 aims to cover the need for a centralized repository of validated common and domain specific PCOMs/PROMs for RDs.

The ERICA WP3 closely works with and for **European Reference Networks** (ERNs), collaborative RDs' networks involving healthcare providers and patients' associations across Europe. ERNs aim to tackle complex or rare diseases and conditions that require highly specialized treatments as well as a concentration of knowledge and resources. There are 24 ERNs covering 24 different clinical areas, which were officially approved by the European Commission (EC) in December 2016 and started their activity 1st March 2017.

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ERICA, the **European Rare Disease Research Coordination and Support Action** consortium is the most effective background for developing such an ambitious WP3 objective since it provides the means and support to coordinate the necessary resources and cooperation among the 24 ERNs.

Accordingly, ERICA WP3 aims to facilitate the Europe-wide implementation of PCOMS including PROMs, ObsRO, ClinRO, and PerfO instruments for RDs. More specifically, **objectives** are:

- **3.1. To create a central repository of validated common and domain specific RD PCOMs/PROMs for ERNs.**
- **3.2. To define priority areas for future PCOMs/PROMs development.**
- **3.3. To support ERNs in the implementation of validated instruments for PCOMs/PROMs.**

Those accomplishments will have a high impact in the RD field by promoting Patient-Centered Research and the adoption of PCOMs/PROMs in health assessment.

This deliverable will describe the methods and results for establishing the state-of-the-art of available PCOMs/PROMs in RDs in addition to the gap analysis by medical domain and by ERN.

Description of work

WP3 Team has established a roadmap for identifying existing PCOMs/PROMs in RDs, making them findable/ accessible and increasing their implementation by ERNs and the greater RD community. The defined state-of-the-art of available PCOMs/PROMs allowed us to also identify gaps for RDs. In light of the results obtained so far, a strategy for supporting the adoption and development of standardized RD PCOMs/PROMs will be developed for fostering their implementation in clinical practice, evaluation of care and clinical research.

First step was to establish a **Patient-Centered Expert Working Group (PCEWG)** to guarantee a European multi-stakeholder and collaborative approach for the implementation of ERICA WP3. Second, the state-of-the-art of available PCOMs/PROMs in RDs was established through two main actions a) selection of the PCOMs/PROMs described in the Mapi Research Trust database (PROQOLID™) developed and validated for RDs and for measuring specific functional impacts (i.e. mobility, self-care or communication) relevant for RD and b) conduction of a survey among the 24 ERNs and their affiliated ePAGs to collect additional PCOMs/PROMs of interest. Third, to develop coding rules for PCOMs/PROMs based on the International Classification of Functioning, Disability and Health (ICF)[2] code. The resulting ICF-coded PCOMs/PROMs had to match the ICF-coded functional impacts of RDs, generated by semi-structured interviews with the Orphanet Disability Questionnaire based on the Orphanet Functioning Thesaurus[3] Finally, a workshop was held with the PCEWG in order to customize the RD PCOMs/PROMs repository according to the RD community needs and expectations of users.

Methods and Means

*Establisment of the **PCEWG***

The WP3 PCEWG has been established to guarantee a European multi-stakeholder and collaborative approach for the implementation of ERICA WP3. As of year 2022, the PCEWG is composed of 20 members:

[2] World Health Organization. ICF: International Classification of Functioning, Disability and Health. Geneva, Switzerland: World Health Organization; 2001

[3] https://www.orpha.net/orphacom/cahiers/docs/GB/Orphanet_Functioning_Thesaurus_EN.pdf

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- WP3 Team: Orphanet, Mapi Research Trust and University Hospital Vall d'Hebron and Assistance Publique - Hôpitaux de Paris representing ERN-EuroBloodNet.
- ERN Coordinators for Endo-ERN, Transplantchild, Cranio, ERNICA, ERN-RND, Guard-Heart, RITA.
- H. Sant Joan de Déu – Transversal ERNs unit support
- EURORDIS.
- EJP-RD

The PCEWG oversees the work performed in WP3, such as:

- Analyse the results of the currently available instruments for RD PCOMs and PROMs
- Analyse the priority areas for future PCOM/PROM development identified by the ERICA WP3
- Support the strategy of implementation of standardized PCOMs for RDs within ERNs

State-of-the-art of available PCOMs/PROMs in RDs

1. PCOMs/PROMs Database analysis: **PROQOLID™ and Orphanet Disability Database (ODB)**

Mapi Research Trust is an organization that provides information on available PCOMs/PROMs to all stakeholders. With this aim, they launched in 2002 a database specifically dedicated to PCOMs/PROMs named **PROQOLID™**[4]. It provides descriptive information on PCOMs/PROMs for their relevant use (i.e.. type of COAs, objectives, therapeutic areas, languages, domains, scoring, and measurements properties).

