

Annex 1: List of Efforts to Develop and Standardize Outcome Measures

Common Disease Initiatives

Consensus-based Standards for the selection of health Measurement INstruments (COSMIN)

Goals	The COSMIN initiative aims to improve the selection of evidence-based health measurement instruments. The COSMIN checklist contains standards for design requirements and preferred statistical methods of studies on the measurement properties of health measurement instruments. Additionally, COSMIN published an online database of systematic articles of outcome measurement instruments, which could be found at database.cosmin.nl . The articles of outcome measurement directly or indirectly related to rare diseases can be found in Annex 4.
Website	http://www.cosmin.nl/
Active years	2005 to present
Relevant contacts	<ul style="list-style-type: none"> ▪ Wieneke LB Mokkink, Assistant professor in Clinimetrics, Department of Epidemiology and Biostatistics, EMGO Institute for Health and Care Research, VU University Medical Center, w.mokkink@vumc.nl ▪ Caroline B Terwee, Associate professor in Clinimetrics, Department of Epidemiology and Biostatistics, EMGO Institute for Health and Care Research, VU University Medical Center, cb.terwee@vumc.nl ▪ Jordi Alonso, Head of the Health Services Research Group. Epidemiology and Public Health Program. Institut Municipal d'Investigació Mèdica (IMIM-Hospital del Mar), Barcelona, Spain, Jalonso@IMIM.ES ▪ Donald L Patrick, Professor of Health Services and Director of the Social and Behavioral Sciences Program at the University of Washington, Director of the Seattle Quality of Life Group, donald@uw.edu ▪ Lex M Bouter, Professor of Research Integrity and Methodology, Department of Epidemiology and Biostatistics, EMGO Institute for Health and Care Research, VU University Medical Center, lm.bouter@vumc.nl ▪ Henrica CW de Vet, Professor of Clinimetrics, Department of Epidemiology and Biostatistics, EMGO Institute for Health and Care Research, VU University Medical Center, hcw.devet@vumc.nl
Status	Academic, multidisciplinary team of epidemiologists, psychologists, physicians, statisticians, with expertise in the development and evaluation of health status measurement instruments.
Funding	The COSMIN Delphi study was financially supported by the EMGO Institute for Health and Care Research of the VU University Medical Centre, Amsterdam, and the Anna Foundation, Leiden, the Netherlands.
Deliverables	The COSMIN checklist was developed in an international Delphi study, which aims to: <ul style="list-style-type: none"> ▪ Reach consensus on which measurement properties should be evaluated of

	<p>Health-Related Patient-Reported Outcomes and how they should be defined;</p> <ul style="list-style-type: none"> Develop standards on how these measurement properties should be evaluated in terms of study design and statistical analysis. <p>The COSMIN group developed a checklist containing standards to evaluate the methodological quality of studies on the measurement properties of health measurement instruments. The checklist – when conducting a systematic review of measurement instruments, when designing your own study, to report your own study (as explained below), or when peer reviewing a manuscript on a study on measurement properties – was developed in an international Delphi study as a multidisciplinary, international collaboration with all relevant expertise involved. The focus was on Health-Related Patient-Reported Outcomes but the checklist is also useful to evaluate studies on other types of health measurement instruments, such as performance-based tests or clinical rating scales. Subsequently, a methodology for systematic reviews of PRO instruments was developed.</p> <p>The COSMIN checklist can also be applied to reporting a study on measurement properties. Researchers can use the COSMIN checklist to ensure they report information required to evaluate the quality of their study, and provide uniform reporting based on standardized terms and definitions. For instance, when a new instrument is developed, the content focus and detail must correspond to the target population.</p> <p>The COSMIN manual: http://www.cosmin.nl/images/upload/files/COSMIN%20checklist%20manual%20v9.pdf</p>
Scope of disease	General (neuropathic pain screening, intermittent claudication, shoulder kinematics, pain, type-2 diabetes, knee injury and osteoarthritis, autism spectrum disorder)
Relevance for rare diseases	None to date

EuroQol Research Foundation

Goal	Test the feasibility of jointly developing a standardized non disease specific instrument for describing and valuing health-related quality of life.
Website	http://www.euroqol.org/
Active years	Since 1987
Relevant contacts	<ul style="list-style-type: none"> Jan Busschbach, Erasmus MC, The Netherlands (j.vanbusschbach@erasmusmc.nl) Paul Krabbe, The University of Groningen/UMCG (p.f.m.krabbe@umcg.nl) Bernhard Slaap, Executive Director Bas Janssen, Senior Scientist
Status	Non-profit organization. Network of international, multidisciplinary researchers, originally from seven centers in England, Finland, the Netherlands, Norway and Sweden. Currently over 75 members worldwide.

Funding	Member in kind contributions. Membership of the EuroQol Group Association is reserved for those who actively support the work of the EuroQol Group and make a positive and sustained commitment to it (e.g., attendance and scientific contributions to the EuroQol Annual Plenary Meetings, participation in Working Groups).
Deliverables	<p>The process of shared development, local experimentation and lively discussion resulted in EQ-5D, a measure generating a single index value for health status with considerable potential for use in health care evaluation.</p> <p>EQ-5D was initially developed simultaneously in Dutch, English, Finnish, Norwegian and Swedish. It is now widely used in many countries around the world and has been translated into most major languages with the Foundation closely monitoring the process.</p> <p>EQ-5D is a standardized measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal.</p> <p>Applicable to a wide range of health conditions and treatments, EQ-5D provides a simple descriptive profile and a single index value for health status that can be used in clinical and economic evaluation of health care as well as in population health surveys.</p>
Scope of disease	General
Relevance for rare diseases	None to date

International Consortium for Health Outcomes Measurement (ICHOM)

Goals	<p>Bring together global working groups to develop standard sets of outcomes that aim to reflect what really matters most to patients. ICHOM standard sets are parsimonious, aiming to reflect what is essential to measure.</p> <p>Support organizations to systematically measure outcomes in routine clinical practice.</p> <p>Benchmark on value (outcomes relative to cost) globally and support learning from those highest value providers.</p>
Website	http://www.ichom.org/
Active years	Since 2006
Relevant contacts	<ul style="list-style-type: none"> ▪ Christina Rångemark Åkerman, MD, PhD, President of ICHOM ▪ Caleb Stowell, MD, VP of Research and Development (c.stowell@ichom.org) ▪ Thomas Kelley, Europe Director (t.kelley@ichom.org)
Status	Independent, non-profit organization. Co-founded by The Boston Consulting Group, Karolinska Institutet and the Harvard Institute for Strategy and Competitiveness
Funding	Sponsor donations (e.g. Movember Foundation, the Scottish Government, Alliance of Dedicated Cancer Centers, American Heart Association/American Stroke Association, Carl Bennet AB, Générale de Santé, The Children’s Hospital of Philadelphia, etc.)

	Cofounders also support ICHOM through secondment of staff and sponsorship.
Deliverables	<p>Standard Sets and accompanying Reference Guides freely available on ICHOM website.</p> <p>Implementation support – includes on-site support (ICHOM works with individual providers to support the routine measurement of outcomes) and implementation communities (groups of providers virtually supported by ICHOM to begin measurement).</p> <p>ICHOM develops case studies and video documentaries to showcase where (and therefore, how) outcomes are being routinely measured and to showcase the impact of value based healthcare.</p> <p>ICHOM is currently developing the methodology for the global benchmarking program, which it plans to launch in early 2016.</p>
Scope of disease	Cardiovascular, musculoskeletal, sense organ, malignant neoplasms, congenital anomalies, mental and behavioral disorders, nervous system
Relevance for rare diseases	Interest in producing sets of outcomes for conditions where there is a wide variation in outcome. ICHOM has produced a set of outcomes for cleft lip and palate and is currently working on one for craniofacial microsomia.

Patient-Centered Outcomes Research Institute (PCORI)

Goals	<p>PCORI supports research that develops and promotes the utility, performance and efficiency of large clinical data networks or registries supporting PRO research for patients with rare diseases.</p> <p>PCORI aims to promote studies that compare situations in which the effectiveness of strategies for prevention, treatment, screening, diagnosis or surveillance have not been adequately studied against alternative options, and where better evidence is needed to support decision making by patients, caregivers and healthcare professionals.</p>
Website	http://www.pcori.org/
Active years	Since 2012
Relevant contacts	<p><u>Advisory Panel on Rare Disease:</u></p> <ul style="list-style-type: none"> ▪ Marshall L. Summar, MD (Chair) ▪ Vincent Del Gaizo (Co-Chair) ▪ Sindy N. Escobar-Alvarez, PhD ▪ Kate Lorig, MS, MPH, DrPH ▪ Yaffa R. Rubinstein, MS, PhD ▪ Philip W. Ruff, PhD, BSc, CChem MRSC, CSci <p><u>Ex-Officio Member from PCORI's Methodology Committee:</u></p> <ul style="list-style-type: none"> ▪ Naomi Aronson, PhD
Status	Non-profit, non-governmental organization.

Funding	<p>PCORI is funded through the Patient-Centered Outcomes Research Trust Fund (PCORTF), which was authorized by the US Congress as part of the Patient Protection and Affordable Care Act of 2010 and receives income from two funding streams: the general fund of the Treasury and a small fee assessed on Medicare, private health insurance and self-insured plans. PCORI is expected to receive an estimated \$3.5 billion from the PCORTF to fund patient-centered outcomes research until September 30, 2019, the date through which the Act authorizes the fund to remain in operation.</p>
Deliverables	<p>In 2011, the PCORI Methodology Committee drafted an extensive, iterative and transparent process to define patient-centered outcomes research.</p> <p>In response to its legislative mandate, PCORI developed a strategic plan in 2013. The plan focuses on funding and conducting relevant research that is likely to change practice and improve patient outcomes; on disseminating and promoting the implementation of the results of research; and on influencing how clinical research is conducted by others, so that a greater proportion of all clinical research is useful to patients and other healthcare decision makers.</p> <p>The charter for the Advisory Panel on Rare Disease was approved by the PCORI Board of Governors on November 18, 2013. http://www.pcori.org/sites/default/files/PCORI-Advisory-Panel-Rare-Disease-Charter.pdf</p> <p>The Advisory Panel on Rare Disease (“RD Panel”) will advise and provide recommendations to PCORI’s Board of Governors, Methodology Committee and staff on the conduct of patient-centered comparative clinical effectiveness research in rare diseases and on coordination and engagement with the rare disease research community.</p> <p>The RD Panel will:</p> <ul style="list-style-type: none"> ▪ Provide input to PCORI on research needs of the rare diseases community and on specific issues and concerns in conducting research on rare diseases; ▪ Identify infrastructure (data sources, tools, etc.) that currently exist and can be a resource for conducting research; ▪ Serve on or assist in identifying experts to serve on ad hoc panels to help evaluate, design and conduct PCORI-funded research specific to a rare disease; ▪ Provide ongoing feedback and advice on evaluating and disseminating PCORI’s research portfolio on rare diseases; ▪ Consider study findings and advise on targets and strategies for PCORI dissemination efforts; ▪ Identify opportunities for collaboration with existing international, federal, public and private entities doing similar work in the rare disease space; ▪ Advise other PCORI committees and panels to ensure the unique considerations of rare disease are addressed. <p>The Advisory Panel on Rare Disease Winter 2015 Meeting was held on January 13, 2015. Teleconference Audio Recording available at http://www.pcori.org/events/2015/advisory-panel-rare-disease-winter-2015-meeting</p>
Scope of disease	<p>General</p>
Relevance for rare diseases	<p>Beginning</p>