1.a. ORPHAcodes-MeSH semantic mappings approach

Orphanet and Mapi Research Trust has mapped existing validated tools for PCOMs/PROMs in RDs in PROQOLID™ using ORPHANET alignments of RD nomenclature with other terminologies, in particular MeSH terms, for they are used as meta-data in PROQOLID™. This allowed initially the identification of 112 mainly PCOMs for 64 RDs. This effort continues as the terminologies evolve.

1.b. Functional consequences of RDs-based approach: coding PCCOMs in PROQOLID™

In order to detect PCOMs/PROMs that are not specific to RD but that measure functional impacts relevant to RDs, an analysis has been initiated based on functional consequences of RDs according to the Orphanet Disability database[5]. Looking at instruments measuring functional impact helped identify those that are applicable to many RDs, including specific instruments designed for paediatric patients.

This approach utilizes the Orphanet Disability database, aimed to categorize RDs given their functional consequences and impact on daily life using the Orphanet Disability Questionnaire (ODQ). The objective of the ODQ, a collaborative project involving medical experts, patient organizations and ERNs, is to measure the impact of RD on daily life using the Orphanet Functioning Thesaurus[6]. This thesaurus is based on the International Classification of Functioning, Disability and Health (ICF) with the addition of some terms not present in ICF but important for many RDs, such as sleep disturbances. RDs and their subtypes are prioritized according to prevalence and following the Orphanet classification. Therefore, through structured interviews using this questionnaire, functional consequences are annotated according to their severity, from low to complete, frequency; occasional, frequent or very frequent, and temporality; meaning permanent limitation, delay in acquisition of a skill, transient limitation or loss of an ability

[4] https://eprovide.mapi-trust.org

[5] https://www.orphadata.com/functional-consequences/

[6] https://www.orpha.net/orphacom/cahiers/docs/GB/Orphanet_Functioning_Thesaurus_EN.pdf

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limiting the activity. This activity results in a database containing the systematic accumulation of standardized information based on the ICF.

This database currently contains a total of 566 disorders that have been already coded for impact on function. They are described with the full set of 113 items, that are grouped in 10 principal subjects describing patients' functional limitations (environmental factors are not included in this list, but considered in the ODQ):

1. Understanding
2. Communication with others
3. Motor skills
4. Self-care
5. Sleeping/Staying awake
6. Temperament and behaviour
7. Moving around
8. Interpersonal skills
9. Daily activities
10. Social life

In addition, 372 disorders were also annotated with the help of medical experts as either: early-death, hypervariable, no functional disability or not applicable: therefore, these disorders were not annotated with the Orphanet Functioning thesaurus terms.

2. Survey on available PCOMs/PROMs among the ERNs: "**Available PROMs and ObsRO in Rare Diseases"**

A survey named "**Available PROMs and ObsRO in Rare Diseases**" has been submitted to the 24 ERNs Coordinators, ERN Members, ERNs Affiliated partners and ePAGs in order to identify available PCOMs/PROMs and areas for future PCOMs/PROMs development. Specifically, survey's objectives are:

- Landscape analysis of available RD PROMs or ObsRO among ERNs
- Identification of RD PROMs Gaps
- Implement the repository of existing PROMs of interest for ERNs to use in RDs

The survey collected evidence on clinical outcome data defined by the 24 ERNs to determine their specific criteria (i.e. therapeutic indication, context of use, population, ERN study), assess the level of development and implementation of PCOMs/PROMs within ERNs and identify successful examples of their use as well as gaps.

The first round of the survey gathered 219 contributions covering 23 ERNs. Respondents were ERN coordinators/members/affiliated (81%), ePAGs (11%) and Other (8%) (Figure 1 A). It was decided to keep the survey open (as a dynamic tool) to receive continuous input from ERNs stakeholders regarding PROMs use, development and validation.