University of Birmingham: ICECAP capability measures

Goals	Measures of wellbeing for use in economic evaluation. The measures are conceptually linked to Amartya Sen's capability approach which defines wellbeing in terms of an individual's ability to 'do' and 'be' the things that are important in life.
Website	http://www.birmingham.ac.uk/research/activity/mds/projects/HaPS/HE/ICECAP/index.aspx X
Active years	2007 to present
Relevant contacts	<ul style="list-style-type: none"> ▪ Joanna Coast, PhD, Health Economics Unit, School of Health & Population Sciences, University of Birmingham
Status	Academic
Funding	
Deliverables	<ul style="list-style-type: none"> ▪ ICECAP-A: a measure of capability for the adult population (under development) ▪ ICECAP-O: a measure of capability for older people ▪ CES: (Carer Experience Scale): a measure of care-related wellbeing ▪ ICECAP-SCM: a measure of capability for use in the end of life care (under development).
Scope of disease	General
Relevance for rare diseases	Measures for both the normal and aging population and measures for carers

Rare Disease-Relevant Initiatives

Brain-CODE - “Centre for Ontario Data Exploration”

Goals	<p>The Ontario Brain Institute (OBI) and its informatics partners are building a centralized neuroscience data platform called Brain-CODE to enable researchers to make a vast array of comparisons across a range of brain-related diseases.</p> <p>Brain-CODE is an extensible large-scale informatics platform that manages the acquisition, storage, processing, and analysis of multidimensional data collected from patients with a variety of brain disorders.</p> <p>Brain-CODE supports the collection, storage and integration of diverse types of data across several brain disorders in order to enable researchers to discover and explore new and complex relationships, leading to innovative new avenues of research and treatment.</p> <p>The key purpose of the platform is to provide neuroscience researchers with the ability to store their data securely, share their data with other researchers, access enhanced datasets, and analyze their data with an increasingly rich set of web-based tools.</p>
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	Its web portal provides public access to data standards, governance policies, and architecture specifications about Brain-CODE.
Website	http://www.braininstitute.ca/brain-code
Active years	Since April 2012
Relevant contacts	<ul style="list-style-type: none"> ▪ Donald Stuss, President & Scientific Director (dstuss@braininstitute.ca) ▪ John Clarkson, Senior Vice President (jclarkson@braininstitute.ca) ▪ David Bogart, Vice President, Research Programs & Informatics (dbogart@braininstitute.ca)
Status	The Ontario Brain Institute is a not-for-profit research institute
Funding	Provincially-funded. To create Brain-CODE, the OBI partnered with four not-for-profits including Indoc Research (formerly the Ontario Cancer Biomarker Network), the Rotman Research Institute at Baycrest hospital, the Electronic Health Information Laboratory (EHIL) at Children’s Hospital of Eastern Ontario, and the High Performance Computing Virtual Laboratory (HPCVL) at Queen’s University.
Deliverables	The OBI supports multi-disciplinary collaborative research networks across the province of Ontario focused on various brain conditions (“Integrated Discovery Programs” or “IDPs”). The 5 funded IDPs include the Province of Ontario Neurodevelopmental Disorders Network (POND), Childhood Hemiplegic Cerebral Palsy Integrated Neuroscience Discovery Network (CP-NET), New Approaches to Intractable Epilepsy (or EpLink), Canadian Biomarker Integration Network for Depression (CAN-BIND) and Ontario Neurodegenerative Disease Research Initiative (ONDRI).
Scope of disease	Brain disease
Relevance for rare diseases	Some

Core Outcome Measures in Effectiveness Trials (COMET)

Goals	<p>Bring together researchers focused on developing and applying validated and standardized sets of outcomes. These ‘core outcome sets’ represent the minimum criteria to be measured and reported in clinical trials and other forms of research on a specific condition.</p> <p>Collate relevant applied and methodological resources to facilitate exchange of ideas and information, and to foster methodological research in this area. This is being achieved through:</p> <ul style="list-style-type: none"> ▪ Development of a searchable database of completed and ongoing projects in core outcome sets; ▪ Development of a repository for project protocols and other documents (such as questionnaires), with the intention that this will be searchable; ▪ Maintenance of these resources in a publicly available searchable database; ▪ Preparing guidance on developing and reporting core outcome sets;
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	<ul style="list-style-type: none"> ▪ Preparing guidance on integrating PRO into core outcome sets; ▪ Guidance on obtaining funding to develop core outcome sets.
Website	http://www.comet-initiative.org/
Active years	Since 2010
Relevant contacts	<ul style="list-style-type: none"> ▪ Paula Williamson PhD, University of Liverpool ▪ Mike Clarke, Queen’s University Belfast ▪ Doug Altman, University of Oxford ▪ Jane Blazeby, University of Bristol ▪ Sean Tunis, Centre for Medical Technology and Policy, Baltimore
Status	Non-governmental Initiative.
Funding	Launched at a meeting in Liverpool (UK) in January 2010 and funded by the MRC North West Hub for Trials Methodology Research (NWHTMR) Network through a cross-Hub funding award, now MRC. The COMET Initiative also receives funding from the European Commission (FP7-HEALTH-2012-INNOVATION-1) and from the NHS National Institute for Health Research (NIHR).
Deliverables	<p>COMET launched a joint initiative with COSMIN to improve the selection of outcome measurement instruments and standards to assess methodological quality of studies.</p> <p>Development of a publically available internet-based resource to collate the knowledge base for core outcome set development.</p> <p>It will provide a resource for trial funders to refer to, for researchers to see what work has been done in their area of interest and for research funders who are looking to fund work in this area and wish to avoid unnecessary duplication. It will include planned and ongoing work as well as published accounts of core outcome set development.</p> <p>Development and application of an optimal, multi-faceted search strategy to identify work related to the development of core outcome sets.</p>
Scope of disease	General
Relevance for rare diseases	Some (Friedreich’s ataxia, Systemic lupus erythematosus, Sjogren's syndrome)

Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT)

Goals	Develop consensus reviews and recommendations to improve the design, analysis, execution and interpretation of clinical trials on treatments for pain.
Website	http://www.immpact.org/
Active years	Since 2002
Relevant contacts	<ul style="list-style-type: none"> ▪ Robert H. Dworkin, PhD (robert_dworkin@urmc.rochester.edu) ▪ Dennis C. Turk, PhD (turkdc@u.washington.edu)

Status	<p>Non-profit organization. Conducted under the auspices of the Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks (ACTTION) public-private partnership with the FDA.</p> <p>Invites participants from academia, regulatory agencies (FDA, EMA), NIH, US Veterans Administration, consumer support and advocacy groups and industry.</p> <p>See www.impact.org and www.action.org for regularly updated information.</p>
Funding	Funded by by ACTTION, which has received research contracts, grants, or other revenue from the FDA, multiple pharmaceutical and device companies, and other sources.
Deliverables	<ul style="list-style-type: none"> ▪ IMMPACT Consensus Recommendations ▪ IMMPACT Systematic Reviews ▪ IMMPACT Research Studies <p>Consensus meetings are planned and research initiatives involving the assessment of pain and the design and interpretation of clinical trials are ongoing.</p>
Scope of disease	Acute and chronic pain in adults and children, anesthesiology, clinical pharmacology, internal medicine, law, neurology, nursing, oncology, outcomes research, psychology, rheumatology and surgery.
Relevance for rare diseases	Some

International Society for Pharmacoeconomics and Outcomes Research (ISPOR)

Goals	<p>Promote outcomes research and facilitate the translation of this research into useful information for health care decision makers and researchers.¹</p> <p>Special Interest Groups</p> <p>1) The ISPOR Rare Disease Special Interest Group has four goals: (1) clarify definitions for the terminology used in rare disease research and assessment, (2) catalogue the challenges in assessing and appraising diagnostics and treatments for rare diseases, (3) focus on health technology assessment of these rare disease technologies and (4) focus on methodology, specifically measuring the use, costs and effectiveness of rare disease care.</p> <p>Working Groups:</p> <ul style="list-style-type: none"> ▪ Rare Disease Terminology & Definitions Used in Outcomes Research Working Group: compile definitions for rare disease terms used in outcomes research (regulatory, HTA, payer and rare disease organizations) from North America, Europe, Asia-Pacific, Central & South America and Africa ▪ Rare Disease: Challenges in Assessment and Appraisal of Diagnostics & Treatments Working Group ▪ HTA of Rare Disease Diagnostics and Treatments Working Group [in development] ▪ Methodology - Measuring Use, Costs and Effectiveness of Rare Disease Care Working Group [in development]
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	<p>2) The ISPOR Patient Centered Special Interest Group aims to determine how best to involve patients and their representatives, in all stages of the decision making, to improve health care delivery and outcomes.</p> <p>Working Group:</p> <ul style="list-style-type: none"> ▪ Patient Engagement in Research Working Group: To determine how best to involve patients and their representatives in the research process by identifying (a) stages at which patients should be involved; (b) level of their involvement in each stage; (c) challenges that will face the researchers; and (d) make recommendations. <p>Task Forces</p> <p>Patient- and observer-reported outcomes (PROs & ObsROs) measurement in rare disease clinical trials task force aims to develop emerging good research practice recommendations on measuring PROs and ObsROs in rare disease clinical trials.</p> <p>Patient Reported Outcomes (PRO) Content Validity Good Research Practices task force aims to address and develop methods to ensure and document the content validity of newly developed PRO instruments to support medical product indications and labeling claims.</p> <p>ePRO Systems Validation Good Research Practices task force aims to develop an outline to generate guidelines to inform system users of the quality and content required for validated data collection systems.</p>
<p>Website</p>	<ul style="list-style-type: none"> ▪ ISPOR Rare Disease Special Interest Group http://www.ispor.org/sigs/RareDiseases.asp ▪ ISPOR Patient Centered Special Interest Group http://www.ispor.org/sigs/PatientCentered.aspx ▪ Patient Reported Outcomes and Quality of Life Initiatives http://www.ispor.org/research_initiatives/qol_initiatives.asp ▪ Patient Engagement in Research Working Group http://www.ispor.org/sigs/PatientCentered/PC_EngagementInResearch.aspx
<p>Active years</p>	<p>Since 1995</p>
<p>Relevant contacts</p>	<p><u>Rare disease terminology & definitions used in outcomes research working group:</u></p> <ul style="list-style-type: none"> ▪ Dyfrig Hughes, PhD, MSc, Bangor University, Wales, UK ▪ Zeba M. Khan, RPh, PhD, Celgene Corporation, Summit, New Jersey, USA <p><u>Patient and observer-reported outcomes (PRO & ObsRO) measurement in rare disease clinical trials – Emerging good practices:</u></p> <ul style="list-style-type: none"> ▪ Katy Benjamin, PhD, SM, ICON Commercialisation and Outcomes, Bethesda, MD, USA ▪ Margaret K. Vernon, PhD, EU Director, Outcomes Research, Evidera, London, England, UK <p><u>Patient engagement in research working group:</u></p> <ul style="list-style-type: none"> ▪ François Houyez, Director Treatment Information & Access, Health Policy Advisor EURORDIS, Paris, France