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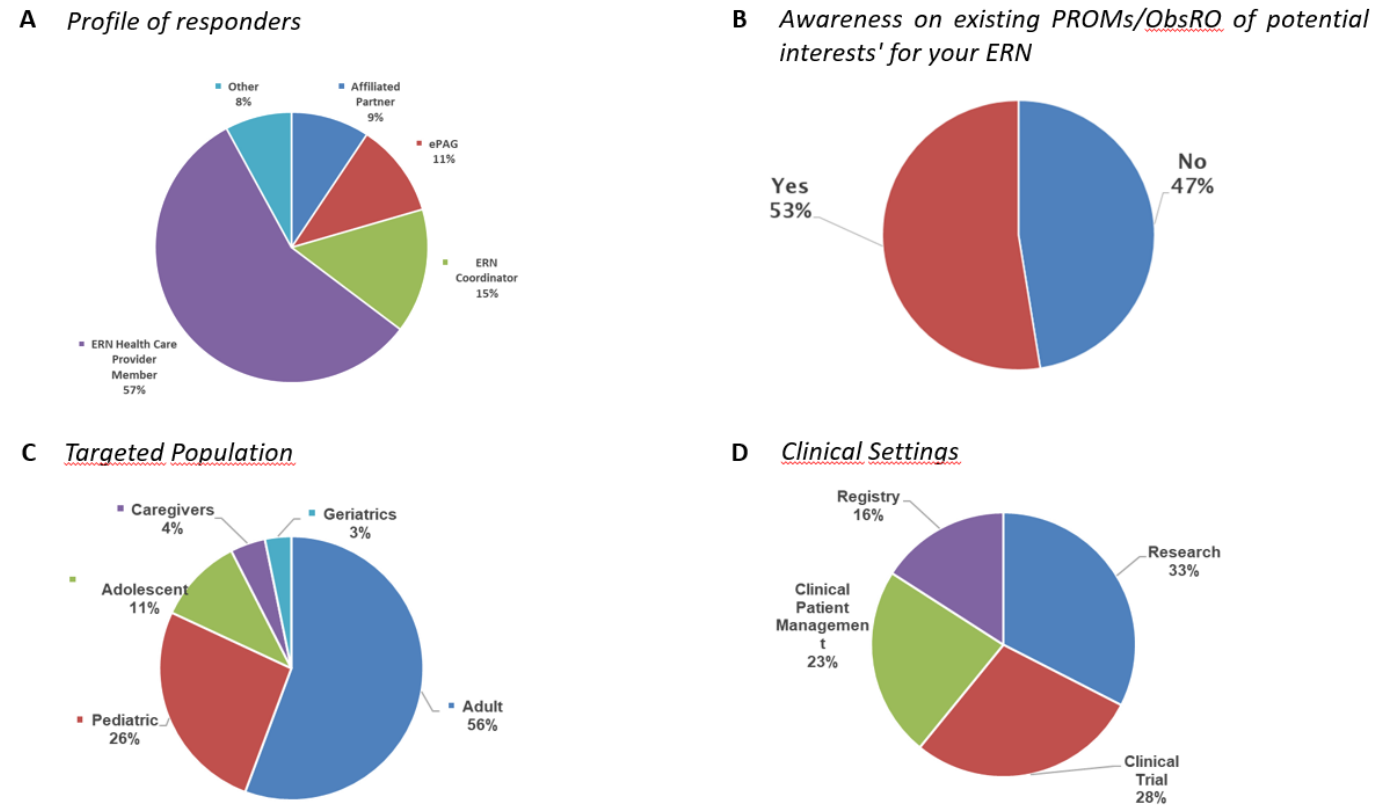

Figure 1 Results from survey among ERNs on "Available PRO and ObsRO in Rare Diseases"

The first question of the survey allows us to understand the PROMs/ObsRo awareness: *"In your area of expertise, do you know any PROMs or ObsRO of potential interests' for your ERN?"*

Around half of the responders (47%) were not aware of any PCOMs/PROMs in their area of expertise, meaning that their actual implementation is not a standard. (Figure 1 B).

Other relevant key findings of the survey to underline are the target population of the questionnaires, that is to say the age range of PCOMs/PROMs administration (paediatric, adolescent, adult, aged), and the clinical settings of their context of use. More than half of PCOMs/PROMs are used in the adult population and many contributors commented on the lack of validated tools, mostly for the adolescent population. Regarding context of use, the same PCOM/PROM was found to be used in a variety of clinical settings; registry, research, clinical trials and clinical Patient Management. (Figure 1 C and D)

3. Crossing PCOMs/PROMs results from PROQOLID™ and ERNs Survey

Results of available PCOMs/PROMs obtained via PROQOLID™ and via ERN Survey have been crossed to remove duplicates. Resulting data have been merged and classified according to established criteria on:

1. Official name and abbreviation of PCOMs/PROMs
2. Type of PCOMs/PROMs (PRO, ObsRO, ClinRO, PerfO)
3. Target age range (Pediatric: 0-12; Adolescent: 13-18; Adult: 19-65; Aged: >65) for which the Questionnaire was developed
4. Target disease (Mesh Term, ORPHAcode and Orphanet preferred term) for which the questionnaire was developed

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5. Related ERN(s)
6. Use in ERN Context- Therapeutic Indication (only for ERN survey's source of identification, when the responder is an ERN member)

Finally, the merged list of identified PCOMs/PROMs, which gathers PROQOLID™ results and ERN Survey results, has been split according to each ERN and sent to: ERNs Coordinators and Project managers, ERN Surveys' contributors and members of the WP3 PCEWG belonging to a ERN. This action aims not only to communicate to each ERN its related landscape panorama of available PCOMs/PROMs and get expert validation, but also to further nourish the state-of-the-art of existing PCOMs/PROMs in RDs.

PCEWG Kick-off meeting & Workshop

A two-day **Kick-off meeting & Workshop of ERICA WP3 PCEWG** was organized on March 8th and 10th, 2022. It had two main aims: 1) To present the WP3 objectives and achievements so far and b) To discuss how to build an accessible repository for RD PCOMs/PROMs, customized to RD community needs. The first day included 55 participants and, on the second day, 38 participants. Attendees were primarily composed of ERNs Coordinators, project managers and members (35%), ePAGS and patients' representatives (34%), researchers (8%) and Other (23%).

Feedback from participants were gathered via an interactive polling tool (Mentimeter) on a) needs for the use of ERICA PCOMs/PROMS repository, b) the ideal context of use of RDs PCOMs/PROMs, c) the expected search engine terms to be included in the repository and d) the expected results.

Concerning "Context of use":

- Evaluation of efficiency of care in real world practice (13 votes)
- Evaluation of intervention effects (12 votes)
- Support medical decision-making (10 votes)
- Enhance communication between Patients and physician (10 votes)
- Health care staff guidance (6 votes)

Concerning "Concept to be measured", the following concepts were mentioned :

- Patient satisfaction/expectation/preference (10 votes)
- Patient adherence/engagement/participation (8 votes)
- Quality of life (6 votes)
- Quality of care (6 votes)
- Patient/Families needs (6 votes)
- Burden (of the disease, of care, of participating in a trial) (5 votes)
- Self-efficacy / self-image (4 votes)
- Independence and awareness (4 votes)
- Pain (4 votes)
- Psychosocial burden (3 votes)
- Efficacy & Safety of treatment (3 votes)
- Patient understanding of the disease (2 votes)
- Symptoms (2 votes)
- Diagnostic (2 votes)

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- Access to treatments (1 vote)
- Loss of function (1 vote)
- Disease severity (1 vote)

Concerning "Expected search terms", most mentioned terms were:

- PROMS Concepts/Domains (Functional disabilities, symptoms, Pain, ADL, emotional/family/Social functioning, drug side effects)
- Population age range (pediatric, adult, adolescent, elderly)
- Disease (ORPHAcode, ICD-10 code / Disease name /Gene)
- PCOMs/PROMs name

Concerning "Expected results", most mentioned ones were:

- PCOMs/PROMs name
- Type of questionnaire
- Population age range
- Concepts measured by the questionnaire

The outcomes have been taken into consideration for the creation of the ERICA Repository of RD PROMs, as demonstrated in the "**Deliverable 3.1 Central repository of (validated) PCOMs for RDs".**

Detailed results of the Kick-off meeting of ERICA WP3 PCEWG are shown in "**Annex 1 - WP3 Patient-Reported Outcome Measures (PROMs) Repository Workshop**".

Results

The combination of the different steps to identify RD specific or suitable PCOMs/PROMs resulted in 781 unique instruments of which 364 address specifically a RD or a group of RDs (46.6%) and 417 were generic.
259 instruments were identified as developed for RDs in PROQOLID™, 211 thanks to the ERN survey, and 151 instruments were identified in PROQOLID™ as addressing specific functional impacts included in the Orphanet Functioning Thesaurus. Finally, 160 instruments were included for they address generic concepts identified as interesting during the ERICA 2022 General Assembly.

Most of the instruments identified are PROMs (99.5%), exclusively or in combination with other types of instruments, as shown in table 1.

Table 1 Number of PCOMs/PROMs by Type

Type of PCOM/PROM	Counts
ClinRO	4
ObsRO	1
PRO	686
PRO and ClinRO	6

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PRO and ObsRO	3
PRO and PerfO	1
PRO or ObsRO	80
PRO or ObsRO and ClinRO and Biomarker	1

Further analysis of PCOMs/PROMs specific for a RD or groups of RDs (grouped under the term “clinical entity”) were done in order to understand the distribution of PCOMs/PROMs by rare clinical entities, to analyse the RD coverage and to identify the gaps.