	<ul style="list-style-type: none"> Todd Berner, MD, Executive Medical Director, Urology Astellas Scientific and Medical Affairs, Inc. Northbrook, IL, USA
Status	Non-profit, public organization for educational and scientific purposes.
Funding	Financial support for ISPOR's core operations are supplied by its members through membership dues. Meetings, Congresses, and Conferences are supported through registration fees and event and corporate sponsorship.
Deliverables	<ul style="list-style-type: none"> ISPOR Good Practices for Outcomes Research http://www.ispor.org/workpaper/practices_index.asp Contains all published ISPOR Good Practices for Outcomes Research Reports. Guidelines for Outcomes Research and use in Health Care Decision Making http://www.ispor.org/GuidelinesIndex/Default.aspx To improve state-of-the-art methods in outcomes research and gain acceptance of their use in research and decision-making. Outcomes Research Issues http://www.ispor.org/workpaper/OutcomesResearchMethods_index.asp ISPOR develops articles and books on outcomes research methods. Oncology Outcomes Research Resources (OORR) http://www.ispor.org/OncologyORResources/SearchOologyResources.aspx Provides relevant information and resources related to oncology outcomes research with three main areas of focus: oncology seminal articles and books; oncology databases and registries; oncology organisations. ISPOR Patient Reported Outcomes / Quality of Life Initiatives publications http://www.ispor.org/research_initiatives/qol_initiatives.asp Rare Disease Terminology & Definition: A Systematic Global Review http://www.ispor.org/sigs/RareDisease/RareDiseaseTerminology.asp "Rare Disease Terminology & Definition: A Systematic Global Review" submitted to <i>Value in Health</i> in December 2014. Patient- and observer-reported outcomes (PROs & ObsROs) measurement in rare disease clinical trials: emerging good practices http://www.ispor.org/taskforces/pros-and-obsros-raredisease-clinicaltrials.asp 19th Annual International Meeting, held in Montreal, AB, Canada, in June 2014. A manuscript was submitted to <i>Value in Health</i> in January 2015. Patient engagement in research working group http://www.ispor.org/sigs/PatientCentered/PC_EngagementInResearch.aspx Held its 17th Annual European Congress, Workshop Presentation, Amsterdam, The Netherlands, in November 2014 (http://www.ispor.org/sigs/PatientCentered/WorkshopPresentation-2014Amsterdam.pdf)
Scope of disease	General (Oncology)
Relevance for rare diseases	Some

Neuro-QoL^{2,3,4}

<p>Goals</p>	<p>Neuro-QoL is a bilingual (English/Spanish), clinically relevant and psychometrically robust set of self-report measures assessing the health-related quality of life (HRQOL) of adults and children with neurological disorders.</p> <p>Specific goals of the initiative include:</p> <ul style="list-style-type: none"> ▪ Development of a core set of questions that address dimensions of HRQL universal to patients with chronic neurological diseases ▪ Development of supplemental questions that address HRQL concerns specific to particular groups of patients based on disease status and other characteristics such as age and ethnicity ▪ Creation of publicly available, adaptable and sustainable system allowing clinical researchers access to a common item repository and computerized adaptive testing (CAT). <p>Neuro-QoL measures were developed through a collaborative, multisite NINDS-sponsored research initiative (Contract HHSN 2652004236-01C) to construct a psychometrically-sound, and clinically-relevant, health-related quality of life measurement tools for individuals with neurological conditions such as stroke, multiple sclerosis, amyotrophic lateral sclerosis, Parkinson’s disease, epilepsy and muscular dystrophy.</p> <p>Neuro-QoL is comprised of item banks and scales that evaluate symptoms, concerns, and issues that are relevant across disorders - along with measures that assess areas most relevant for specific patient populations.</p> <p>The Neuro-QoL measures enable within-disease as well as cross-disease comparisons and are intended for use in both neurology clinical trials and clinical practice.</p> <p>Intended uses of Neuro-QoL measures:</p> <ul style="list-style-type: none"> ▪ Clinical trials: primary, secondary, or exploratory endpoints ▪ Observational research: predictors, mediators, moderators, or outcome variables ▪ Comparative Effectiveness Research: indicators of the effectiveness of an intervention ▪ Population surveys: measures of disease burden or the health of populations
<p>Website</p>	<p>www.neuroqol.org/</p>
<p>Active years</p>	<p>Beginning in 2005, 6-year, multi-site project.</p> <p>There are several government funded extensions of the Neuro-QOL measurement tool, in the areas of spinal cord injury, traumatic brain injury, and Huntington’s disease.</p> <p>NINDS and National Institute on Disability and Rehabilitation Research NIDRR-funded studies are currently underway to expand Neuro-QOL into spinal cord injury.</p>
<p>Relevant contacts</p>	<ul style="list-style-type: none"> ▪ David Cella, PhD; Principal Investigator; Professor and Chair; Department of Medical Social Sciences, Northwestern University; Feinberg School of Medicine;

	<p>d-cella@northwestern.edu</p> <ul style="list-style-type: none"> ▪ Claudia Moy, PhD; NINDS/NIH; moyc@ninds.nih.gov
Status	National Institute of Neurological Disorders and Stroke (NINDS)-funded initiative
Funding	NINDS
Deliverables⁵	<p>Item Banks Developed:</p> <ul style="list-style-type: none"> ▪ Physical Health (e.g. mobility, fine motor/ADL, fatigue, sleep disturbance) ▪ Social Health (ability to participate in social roles and activities, satisfaction with social roles and activities) ▪ Emotional Health (e.g. depression, anxiety, stigma, positive affect and well-being, emotional-behavioral dyscontrol) ▪ Cognitive Health (e.g. general concerns and executive function) <p>Assessment Center:</p> <p>A free, online research management tool to enable researchers to create study-specific websites to capture participant data securely. Studies can include measures within the Assessment Center library as well as custom instruments created or entered by the researcher.</p> <p>Assessment Center enables customization of items or instruments (e.g., format, randomization, skip patterns), real-time scoring of CAT, storage of protected health information in a separate, secure database, automated accrual reports, real-time data export, graphing of individual CAT or Profile scores, and ability to capture endorsement of online consent forms among other features.</p> <p>Reports and Manuals:</p> <p><u>1. Neuro-QOL User Manual</u></p> <p>User Manual for the Quality of Life in Neurological Disorders (Neuro-QOL) Measures, Version 2.0, March 2015. The User Manual provides a thorough explanation of the Neuro-QOL development, measures, domain definitions, terms of use, instrument properties, scoring instructions and tables, additional statistics. This document serves as the Neuro-QOL scoring manual.</p> <p><u>2. Neuro-QOL Technical Report</u></p> <p>Neuro-QOL Technical Report: Item Bank Development and Item Response Theory Statistics. Submitted to the National Institute of Neurological Disorders and Stroke (NINDS) on behalf of the Neuro-QOL investigators, March 2015. This report provides an overview of the Neuro-QOL study, background on the development of item banks, sampling and pilot testing, item and instrument statistics, field testing & clinical validation, disease specific measures and results, general conclusions</p> <p><u>3. Neuro-QOL Final Report</u></p> <p>Measuring Quality of Life in Neurological Disorders - Final Report of the Neuro-QOL Study. This final project report was submitted to the National Institute of Neurological Disorders and Stroke (NINDS) on behalf of the Neuro-QOL investigators, September 2010</p> <p><u>4. Neuro-QOL Progress Report 2004-2007</u></p> <p>Interim report of the Neuro-QOL project to NINDS</p>

Scope of disease	Neurological disorders: stroke, multiple sclerosis, amyotrophic lateral sclerosis, Parkinson's disease, epilepsy and muscular dystrophy.
Relevance for rare diseases	Some: amyotrophic lateral sclerosis, muscular dystrophy. Also relevant for any rare disease that can follow a practice of supplementing content with disease-specific questions as needed.

Outcome Measures in Rheumatology Clinical Trials (OMERACT)

Goals	<p>OMERACT is an independent initiative of international health professionals, patients, biomedical researchers, biomedical industry representatives, and others interested in development and validation of data-driven outcome measures in rheumatology. OMERACT develops core sets of outcome measures for rheumatological conditions.</p> <p>The goals of this initiative are:</p> <ul style="list-style-type: none"> ▪ Improve endpoint outcome measurements in rare diseases through a data-driven, iterative, consensus process involving relevant stakeholder groups. ▪ Identify and improve relevant health outcome domains in rare diseases, endorsing valid, responsive, feasible health outcome measures in patients with rheumatologic conditions.
Website	http://www.omeract.org/
Active years	Since 1992
Relevant contacts	<ul style="list-style-type: none"> ▪ Behçet's Syndrome: Peter Merkel ▪ Fibromyalgia: Leslie Crofford ▪ Myositis: Lisa Christopher-Stine ▪ Systemic Lupus Erythematosus: Vibeke Strand ▪ Vasculitis: Peter Merkel
Status	Independent
Funding	Industry sponsors
Deliverables	<p>The OMERACT Filter was published in 1998, summarizing key instrument properties, namely validity, reliability, responsiveness and usability. OMERACT began involving patients in 2002 to identify criteria and ensure they are appropriately addressed.</p> <p>One example of OMERACT's work on rare diseases is the OMERACT Vasculitis Working Group, formed in 2004 to develop validated and accepted outcomes in vasculitis using data-driven analyses. This work led to OMERACT's endorsement of the core set of domains and associated outcome measures for antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV), a group of rare diseases characterised by inflammatory cell infiltration and necrosis of blood vessel walls. Randomised controlled trials for vasculitis have improved through the application of validated outcome measures. Trials are able to now provide reliable and valid outcome measures for these multi-systemic and relapsing rare diseases. Further steps to improve outcome tools in AAV include better defining response criteria through the development of weighting measures for activity and damage assessment. The Working Group has also been</p>

	<p>studying how the WHO's International Classification of Function can inform methods of disease assessment and plans for new outcomes.</p> <p>The Working Group's success in AAV has led to the development of outcomes for large vessel vasculitides (Takayasu arteritis and giant cell arteritis) and Behçet syndrome.</p> <p>Agreement regarding the use of standardized endpoints in randomized controlled trials and longitudinal observational studies is extremely important. Their use facilitates comparisons of outcomes across studies to provide the best estimates of benefit and safety of therapeutic interventions across differing patient populations.</p> <p>Consensus conferences take place every two years, in North America, Europe and Asia-Pacific.</p> <p>The OMERACT handbook was published in July 2014 (Boers M, Kirwan JR, Tugwell P <i>et al.</i>) http://www.omeract.org/pdf/OMERACT_Handbook.pdf</p>
Scope of disease	Rheumatoid arthritis, osteoarthritis, psoriatic arthritis, fibromyalgia and other rheumatic diseases.
Relevance for rare diseases	Some (AAV, Large vessel vasculitides, Behçet syndrome, Systemic Lupus Erythematosus, Myositis)