Using the Orphanet nomenclature of RDs, in which it is possible to differentiate Categories (including a heterogeneous, often very broad diseases’ grouping), Clinical groups (including more homogeneous groups of diseases), Disorders, and Sub-types of disorders, it was possible to calculate the individual rare disorders for which specifically a PCOM/PROM was detected and included in the first version of the repository, by considering the individual disorders included in clinical groups. PCOMs/PROMs associated with broad groups of disorders (categories) were excluded from this calculation because of their heterogeneity and low specificity. It appears that 238 RDs are specifically addressed by one or several PCOMs/PROMs, which represents 3.8% of all RDs (according to the July 2022 version of the Orphanet nomenclature, that included 6227 RDs). See **Annex 2 - List of rare disorder and groups of disorders for which PCOMs/PROMs were identified**

While only 238 RDs have dedicated PCOMs/PROMs, the number of instruments available per RD is not uniform, as shown in figure 2, which also excludes broader groups (categories) of RDs. RDs for which more than 10 PCOMs/PROMs have been developed are: Amyotrophic lateral sclerosis, Spinal cord injury, Duchenne muscular dystrophy, Systemic Lupus erythematosus, Hemophilia, Sickle cell anemia, Huntington disease, Systemic sclerosis, Cystic fibrosis and Myelodysplastic syndromes.

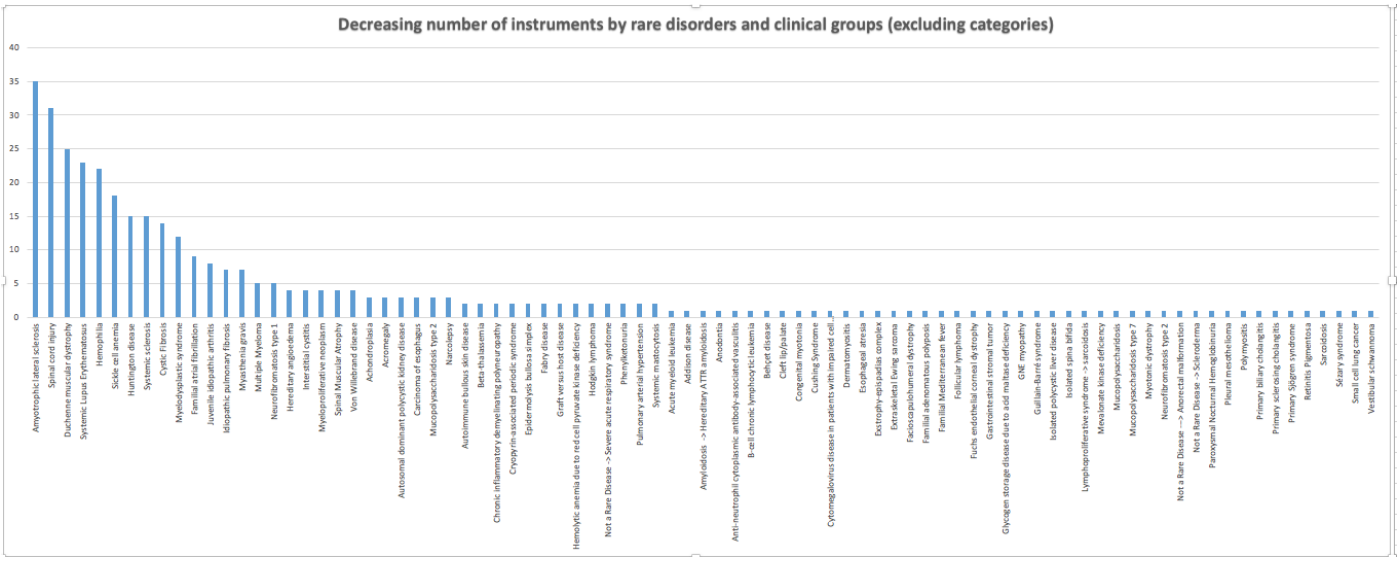

Figure 2 Decreasing number of instruments by RDs and clinical groups (excluding categories)

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According to the Orphanet classification and to published linearization rules[7] (i.e. attributing a main classification to each clinical entity for statistical purposes), the overall distribution of PCOMs by medical domain, including the entirety of disease-specific PCOMs (for categories, clinical groups, disorders and sub-types) is depicted in figure 3. Generic PCOMs/PROMs were excluded from the analysis.

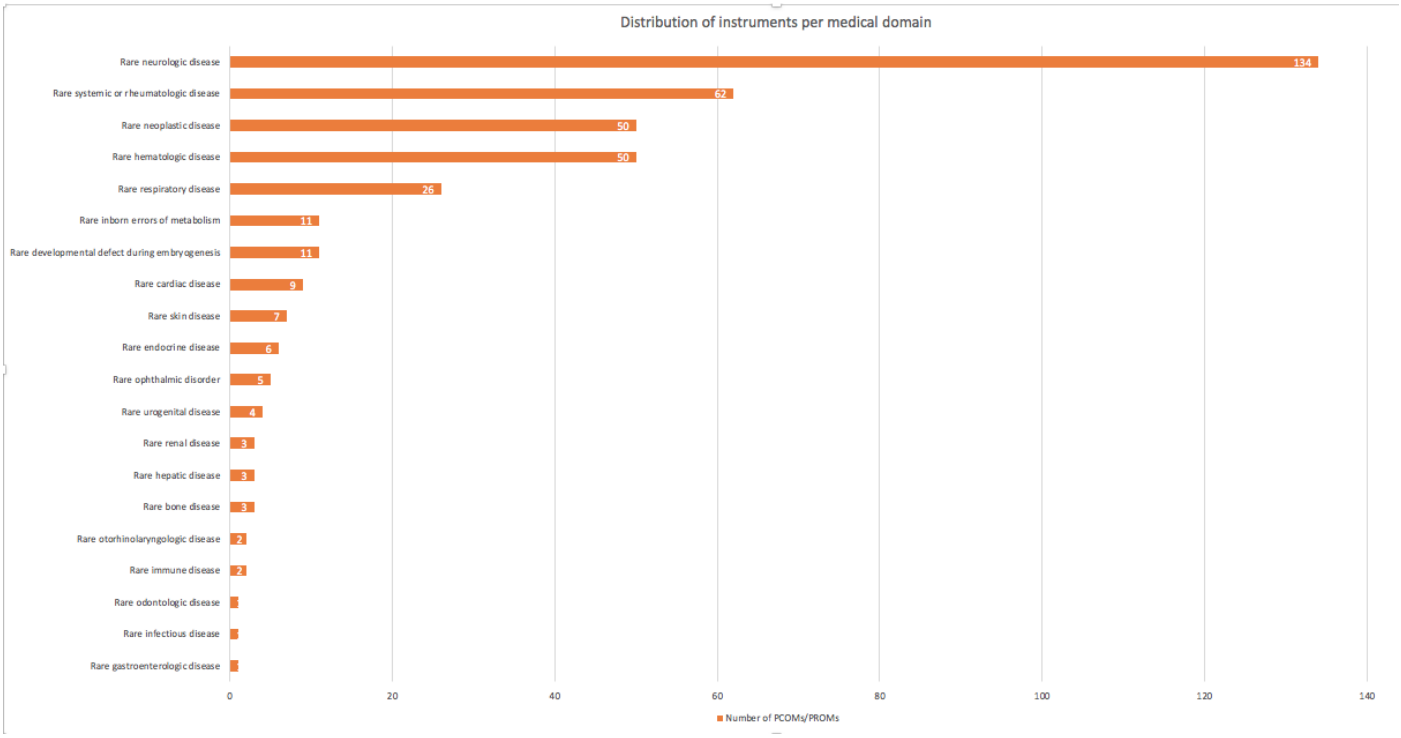
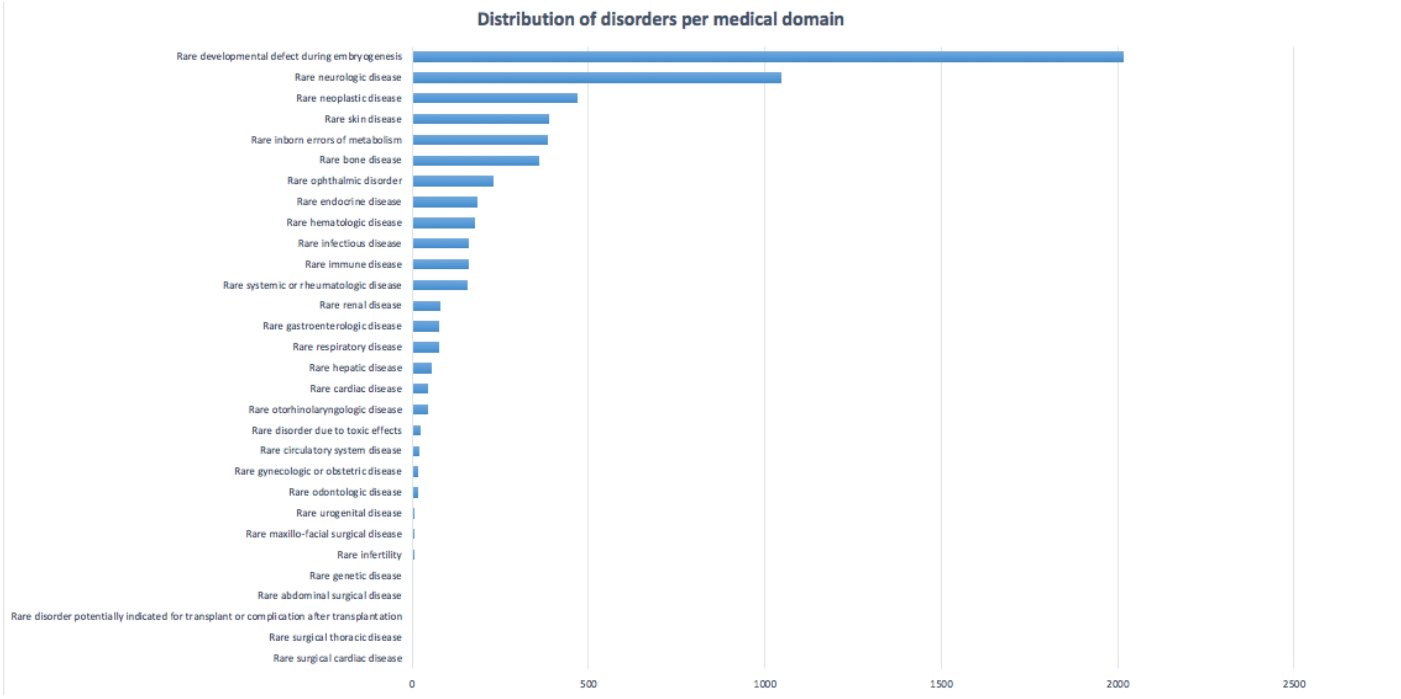