Patient-Reported Outcome (PRO) Consortium

Goals	<p>Collaboration among the US Food and Drug Administration's Center for Drug Evaluation and Research, the Critical Path Institute (C-Path), the pharmaceutical/biotechnology industry and other stakeholders.</p> <p>The purpose of the consortium is to qualify PRO instruments through the Center for Drug Evaluation and Research's drug development tool qualification process for use as clinical trial endpoints to support drug approval and product labeling claims.</p> <p>C-Path's role is to serve as a recognized and respected neutral third party that provides overall administrative support and oversight. C-Path provides an Executive Director responsible for the overall management of the Consortium and establishment of a process to identify, prioritize and develop potential PRO instruments. The Executive Director and staff coordinate all projects and provide financial oversight and project implementation management.</p>
Website	http://c-path.org/programs/pro/
Active years	Since 2008
Relevant contacts	<p><u>PRO Consortium Team:</u></p> <ul style="list-style-type: none"> ▪ Stephen Joel Coons, PhD, Executive Director ▪ Theresa Swentesky, Project Coordinator ▪ Theresa Griffey, Senior Project Manager ▪ Sarah Mann, Senior Project Manager ▪ Christian Noll, Senior Project Manager ▪ Margo Panke, Senior Project Manager <p><u>Industry Co-Director:</u></p>

	<ul style="list-style-type: none"> ▪ Katarina Halling, Group Director, PRO Center of Excellence, AstraZeneca
Status	Independent, non-profit organization, public-private partnership with the FDA. The PRO Consortium’s membership includes pharmaceutical companies; representatives from the FDA, EMA and NIH provide advice to the Coordinating Committee.
Funding	FDA, State of Arizona, Science Foundation Arizona, The University of Arizona
Deliverables	<p>Develops qualified and publicly available PRO instruments for use in clinical trials in order to support labeling claims.</p> <p>Working with other Consortium participants, C-Path will develop and publish scientific articles and support educational activities with data, expertise and other outcomes from the projects supported under the Consortium.</p> <p><u>Best Practice Documents:</u></p> <ul style="list-style-type: none"> ▪ Considerations For Requiring Subjects To Provide A Response To Electronic Patient-Reported Outcome Instruments ▪ Best Practices for Maximizing Electronic Data Capture Options during the Development of New Patient-Reported Outcome Instruments ▪ Best Practices for Migrating Existing Patient-Reported Outcome Instruments to a New Data Collection Mode ▪ Best Practices for Maximizing Electronic Data Capture Options during the Development of New Patient-Reported Outcome Instruments
Scope of disease	Alzheimer’s disease, multiple sclerosis, asthma, irritable bowel syndrome, depression, functional dyspepsia, lung cancer, rheumatoid arthritis.
Relevance for rare diseases	Some

Patient Reported Outcomes Measurement Information System (PROMIS)^{6,7,8}

Goals	<p>Cooperative group of research sites and centers that employ mixed-methods development processes (including qualitative and quantitative methods) to create domain-specific measures of physical, mental and social health for use across diseases.</p> <p>Provide clinicians and researchers access to efficient, precise, valid and responsive adult- and child-reported measures of health and wellbeing. PROMIS measures can be used as primary or secondary endpoints in clinical studies of treatment effectiveness.</p> <p>The data collected in PROMIS provide clinicians and researchers with patient-reported information about the effect of therapy that cannot be found in traditional clinical measures. When used with traditional clinical measures of health, PROMIS tools allow clinicians to better understand how various treatments might affect what patients are able to do and the symptoms they experience.</p> <p>PROMIS aims to provide:</p> <ul style="list-style-type: none"> ▪ Comparability: standardized measures for common domains and metrics across conditions; ▪ Reliability and Validity: metrics for each domain reviewed and tested;
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	<ul style="list-style-type: none"> ▪ Flexibility: administered in a variety of ways and forms; ▪ Inclusiveness: all individuals, regardless of literacy, language, physical function or life course. <p>In 2010, a second round of PROMIS funding was provided by the NIH expanding the network to 13 researchers at 12 research sites. Expanded aims in the current round of funding include:</p> <ul style="list-style-type: none"> ▪ Develop additional item banks in new content areas (e.g., self-efficacy in management of chronic disease); ▪ Conduct additional longitudinal validation studies to test PROMIS reliability and validity in new populations and treatments; ▪ Expand the public-private partnership to sustain the instrument repository, ensure scientific excellence, improve future data collection activities, add new domains and items to the system, test and adapt the system for new populations, maintain the system with free access to publically available data, and extend the application of the system for clinical research and practice; ▪ Build collaborations; ▪ Develop additional translations for existing and newly produced item banks.
Website	http://www.nihpromis.org
Active years	Since 2004
Relevant contacts	<ul style="list-style-type: none"> ▪ Karon F. Cook; President ▪ David Cella, PhD; Secretary and Treasurer, Principal Investigator, PROMIS Statistical Center, Northwestern University ▪ Kathy Lohr; Vice President ▪ Kevin Weinfurt, PhD, Principal Investigator, PROMIS Research Site, Duke University Medical Center ▪ Helena Correia (helena-correia@northwestern.edu), Translation Manager at the PROMIS Statistical Center ▪ Dennis Revicki, board member
Status	Public organization
Funding	<p>The U.S. National Institutes of Health is providing financial support for Assessment Center until 2019 to maintain and distribute PROMIS instruments and scientific methods.</p> <p>After that date, these functions will be overseen and funded through a sustainable business model managed at Northwestern University (Cella, PI), in collaboration with a newly formed entity called the PROMIS Health Organization, a non-profit organization developed by PROMIS investigators.</p>
Deliverables	<p>PROMIS measures can be used as primary or secondary endpoints in clinical studies of the effectiveness of treatment. Tools can be used across a wide variety of chronic diseases and conditions and in the general population. Several hundred researchers and an increasing number of clinicians have integrated PROMIS tools into their study protocols.</p> <p><u>Results of PROMIS:</u></p>

	<ul style="list-style-type: none"> ▪ Framework and candidate items for an initial set of adult and pediatric items; ▪ Administration of candidate items to large patient samples suffering from chronic diseases; ▪ Analysis of data to calibrate the items to build the PROMIS v1.0 item banks; ▪ Validation studies of the PROMIS v1.0 measures and launch of a study on mode of administration; ▪ Development of web-based resources for clinical research; ▪ Feasibility studies to evaluate the utility of PROMIS and promote widespread use of the instrument for clinical research and clinical care; ▪ Link with external scientists to share PROMIS methodology, instruments and software. <p><u>Published research:</u></p> <p>PROS (Patient Reported Outcomes) for Children and Young Adults with Disabilities: to examine the responsiveness of the current PROMIS item banks for children and young adults with cerebral palsy who receive major musculoskeletal surgeries. Develop a scoring link between current PROMIS pediatric and adult item banks so that the PROMIS measures can be used longitudinally during this child-adult transition using a similar metric.</p>
Scope of disease	Physical health, anxiety, depression, fatigue, sleep disturbance, social function, pain interference and global health.
Relevance for rare diseases	Multiple: many of the PROMIS item banks can be used to capture important content that is relevant to a given rare disease. PROMIS also provides a model for creating disease-specific analogues for relevant content not covered by a PROMIS item bank.

BURQOL-RD Meter: A tool for the assessment of social economic burden and health-related quality of life in patients with rare diseases in Europe and their careers^{9,10}

Goals	BURQOL-RD is aimed a disease based model instrument (BURQOL-RDmeter) to assess the impact of new health policies, interventions and treatments in the field of rare diseases (RDs) by means of quantifying the Economic Burden and Health-Related Quality of Life (HRQOL) for patients and their caregivers, from a macro societal perspective.
Website	http://www.burqol-rd.com/ .
Active years	2011 to present
Relevant contacts	BURQOL-RD-meter Guidance tool team leaders <ul style="list-style-type: none"> ▪ Pedro Serrano, Canary Islands Health service, Spain Renata Linertová, Canary Islands Health service, Spain
Status	Government Public health Services
Funding	<ul style="list-style-type: none"> ▪ European Commission DG-SANTÉ and the Spanish government
Deliverables	Accessible at <ul style="list-style-type: none"> ▪ http://ec.europa.eu/chafea/projects/database.html?prjno=20091204

Scope of disease	Built as a tool for Rare diseases (BURQOL-RD-meter)
Relevance for rare diseases	Relevant and applicable to all RD clinical trials as well as phase IV studies and cost-effectiveness analysis

PRO Reporting Standards in Clinical Trials

Consolidated Standards of Reporting Trials (CONSORT)

Goals	<p>Improve the reporting of randomized controlled trials. The CONSORT group has been building a library of examples that help to explain how to implement the CONSORT standard in clinical trials reporting.</p> <p>CONSORT have collected examples of reporting for all of the CONSORT 2010 checklist items, and for many of the CONSORT extensions. However, they are always looking for examples of good reporting.</p> <p>Investigators can get involved in the effort to improve the quality of trial reporting by submitting examples of good reporting for inclusion in the CONSORT Library of Examples: http://www.biomedcentral.com/content/pdf/1745-6215-12-98.pdf</p>
Website	http://www.consort-statement.org/
Active years	Since 1993
Relevant contacts	<ul style="list-style-type: none"> ▪ Doug Altman, Centre for Statistics in Medicine, Botnar Research Centre, Oxford, UK, doug.altman@csm.ox.ac.uk, www.csm-oxford.org.uk ▪ David Moher, Ottawa Hospital Research Institute, Canada, dmoher@ohri.ca, www.ohri.ca ▪ Kenneth F. Schulz, Quantitative Sciences, Durham, USA, kschulz@fhi360.org, www.fhi.org ▪ Sally Hopewell, Centre for Statistics in Medicine, Oxford, UK, sally.hopewell@csm.ox.ac.uk ▪ Larissa Shamseer, Clinical Epidemiology Program, Ottawa Methods Centre, Ottawa Hospital Research Institute, lshamseer@ohri.ca
Status	Public non-profit organization
Funding	<p>In-kind contributions of experts around the world who constitute the CONSORT Group.</p> <p>Limited funding to support part-time administrative, coordination and research work, including two part-time CONSORT staff:</p> <ul style="list-style-type: none"> ▪ Medical Research Council (2012 – 2015) ▪ US National Library of Medicine (1999 to 2004) <p>Financial support of the following CONSORT activities:</p> <ul style="list-style-type: none"> ▪ <u>CONSORT Group Meeting 2011</u>: President’s Fund - Canadian Institutes of Health Research; Johnson & Johnson; Pfizer USA; AstraZeneca; GlaxoSmithKline ▪ <u>CONSORT Group Meeting 2007</u>: UK National Coordinating Centre for Research