Figure 3 Distribution of PCOMs/PROMs instruments by medical domain

For comparison, the pie below (Figure 4) shows the distribution of RDs per medical domain according to the linearisation rules:



[7] Linearization rules for Orphanet classifications

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Figure 4 Distribution of disorders by medical domain

When comparing the number of RDs having at least 1 PCOM compared to the total number of RDs linearized in a medical domain (according to Orphanet linearization rules) we observe a heterogeneous coverage, and therefore a variable gap amongst medical domains. This is represented in figure 5. It must be noted that neuromuscular diseases and rare epilepsies are included under rare neurological diseases, and that developmental anomalies are considered only in the developmental anomalies group end not in each medical domain (for example: anorectal malformations are not considered in the rare urogenital disorders domain but in the developmental anomalies domain).

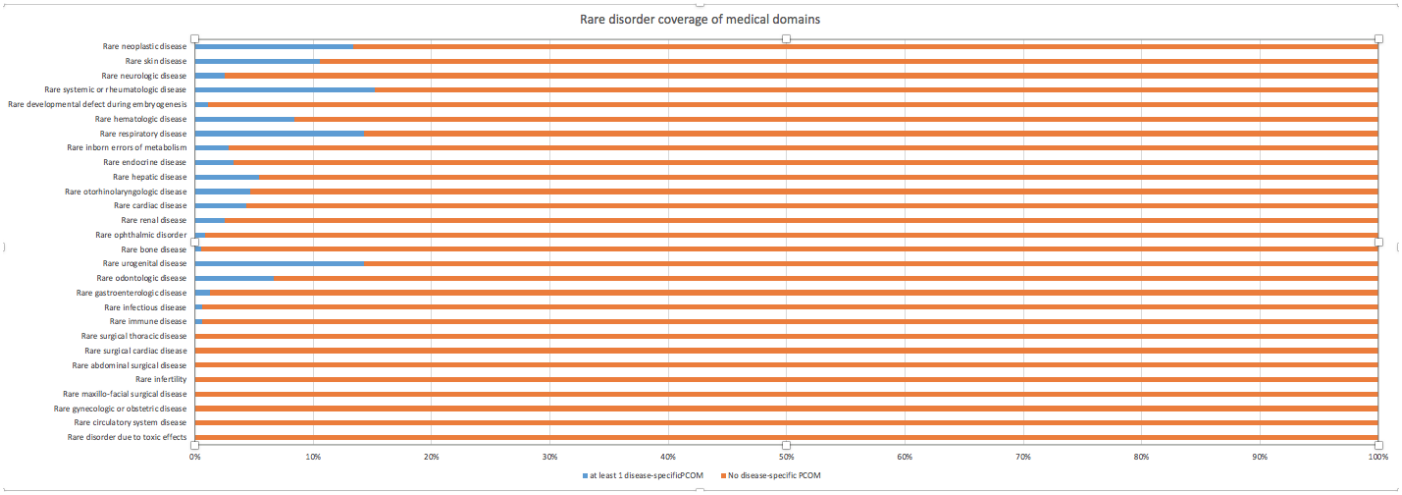

Figure 5 RD coverage of medical domains

PCOMs/PROMs distribution by ERN:

505 unique PCOMs/PROMs could be attributed to one or more ERNs, 25% of them involving more than one ERN. The distribution is shown in figure 6 (instruments are counted as many times as they are associated with an ERN).