	<p>Methodology; American Society of Clinical Oncology; Canadian Institutes of Health Research; Johnson & Johnson; BMJ; UK Cochrane Centre; Nordic Cochrane Centre; The Lancet; PLoS Medicine;</p> <ul style="list-style-type: none"> ▪ <u>CONSORT Group Meetings 1999 and 2000</u>: Abbott Laboratories; American College of Physicians/American Society of Internal Medicine; GlaxoWellcome, Inc. (now part of SmithKline Beecham, Inc.); The Lancet; Merck & Co., Inc.; Canadian Institutes of Health Research; National Library of Medicine; TAP Pharmaceutical Products, Inc.; BMJ; Council of Science Editors; International Committee of Medical Journal Editors (Vancouver Group)
Deliverables	<p>Development of the CONSORT PRO extension (CONSORT 2010 table) based on the methodological framework for guideline development proposed by the Enhancing the Quality and Transparency of Health Research (EQUATOR) Network.</p> <p>The CONSORT PRO extension provides guidance for authors of trials describing patient-reported outcomes. Specifically, it extends five items of the CONSORT 2010 checklist to facilitate optimal reporting of RCTs in which PRO's are primary or secondary end points.</p> <ul style="list-style-type: none"> ▪ Checklist: http://www.consort-statement.org/Media/Default/Downloads/Extensions/CONSORT%20Extension%20for%20Patient%20Reported%20Outcomes.pdf ▪ Explanation & Elaboration http://jama.jamanetwork.com/article.aspx?articleid=1656259 <p>Five CONSORT PRO checklist items recommended for randomized controlled trials in which PROs are primary or important secondary endpoints.</p>
Scope of disease	General
Relevance for rare diseases	Some

International Society Quality Of Life Research (ISOQOL) Reporting Guidelines Task Force/ CONSORT-PRO Executive^{11,12,13,14,15}

Goals	To develop guidance for, and to promote, the transparent reporting of PROs in clinical trials. Through transparent reporting of PRO data we aim to reduce research waste and help ensure that robust PRO data inform patient care, shared-decision making and health-policy.
Website	http://www.isoqol.org/
Active years	2010 to present
Relevant contacts	<p>CONSORT-PRO Guidance Implementation Tools Team Leaders</p> <ul style="list-style-type: none"> ▪ Michael Brundage, MD, Queens University, Canada ▪ Melanie Calvert, PhD, University of Birmingham, United Kingdom
Status	Non-profit organization

Funding	MRC Hub for Trials Methodology Research (Calvert PI)/CIHR (Brundage PI)
Deliverables	The CONSORT-PRO extension has been cited >170 times to date across a range of clinical areas (e.g. cancer/ musculoskeletal/ surgical/ diabetes/ fibromyalgia). The extension has been disseminated across the clinical trials network and has informed the European Society of Cardiology position paper calling for the comprehensive use of PROs in cardiovascular trials and an EMA reflection paper on the use of PROs in Oncology Trials.
Scope of disease	Relevant to all clinical trials including PROs.
Relevance for rare diseases	Relevant to all rare disease trials including PROs.

ISOQOL Best Practices for PROs in Randomized Clinical Trials Task Force

Goals	<p>ISOQOL, in collaboration with the Centre for PROs Research, University of Birmingham and the Psycho-oncology co-operative research group, University of Sydney, are leading the development of best practice guidance for the inclusion of patient-reported outcomes (PROs) in randomized clinical trial (RCTs).</p> <p>Objectives:</p> <ul style="list-style-type: none"> ▪ Develop and evaluate a user-friendly PRO protocol checklist recommending evidence-based items for inclusion in RCT protocols (a SPIRIT-PRO extension) ▪ Develop and evaluate best practice guidance for writing standard operating procedures and other trial manuals that include instructions for collecting RCT PRO data in the field, which address logistical, data quality, and ethical considerations ▪ Develop and evaluate teaching modules that address current knowledge and best practices for designing PRO components of clinical trials ▪ Promote the use of these teaching modules in various contexts (cooperative groups, post-graduate teaching curricula, etc) ▪ Acquire external funding in support of this task force work
Website	http://www.isoqol.org/about-isoqol/committees/best-practices-for-pros-in-randomized-clinical-trials
Active years	2013 to present
Relevant contacts	<p>Protocol Checklist Development Team Leaders</p> <ul style="list-style-type: none"> ▪ Melanie Calvert, PhD, University of Birmingham, UK ▪ Madeleine King, PhD, Psycho-oncology Cooperative Research Group (PoCoG), University of Sydney, Australia
Status	Non-profit organization
Funding	NIHR SPCT (Calvert PI)

Deliverables	<p>Completed</p> <ul style="list-style-type: none"> ▪ PRO assessment in clinical trials: a systematic review of guidance for trial protocol writers¹⁶ ▪ Systematic evaluation of the PRO content of clinical trial protocols¹⁷ ▪ Putting patients at the heart of health-care research¹⁸ ▪ PRO alerts: ethical and logistical considerations in clinical trials¹⁹ <p>Ongoing</p> <ul style="list-style-type: none"> ▪ SPIRIT-PRO Extension
Scope of disease	All clinical areas including rare disease
Relevance for rare diseases	Relevant for all rare disease trials assessing PROs.

University of Birmingham: Centre for PROs Research

Goals	To develop a pathway for the optimal selection of PROs for inclusion within the Centre for Rare Disease in the Birmingham Institute of Translational Medicine clinical information platform.
Website	http://www.birmingham.ac.uk/research/activity/mds/domains/health-pop/healthcare-evaluation-and-methodology/patient-reported-outcomes/index.aspx
Active years	2015 to present
Relevant contacts	<ul style="list-style-type: none"> ▪ Melanie Calvert, PhD, Centre for PROs Research, University of Birmingham, UK ▪ Derek Kyte, PhD, Centre for PROs Research, University of Birmingham, UK
Status	Academic
Funding	Metchley Park Medical Charity (Calvert PI)
Deliverables	<ul style="list-style-type: none"> ▪ Framework for the selection of PROs within rare disease for incorporation within the clinical information platform ▪ Peer reviewed publication outlining the development of the framework and future priority areas for research
Scope of disease	Rare disease
Relevance for rare diseases	Highly relevant

Annex 2: Products on the Market in Europe and in the USA

The number of products with marketing authorizations and the number of diseases for which these products have an indication are shown below. [Note: diseases defined as rare in Europe may not be the case in the USA, and vice versa.]

	Marketing authorizations	Diseases covered
Europe (data from Orphanet)	191	199
USA (data from the FDA)	503	326

Diseases covered in both Europe and the USA

The 75 diseases covered by products with marketing authorizations in both Europe and the USA are listed below.

- Acromegaly
- Acute lymphoblastic leukemia
- Acute myeloid leukemia
- Acute promyelocytic leukemia
- Adenocarcinoma of ovary
- Amyotrophic lateral sclerosis
- Anaplastic large cell lymphoma
- Anthracycline extravasations
- Apnea of prematurity
- Atypical hemolytic-uremic syndrome
- B-cell chronic lymphocytic leukemia
- Carbamoyl-phosphate synthase deficiency
- Chronic inflammatory demyelinating polyneuropathy
- Chronic myeloid leukemia
- Chronic thromboembolic pulmonary hypertension
- Citrullinemia
- Coccidioidomycosis
- Congenital factor VII deficiency
- Congenital factor XIII deficiency
- Cryopyrin-associated periodic syndrome
- Cushing disease
- Cushing syndrome
- Cystic fibrosis
- Cystinosis
- Dermatofibrosarcoma protuberans
- Essential thrombocythemia
- Fabry disease
- Follicular lymphoma
- Gaucher disease type 1
- Gaucher disease type 3
- Giant cell tumor of bone
- Glanzmann thrombasthenia
- Hairy cell leukemia
- Hereditary angioedema type 1
- Hereditary angioedema type 2
- Hereditary thrombophilia due to congenital antithrombin deficiency
- Hodgkin lymphoma
- Homozygous familial hypercholesterolemia
- Idiopathic pulmonary fibrosis
- Immune thrombocytopenic purpura
- Japanese encephalitis
- Juvenile idiopathic arthritis
- Lennox-Gastaut syndrome
- Malaria
- Mantle cell lymphoma
- Medullary thyroid carcinoma
- Melanoma of soft parts

- Microscopic polyangiitis
- Mucopolysaccharidosis type 1
- Mucopolysaccharidosis type 6
- Multifocal motor neuropathy
- Multiple myeloma
- Myelodysplastic syndrome
- Narcolepsy-cataplexy
- Ornithine transcarbamylase deficiency
- Osteosarcoma
- Pancreatic endocrine tumor
- Paroxysmal nocturnal hemoglobinuria
- Patent arterial duct
- Polycythemia vera
- Prader-Willi syndrome
- Primary peritoneal carcinoma
- Pulmonary arterial hypertension
- Renal cell carcinoma
- Severe hemophilia A
- Severe hemophilia B
- Sickle cell anemia
- Soft tissue sarcoma
- Squamous cell carcinoma of head and neck
- Tuberculosis
- Tuberos sclerosis
- Turner syndrome
- Tyrosinemia type 1
- Von Willebrand disease
- Wilson disease

Diseases covered in Europe

The 199 diseases covered by products with marketing authorizations in Europe are listed below.

- Acquired hemophilia
- Acromegaly
- Acute lymphoblastic leukemia
- Acute myeloid leukemia
- Acute myeloid leukemia with multilineage dysplasia
- Acute promyelocytic leukemia
- Adenocarcinoma of esophagus
- Adenocarcinoma of ovary
- Adenocarcinoma of cervix uteri
- Adolescent-onset epilepsy syndrome
- Adrenocortical carcinoma
- Adult hepatocellular carcinoma
- Adult idiopathic neutropenia
- Aggressive B-cell non-Hodgkin lymphoma
- Alagille syndrome
- Alveolar rhabdomyosarcoma
- Alveolar soft-tissue sarcoma
- Amyotrophic lateral sclerosis
- Anaplastic astrocytoma
- Anaplastic large cell lymphoma
- Angiosarcoma
- Anthracycline extravasations
- Apnea of prematurity
- Aspergillosis
- Atypical hemolytic-uremic syndrome
- Autosomal dominant polycystic kidney disease
- B-cell chronic lymphocytic leukemia
- Benign partial infantile seizures
- Beta-thalassemia major
- Carbamoyl-phosphate synthase deficiency
- Carcinoid tumor and carcinoid syndrome
- Cerebrotendinous xanthomatosis
- Childhood-onset epilepsy syndrome
- Cholera
- Chromomycosis
- Chronic eosinophilic leukemia
- Chronic inflammatory demyelinating polyneuropathy
- Chronic myeloid leukemia
- Chronic myelomonocytic leukemia
- Chronic pain requiring intraspinal analgesia
- Chronic thromboembolic pulmonary hypertension
- Citrullinemia
- Classic homocystinuria
- Coccidioidomycosis
- Congenital bile acid synthesis defect type 1
- Congenital bile acid synthesis defect type 2
- Congenital bile acid synthesis defect type 3
- Congenital bile acid synthesis defect type 4
- Congenital erythropoietic porphyria

- Congenital factor VII deficiency
- Congenital factor XIII deficiency
- Cryopyrin-associated periodic syndrome
- Cushing disease
- Cushing syndrome
- Cyclic neutropenia
- Cystic fibrosis
- Cystinosis
- Dermatofibrosarcoma protuberans
- Desmoplastic small round cell tumor
- Differentiated thyroid carcinoma
- Diffuse large B-cell lymphoma
- Dihydropteridine reductase deficiency
- Dravet syndrome
- Duchenne muscular dystrophy
- Enthesitis-related arthritis
- Erythropoietic protoporphyria
- Essential thrombocythemia
- Evans syndrome
- Fabry disease
- Familial amyloid polyneuropathy
- Familial capillary hemangioma
- Familial intrahepatic cholestasis
- Familial lipoprotein lipase deficiency
- Familial medullary thyroid carcinoma
- Familial ovarian cancer
- Familial pancreatic carcinoma
- Familial partial epilepsy
- Fibrosarcoma
- Follicular lymphoma
- Fusariosis
- Gastrointestinal stromal tumor
- Gaucher disease type 1
- Gaucher disease type 3
- Giant cell tumor of bone
- Glanzmann thrombasthenia
- Glioblastoma
- Glycogen storage disease due to acid maltase deficiency
- Gorlin syndrome
- Granulomatosis with polyangiitis
- Growth delay due to insulin-like growth factor type 1 deficiency
- Guillain-Barré syndrome
- Hairy cell leukemia
- Hematopoietic stem cell transplantation
- Hepatic veno-occlusive disease
- Hepatitis B reinfection following liver transplantation
- Hereditary angioedema type 1
- Hereditary angioedema type 2
- Hereditary diffuse gastric cancer
- Hereditary thrombophilia due to congenital antithrombin deficiency
- Hereditary thrombophilia due to congenital protein C deficiency
- Hodgkin lymphoma
- Homocystinuria due to methylene tetrahydrofolate reductase deficiency
- Homocystinuria without methylmalonic aciduria
- Homozygous familial hypercholesterolemia
- Hyperammonemia due to N-acetylglutamate synthetase deficiency
- Hypereosinophilic syndrome of undetermined significance
- Idiopathic and/or familial pulmonary arterial hypertension
- Idiopathic pulmonary fibrosis
- Immune thrombocytopenic purpura
- Immunodeficiency predominantly affecting antibody production
- Inappropriate antidiuretic hormone secretion syndrome
- Infantile epilepsy syndrome
- Isolated congenital hypogonadotropic hypogonadism
- Isovaleric acidemia
- Japanese encephalitis
- Juvenile idiopathic arthritis
- Juvenile rheumatoid factor-negative polyarthritis
- Juvenile rheumatoid factor-positive polyarthritis
- Kaposi sarcoma
- Kawasaki disease
- Lambert-Eaton myasthenic syndrome
- Leiomyosarcoma
- Lennox-Gastaut syndrome
- Limbal stem cell deficiency
- Lymphoma
- Lymphomatous meningitis
- Malaria
- Malignant tumor of fallopian tubes
- Mantle cell lymphoma

- Medullary thyroid carcinoma
- Melanoma of soft parts
- Mesothelioma
- Methylmalonic acidemia with homocystinuria
- Methylmalonic acidemia without homocystinuria
- Microscopic polyangiitis
- Moderately severe hemophilia A
- Moderately severe hemophilia B
- Mucopolysaccharidosis type 1
- Mucopolysaccharidosis type 2
- Mucopolysaccharidosis type 4A
- Mucopolysaccharidosis type 6
- Multicentric Castleman disease
- Multifocal motor neuropathy
- Multiple myeloma
- Mycetoma
- Myelodysplastic syndrome
- Myelodysplastic syndrome associated with isolated del(5q) chromosome abnormality
- Myelodysplastic/myeloproliferative disease
- Myelofibrosis with myeloid metaplasia
- Myxofibrosarcoma
- Narcolepsy-cataplexy
- Niemann-Pick disease type C
- Non-acquired isolated growth hormone deficiency
- Non-infectious posterior uveitis
- Normosmic congenital hypogonadotropic hypogonadism
- Ornithine transcarbamylase deficiency
- Osteosarcoma
- Pancreatic endocrine tumor
- Paroxysmal nocturnal hemoglobinuria
- Partial deep dermal and full thickness burns
- Patent arterial duct
- Pleomorphic rhabdomyosarcoma
- Polycythemia vera
- Prader-Willi syndrome
- Precursor T-cell acute lymphoblastic leukemia
- Primary adrenal insufficiency
- Primary cutaneous T-cell lymphoma
- Primary peritoneal carcinoma
- Propionic acidemia
- Pulmonary arterial hypertension
- Pulmonary arterial hypertension associated with congenital heart disease
- Pulmonary arterial hypertension associated with connective tissue disease
- Rare carcinoma of pancreas
- Rare epithelial tumor of stomach
- Rare pulmonary hypertension
- Renal cell carcinoma
- Rhabdoid tumor
- Secondary short bowel syndrome
- Severe congenital neutropenia
- Severe hemophilia A
- Severe hemophilia B
- Sickle cell anemia
- Small cell lung cancer
- Soft tissue sarcoma
- Solitary fibrous tumor
- Squamous cell carcinoma of head and neck
- Symptomatic form of hemophilia A in female carriers
- Symptomatic form of hemophilia B in female carriers
- Synovial sarcoma
- Systemic sclerosis
- Systemic-onset juvenile idiopathic arthritis
- Tetrahydrobiopterin-responsive hyperphenylalaninemia/phenylketonuria
- Tuberculosis
- Tuberous sclerosis
- Turner syndrome
- Tyrosinemia type 1
- Undifferentiated pleomorphic sarcoma
- Von Willebrand disease
- Wilson disease

Diseases covered in the USA

The 326 diseases covered by products with marketing authorizations in the USA are listed below.

- Acne rosacea
- Acromegaly
- Acute and chronic eosinophilic leukemia
- Acute cyanide poisoning
- Acute herpetic keratitis
- Acute intermittent porphyria
- Acute lymphoblastic leukemia
- Acute lymphocytic leukemia
- Acute myeloid leukemia
- Acute promyelocytic leukemia
- Acute renal allograft rejection
- Adenocarcinoma of colon and rectum
- Adenocarcinoma of ovary
- Advanced breast cancer in postmenopausal women
- AIDS
- AIDS associated pneumocystis carinii pneumonia
- AIDS related kaposi's sarcoma
- Allodynia (painful hypersensitivity), and chronic pain in postherpetic neuralgia
- Alpha-1-proteinase inhibitor congenital deficiency
- Alpha-thalassemia
- Amebiasis
- Amyotrophic lateral sclerosis
- Anaplastic large cell lymphoma
- Anaplastic thyroid carcinoma
- Anemia associated with end stage renal disease
- Anemia associated with HIV infection or HIV treatment
- Angioedema
- Angioedema caused by hereditary or acquired c1-esterase inhibitor deficiency
- Anorexia, cachexia, or significant weight loss ($\geq 10\%$ of baseline body weight) and confirmed diagnosis of AIDS
- Anthracycline extravasations
- Anthrax
- Aplastic anemia
- Apnea of prematurity
- Argininosuccinic acid synthetase deficiency
- Atypical hemolytic-uremic syndrome
- Bacterial corneal ulcers
- Barrett's esophagus
- B-cell chronic lymphocytic leukemia
- B-cell non-hodgkin's lymphoma
- Botulism
- Breast cancer
- Breast cancer in postmenopausal women
- Cancer of the head and neck
- Carbamoyl-phosphate synthase deficiency
- Carcinoma in situ of the urinary bladder
- Cardiomyopathy associated with doxorubicin administration
- Carnitine deficiency in patients with end stage renal disease who require dialysis
- Castleman's disease
- Central precocious puberty
- Cervical dystonia
- Cholesterol gallstones retained in the common bile duct
- Chronic anovulation due to hypogonadotropic hypogonadism
- Chronic granulomatous disease
- Chronic inflammatory demyelinating polyneuropathy
- Chronic iron overload in patients with transfusion-dependent anemias
- Chronic lymphocytic leukemia
- Chronic myelogenous leukemia
- Chronic myeloid leukemia
- Chronic thromboembolic pulmonary hypertension
- Churg-strauss syndrome
- Cias1-associated periodic syndromes
- Citrullinemia
- Coccidioidomycosis
- Complications of vaccinia vaccination
- Congenital antithrombin deficiency
- Congenital factor VII deficiency
- Congenital factor XIII deficiency
- Congenital protein c deficiency

- Congenital sucrase-isomaltase deficiency
- Contamination with plutonium, americium, or curium
- Crohn's disease
- Cryopyrin-associated periodic syndrome
- Cryptococcal meningitis
- Cryptosporidiosis
- Cushing disease
- Cushing syndrome
- Cutaneous T-cell lymphoma
- Cyanide poisoning
- Cystic fibrosis
- Cystinosis
- Cystinuria
- Cytomegalovirus retinitis
- Cytomegalovirus retinitis in immunocompromised patients with AIDS
- Deficiencies in enzymes of the urea cycle
- Dermatofibrosarcoma protuberans
- Detection of ovarian carcinoma
- Dupuytren's disease
- End stage renal disease
- Endogenous and traumatic anterior uveitis and panuveitis
- Envenomation by crotaline snakes
- Epilepticus of the grand mal type
- Erythema nodosum leprosum
- Esophageal carcinoma
- Esophageal varices that have recently bled, to prevent rebleeding
- Essential thrombocythemia
- Evaluation of exocrine pancreas function
- Excessive daytime sleepiness in narcolepsy
- Extranodal marginal zone b-cell lymphoma of mucosa-associated lymphoma tissue (malt)
- Fabry disease
- Fallopian tube carcinoma
- Familial mediterranean fever
- Fibrinogen deficient patients
- Follicular lymphoma
- Follicular thyroid carcinoma
- Gaucher disease
- Gaucher disease type 1
- Gaucher disease type 2
- Gaucher disease type 3
- Genetic carnitine deficiency
- Giant cell tumor of bone
- Giardiasis
- Glanzmann thrombasthenia
- Glioma
- Glycogen storage disease type II
- Growth failure
- Growth failure due to a lack of adequate endogenous growth hormone secretion
- Growth hormone deficiency
- Growth hormone deficiency in adults after epiphyseal closure
- Growth hormone insensitivity syndrome
- Growth retardation associated with chronic renal failure
- Hairy cell leukemia
- Head and neck cancer
- Hematologic disorders requiring chronic transfusion therapy
- Heparin-associated thrombocytopenia type II
- Hepatic encephalopathy
- Hepatitis b
- Hepatitis c
- Hepatocellular carcinoma
- Her2-overexpressing advanced adenocarcinoma of the stomach
- Hereditary angioedema type 1
- Hereditary angioedema type 2
- Hereditary angioedema type 3
- Hereditary angioneurotic edema
- Hereditary coproporphyrria
- Hereditary thrombophilia due to congenital antithrombin deficiency
- Heroin addicts suitable for maintenance on opiate agonists
- Hodgkin lymphoma
- Homocystinuria
- Homozygous familial hypercholesterolemia
- Hormone refractory prostate cancer
- Hunter syndrome
- Huntington's disease
- Hydatid disease
- Hypercalcemia of malignancy
- Hyperphenylalaninemia
- Hyperphosphatemia in end stage renal failure