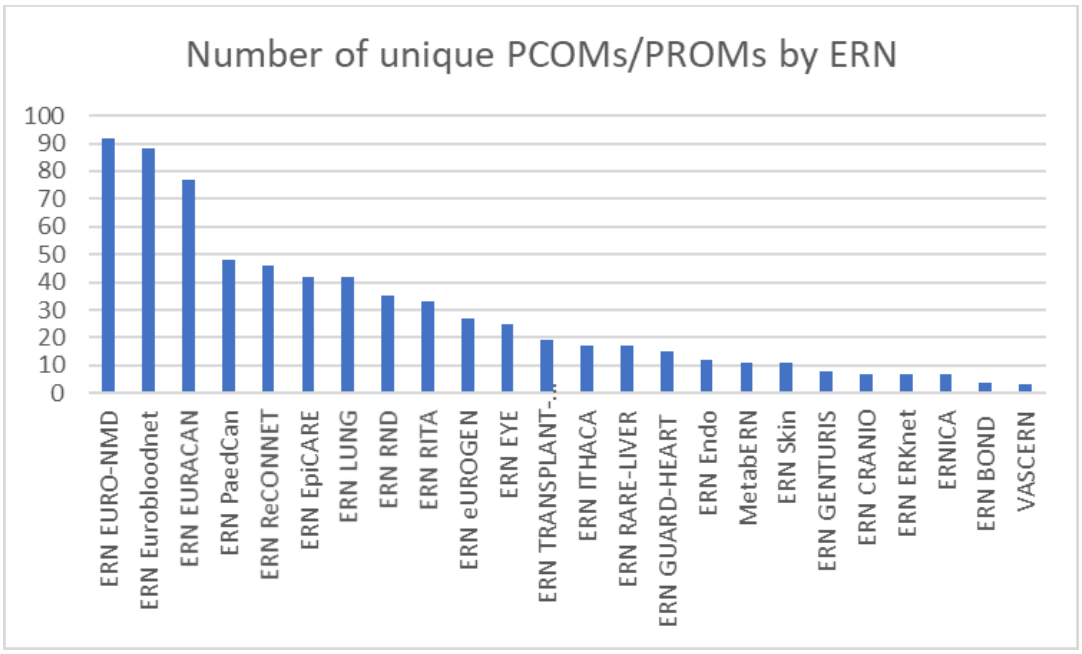

Figure 6 RD coverage of medical domains

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Conclusions

ERICA WP3 established the State-of-the-art of available PCOMs/PROMs in RDs including a first set of 781 unique instruments of which 364 address specifically a RD or a group of RDs (46.6%) and 417 were generic. They are included in the ERICA RD PCOMs/PROMs repository, https://erica-rd.eu/proms-repository/.

Through the ERICA repository, PCOMs/PROMs in RDs are now searchable and accessible in a structured way, which marks an important first step in increasing awareness and implementation of these instruments in the RD field. By making these tools more readily available, healthcare providers and patients associations belonging to ERNs can help disseminate current knowledge to physicians thanks to patients' reported experiences. For example, the description of rare disease symptoms, complaints about functional impacts as well as expected treatment benefits - with the aim of enhancing communication between healthcare professionals and patients. This work also has strong implications for improving healthcare management as well as clinical research. In other words, the central Repository can now help ERNs better contribute to evaluating efficiency of care in real-life practice or, additionally, intervention effects (such as drugs, medical devices, surgery, physiotherapy, etc.).

To maximize the impact of the anticipated ERN PCOMs/PROMs Roadmap, representatives from the European Medicine Agency, the Board of member States, IRDiRC, NIH-RDCRN, and EUnetHTA, will be invited to join WP3 PCEWG as experts on PCOMs/PROMs development and validation.

The next steps in accomplishing WP3's ambitious goals are to finalize the coding model for the full set of PCOMs/PROMs, to operationalize the repository platform for both researchers and clinicians and to routinely code new eligible/available PCOMs/PROMs. Then, build upon the gap analysis and the clustering exercise to define priority areas for future PCOMs/PROMs development and define a strategic plan for supporting the implementation of standardized PCOMs/PROMs within ERNs.

Questions and access requests: info@erica-rd.eu

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