- Hypertension in pediatric patients
- Hyperuricemia
- Hypocalcemia due to either hypoparathyroidism or pseudohypoparathyroidism
- Hypocitraturia
- Hypoparathyroidism
- Idiopathic hypereosinophilic syndrome
- Idiopathic or organic growth hormone deficiency in children with growth failure
- Idiopathic pulmonary fibrosis
- Idiopathic thrombocytopenic purpura
- Ifosfamide-induced hemorrhagic cystitis
- Immune thrombocytopenic purpura
- Inborn errors of cholesterol and bile acid synthesis and metabolism
- Infantile spasms
- Inhalational anthrax
- Interstitial cystitis
- Intestinal giardiasis
- Intractable chronic pain
- Intravenous moderate to severe acetaminophen overdose
- Invasive aspergillosis
- Invasive fungal infections
- Japanese encephalitis
- Juvenile idiopathic arthritis
- Juvenile rheumatoid arthritis
- Lead poisoning
- Leishmaniasis
- Lennox-Gastaut syndrome
- Leprosy
- Life-threatening ventricular tachyarrhythmias
- Lymphangioliomyomatosis
- Lymphoblastic lymphoma
- Lymphocytic lymphoma
- Lymphoplasmacytic lymphoma
- Malaria
- Malignancies with bone marrow transplantation
- Malignancy-associated or chemotherapy-induced hyperuricemia
- Malignant glioma
- Malignant hyperthermia syndrome
- Malignant osteopetrosis
- Malignant pleural effusion
- Malignant pleural mesothelioma
- Mantle cell lymphoma
- Mastocytosis
- Medullary thyroid carcinoma
- Melanoma of soft parts
- Metabolic disorders secondary to lipodystrophy
- Metastatic breast cancer
- Metastatic colorectal cancer
- Metastatic melanoma
- Metastatic renal cell carcinoma
- Methanol or ethylene glycol poisoning
- Methotrexate toxicity
- Microscopic polyangiitis
- Mild hemophilia type A
- Mucopolysaccharidosis type 1
- Mucopolysaccharidosis type 6
- Multifocal motor neuropathy
- Multiple myeloma
- Multiple sclerosis
- Mycobacterium avium complex disease in patients with advanced HIV infection
- Mycosis fungoides
- Myelodysplastic syndrome
- Myelofibrosis
- Myxedema coma/precoma
- N-acetylglutamate synthetase deficiency
- Narcolepsy-cataplexy
- Neonatal respiratory distress syndrome
- Neoplastic meningitis
- Nephropathic cystinosis
- Neuroblastoma
- Neurocysticercosis
- Neuroendocrine tumors
- Neuropathic pain in patients with postherpetic neuralgia
- Neutropenia
- Neutropenia associated with bone marrow transplants
- Nodal marginal zone lymphoma
- Non-hodgkin T-cell lymphoma
- Non-hodgkin B-cell lymphoma
- Non-small cell lung cancer
- Noonan syndrome

- Opacifying gallbladders
- Opiate addiction
- Organ rejection in patients receiving heart transplants
- Organ rejection in renal allograft recipients
- Ornithine transcarbamylase deficiency
- Orthostatic hypotension
- Osteogenic sarcoma
- Osteosarcoma
- Ovarian cancer
- Paget's disease
- Pancreatic disorders
- Pancreatic endocrine tumor
- Panuveitis
- Papillary thyroid carcinoma
- Parathyroid carcinoma
- Parkinson's disease
- Paroxysmal nocturnal hemoglobinuria
- Patent arterial duct
- Pathologic (chronic moderate to severe) drooling in pediatric patients
- Patients undergoing continuous renal replacement therapy
- Pediatric (0 to 16 years of age) crohn's disease
- Pediatric crohn's disease
- Peripheral T-cell lymphoma
- Persistent pulmonary hypertension
- Peyronie's disease
- Pheochromocytoma
- Philadelphia-positive acute lymphoblastic leukemia
- Pneumocystis carinii pneumonia
- Pneumocystis carinii pneumonia in AIDS patients
- Polyarticular-course juvenile rheumatoid arthritis
- Polycystic ovarian disease
- Polycythemia vera
- Porphyria variegata
- Postherpetic neuralgia
- Potentially life threatening digitalis intoxication
- Prader-Willi syndrome
- Preterm birth in singleton pregnancies
- Prevention of severe chemotherapy-induced thrombocytopenia
- Primary and secondary carnitine deficiency of genetic origin
- Primary biliary cirrhosis
- Primary cytomegalovirus disease in immunosuppressed recipients of organ transplants
- Primary periodic paralyses
- Primary peritoneal carcinoma
- Primary pulmonary hypertension
- Proliferating infantile hemangiomas
- Prophylaxis of organ rejection in patients receiving allogeneic kidney transplant
- Pulmonary arterial hypertension
- Pulmonary tuberculosis
- Refractory childhood acute lymphocytic leukemia
- Refractory glaucoma
- Refractory patients
- Renal and bladder calculi of the apatite or struvite variety
- Renal cell carcinoma
- Reproductive failure due to hypothalamic or pituitary dysfunction, hypogonadotropic hypogonadism
- Respiratory distress syndrome
- Respiratory failure due to pulmonary surfactant deficiency in preterm infants
- Respiratory syncytial virus
- Scorpion envenomation
- Secondary pulmonary hypertension due to intrinsic precapillary pulmonary vascular disease
- Severe chronic neutropenia
- Severe combined immunodeficiency
- Severe complications from the smallpox vaccine
- Severe diarrhea and flushing associated with malignant carcinoid tumors
- Severe hemophilia A
- Severe hemophilia B
- Short bowel syndrome
- Short stature homeobox-containing gene (shox) deficiency
- Sickle cell anemia
- Sjogren's syndrome patients

- Small lymphocytic lymphoma
- Soft tissue sarcoma
- Solid organ rejection
- Splenic marginal zone lymphoma
- Squamous cell carcinoma of head and neck
- Strabismus and blepharospasms
- Subarachnoid hemorrhage
- Systemic mastocytosis without the d816v c-kit mutation
- T-cell lymphoma
- Testicular cancer
- Thyroid cancer
- Tourette's syndrome
- Toxoplasma gondii encephalitis
- Trypanosoma brucei gambiense infection
- Tuberculosis
- Tuberous sclerosis
- Tumor induced hypercalcemia
- Turner syndrome
- Tyrosinemia type 1
- Ulcerative colitis
- Uric acid nephrolithiasis
- Uveitis involving the posterior segment of the eye
- Varicella
- Vernal keratoconjunctivitis
- Vipoma
- Visceral leishmaniasis
- Von Willebrand disease
- Waldenstrom's macroglobulinemia
- Wegener's granulomatosis
- Well-differentiated papillary, follicular or combined papillary/follicular carcinomas of the thyroid
- Wilson disease
- Zygomycosis

Annex 3: Classification According to Disease Categories and Disease Names (300 studies)

Rare Disease

Group of conditions including some RD or phenotypic expression of some RD

Disease Category	Disease Name	N for each
Anesthesia & pain control (N=7)	Chronic pain	1
	Chronic pain/ recurrent pain and acute pain	1
	Post-operative nausea and vomiting	1
	Chronic post-surgical pain after total knee replacement	1
	Regional Anesthesia	1
	Perioperative and Anesthetic Care	1
	Multimodal pain	1
Blood disorder (N=3)	Chronic graft-versus-host disease (GVHD)	1
	Hemophilia and other bleeding disorders	1
	Immune thrombocytopenic purpura	1
Cancer (N=48)	Acute myeloid leukemia	1
	Rectal Cancer	1
	Bone metastases	1
	Breast cancer related lymphedema (BCRL)	1
	Breast cancer	1
	Solid tumors	1
	Colorectal cancer	3
	Colorectal Liver Metastases	1
	Hepatocellular carcinoma	1
	Human papillomavirus (Cervical cancer)	1
	Localized prostate cancer	2
	Advanced non-small-cell lung cancer	2
	Leukemia	1
	Systemic light-chain amyloidosis	1
	Chemotherapy-induced nausea and vomiting	2
	malignant lymphoma/non-Hodgkin's lymphoma	1
	Hodgkin's disease and lymphoma	1
	neuroendocrine tumors	1
	Cancer (not specified types)	1
	Cancer/Malignant disease	3
	head and neck cancer	5
	Prostate cancer	6
Oral Mucositis (OM)	2	

	Ovarian Cancer	2
	Myeloma	1
	Anal cancer	1
	Pancreatic cancer	1
	Liver cancer	1
	Colon polyps	1
	Bereavement research in palliative care	1
Child health (N=2)	Children with neuro-disability and gastrostomy tube dependency	1
	Cleft palate	1
Dentistry & oral health (N=16)	Supragingival dental plaque and gingivitis	1
	Plaque and gingivitis	1
	Caries	2
	Chronic periodontitis (Anterior teeth)	1
	Chronic periodontitis (Posterior teeth)	1
	Edentulous/missing teeth	3
	Extensive tooth decay	1
	Implants in regenerated bone	1
	Apthous ulcers	1
	Traumatic dental injuries	1
	Periodontitis	3
Ear, Nose & Throat (N=3)	Tinnitus	2
	Hearing loss - cochlea implant	1
Endocrine & metabolic (N=6)	Obesity	3
	Thyroid Eye Disease	1
	Nonalcoholic steatohepatitis	1
	Type II diabetes	1
Eyes & vision (N=5)	Intermittent exotropia	1
	Glaucoma	1
	Posterior Segment-Involving Uveitis	1
	Diabetic retinopathy (macular edema and proliferative retinopathy)	1
	Age-related macular degeneration	1
Gastroenterology (n=9)	Chronic Hepatitis C	1
	Hepatic encephalopathy	1
	Crohn's disease	1
	Nonvariceal upper gastrointestinal bleeding	1
	Gastro-esophageal reflux disease (GERD)	1
	Irritable Bowel Syndrome	1
	Antibiotic associated colitis, also known as clostridium difficile colitis, AKA pseudomembranous colitis	1
	Inflammatory bowel disease (IBD)	1
	Chronic hepatitis B	1
Genetic disorders (N=2)	Cystic Fibrosis	1
	Neurofibromatosis	1
Gynaecology (N=7)	Endometriosis	1
	Endometriosis-related pain	1
	Abnormal uterine bleeding	1
	Deeply infiltrative endometriosis (DIE)	1
	Uterine Fibroids	1

	Female sexual dysfunction	2
Health care of older people (N=3)	Sarcopenia	1
	Dyspnoea or Breathlessness in Palliative Care	1
	Physical rehabilitation with frail older people	1
Heart & circulation (N=27)	Cardiac Arrest	2
	Atherosclerosis	1
	Chronic leg edema	1
	Obstructive disease of supra-aortic arteries	1
	Coronary heart disease	1
	Pulmonary arterial hypertension	1
	Pulmonary arterial hypertension related Systemic Sclerosis	1
	Acute coronary syndrome	1
	Acute heart failure syndromes (AKA Acute decompensated heart failure)	1
	Atrial fibrillation	2
	Aortic valve stenosis (AS)/Aortic stenosis (AS);Valvular heart disease	2
	Cardiovascular disease	2
	Obstructive coronary artery disease	1
	Ischemic heart disease	1
	Peripheral arterial occlusive disease(PAOD)	1
	Deep venous thrombosis and pulmonary embolism	1
	Critical limb ischemia	1
	Acute stroke put with cardiovascular	2
	Acute ischemic stroke likewise	1
	Heart failure	1
	Aortic dissection	1
	Stable angina pectoris	1
	Infectious disease (N=13)	Sepsis and Critical care (one for children)
Herpes Zoster		1
HIV		1
Hospital-acquired pneumonia and ventilator-associated pneumonia		1
Community-acquired pneumonia		2
Influenza		1
Leprosy		1
Malaria		1
Acute bacterial meningitis		1
Intra-abdominal infection		1
Tuberculosis		1
Kidney disease (N=3)	Acute renal failure	1
	Acute kidney injury	2
Lungs & airways (N=15)	Respiratory distress	1
	Respiratory allergy	1
	Asthma	4
	COPD (Chronic Obstructive Pulmonary Disorder)	1
	Chronic bronchitis and COPD	1
	Connective tissue disease associated interstitial lung disease (CTD-ILD) and idiopathic pulmonary fibrosis (IPF)	1
	Acute lung injury (ALI)	1

	Bronchiolitis	1
	Acute respiratory failure	1
	Severe acute respiratory infection	1
	Mechanical ventilation	2
Mental health (N=5)	Bipolar disorder	1
	Major Depressive Disorder	1
	Forensic mental health	1
	Prisoners with common mental health problems	1
	Schizophrenia of bipolar disorder	1
Neonatal care (N=3)	Neonatal apnea (also known as Apnea of prematurity, and Apnoea)	1
	Neonatal cardiovascular instability	1
	Neonatal seizures	1
Neurology (N=30)	Epilepsy	2
	Infantile spasms	1
	West syndrome (a form of Epilepsy)	
	Seizures	1
	Headache	1
	Parkinson's disease	1
	Alzheimer's disease	1
	Dementia	4
	Intracranial cerebral atherosclerosis	1
	Multiple Sclerosis (one for children)	2
	Migraine	1
	Cluster headache	1
	Tension type headache	1
	Amyotrophic lateral sclerosis/motor neurone disease	2
	Hypoxic-ischemic brain injury	1
	Traumatic brain injury	1
	Insomnia (children)	1
	Charcot-Marie-Tooth disease type 1A (CMT1A)	1
	Chronic Inflammatory Demyelinating Polyradiculoneuropathy and Multifocal and Motor Neuropathy	1
	Peripheral neuropathy	1
	Cerebral palsy	1
	Unilateral cerebral palsy	1
	Alzheimer's disease and Parkinson's disease	1
	Upper limb (stroke) rehab	1
	Aphasia	1
Orthopaedics & trauma (N=16)	Burns	1
	Muskuloskeletal pain (subacute and chronic)	1
	Fall Injury	1
	Hip fracture	2
	Osteoporosis	1
	Low back pain	1
	Acute low back pain	1
	Spinal Cord Injury	1
	Spinal disorders	1
	Head Injury	1
	ACL Injury	1

	Distal radius fractures	1
	Dupuytren's disease	1
	Rotator cuff disease	1
	Open lower limb fractures	1
Pregnancy & childbirth (N=16)	Maternity care	1
	Gestational diabetes mellitus	2
	Pre-eclampsia	1
	Breech presentation	1
	Epilepsy in pregnancy	1
	Hypertensive Disorders in Pregnancy	1
	Preterm birth	1
	Salutogenic Intrapartum Core Outcomes	1
	Surgical management of miscarriage	1
	Intrauterine growth restriction.	1
	Pregestational diabetes	1
	Induction of labor	1
	Cardiovascular disease risk after reproductive disorders	1
	Postpartum hemorrhage	1
Intrapartum fetal assessment.	1	
Rehabilitation (N=2)	Recovery after surgery	1
	Critical illness	1
Rheumatology (N=31)	Systemic Lupus Erythematosus	3
	Systemic Sclerosis	2
	Systemic Sclerosis - related Arthritis	1
	Systemic Sclerosis-associated Interstitial Lung Disease	1
	Small-vessel Vasculitis/ANCA-associated Vasculitis	1
	Systemic Vasculitis, AAV, anti-neutrophil cytoplasmic antibody-associated vasculitis; WG, Wegener's granulomatosis	1
	Osteoarthritis	1
	Rheumatoid Arthritis	6
	Psoriatic Arthritis	1
	Idiopathic inflammatory myopathies (IIM)	1
	Ankylosing spondylitis	1
	Rheumatic diseases	3
	Fibromyalgia syndrome	2
	Gout	1
	Arthritis	1
	Juvenile systemic lupus erythematosus and juvenile dermatomyositis	1
	Knee,hip and hand osteoarthritis	1
	Sjögren's syndrome	1
Idiopathic arthritis-associated uveitis (juvenile)	1	
Hand osteoarthritis	1	
Skin (N=7)	Vitiligo	1
	Eczema	1
	Cutaneous leishmaniasis	1
	Vulval skin condition	1
	Acne	1
	Incontinence-associated dermatitis (IAD)	1
	Facial photoaging and chronological aging	1

Tobacco, drugs, & alcohol dependence (N=4)	Drug dependence	1
	Addiction (substance)	1
	Nicotine, alcohol and cocaine abuse/dependence	1
	Addiction (gambling)	1
Urology (N=4)	Peyronie's disease	1
	Nocturnal Enuresis	1
	Pelvic organ prolapse	1
	Male sexual dysfunction/disorders	1
Wounds (N=4)	Non-healing wounds	1
	Venous leg ulcers	2
	Pressure wounds	1
Others (N=9)		
Chronic conditions	JIA, OI, Achondroplasia, Hemophilia, Cerebral, Palsy, Spina Bifida, CF, Cancer	1
Intensive care	Critical illness/ ICU disease	1
Benign disease	Benign/ Non-malignant diseases	1
Developmental, psychosocial, & learning problems	Autism	1
N/A	N/A – Platelet transfusion trials	1
N/A	N/A – RCT informed consent	1
N/A	N/A – Transplant surgery	1
N/A	N/A – Health education	1
N/A	N/A – vaccination communication	1
TOTAL		300

Annex 4: COSMIN collection of systematic reviews of measurement properties of health status outcome measurement instruments, published in PubMed or Embase

All systematic articles of outcome measurement instruments addressing directly a rare disease or a group of rare diseases (n=21)

- [1] Ammann-Reiffer C, Bastiaenen CH, de Bie RA, van Hedel HJ. Measurement Properties of Gait-Related Outcomes in Youth With Neuromuscular Diagnoses: A Systematic Review. *Phys Ther* 2014.
- [2] Avina-Zubieta JA, Alarcon GS, Bischoff-Ferrari HA, Fischer-Betz R, Schneider M, Gall V, et al. Measurement of fatigue in systemic lupus erythematosus: A systematic review. *Arthritis Care Res* 2007;57:1348-57.
- [3] Buffart LM, Roebroek ME, Pesch-Batenburg JM, Janssen WG, Stam HJ. Assessment of arm/hand functioning in children with a congenital transverse or longitudinal reduction deficiency of the upper limb. *Disabil Rehabil* 2006;28:85-95.
- [4] Bullinger M, Globe D, Wasserman J, Young NL, von MS. Challenges of patient-reported outcome assessment in hemophilia care-a state of the art review. *Value Health* 2009;12:808-20.
- [5] Castelino M, Abbott J, McElhone K, Teh LS. Comparison of the psychometric properties of health-related quality of life measures used in adults with systemic lupus erythematosus: a review of the literature. *Rheumatology (Oxford)* 2013;52:684-96.
- [6] Chien CW, Rodger S, Copley J, McLaren C. Measures of participation outcomes related to hand use for 2- to 12-year-old children with disabilities: a systematic review. *Child Care Health Dev* 2014;40:458-71.
- [7] De Kleijn P, Heijnen L, Van Meeteren NLU. Clinimetric instruments to assess functional health status in patients with haemophilia: A literature review. *Haemophilia* 2002;8:419-27.
- [8] Deathe AB, Wolfe DL, Devlin M, Hebert JS, Miller WC, Pallaveshi L. Selection of outcome measures in lower extremity amputation rehabilitation: ICF activities. *Disabil Rehabil* 2009;31:1455-73.
- [9] Epton J, Harris R, Jenkinson C. Quality of life in amyotrophic lateral sclerosis/motor neuron disease: a structured review. *Amyotroph Lateral Scler* 2009;10:15-26.
- [10] Gibson F, Auld EM, Bryan G, Coulson S, Craig JV, Glenny AM. A systematic review of oral assessment instruments: what can we recommend to practitioners in children's and young people's cancer care? *Cancer Nurs* 2010;33:E1-E19.
- [11] Gilmore R, Sakzewski L, Boyd R. Upper limb activity measures for 5- to 16-year-old children with congenital hemiplegia: a systematic review. *Dev Med Child Neurol* 2010;52:14-21.
- [12] Hudson M, Steele R, Baron M. Update on Indices of Disease Activity in Systemic Sclerosis. *Semin Arthritis Rheum* 2007.
- [13] Ireland P, Johnston LM. Measures of self-care independence for children with osteochondrodysplasia: a clinimetric review. *Phys Occup Ther Pediatr* 2012;32:80-96.
- [14] Koene S, Jansen M, Verhaak CM, De Vruhe RL, De Groot IJ, Smeitink JA. Towards the harmonization of outcome measures in children with mitochondrial disorders. *Dev Med Child Neurol* 2013;55:698-706.

- [15] Mazzone ES, Vasco G, Palermo C, Bianco F, Galluccio C, Ricotti V, et al. A critical review of functional assessment tools for upper limbs in Duchenne muscular dystrophy. *Dev Med Child Neurol* 2012;54:879-85.
- [16] Osborne TR, Ramsenthaler C, Siegert RJ, Edmonds PM, Schey SA, Higginson IJ. What issues matter most to people with multiple myeloma and how well are we measuring them? A systematic review of quality of life tools. *Eur J Haematol* 2012;89:437-57.
- [17] Pakulis PJ, Young NL, Davis AM. Evaluating physical function in an adolescent bone tumor population. *Pediatr Blood Cancer* 2005;45:635-43.
- [18] Rannard A, Buck D, Jones DE, James OF, Jacoby A. Assessing quality of life in primary biliary cirrhosis. *Clin Gastroenterol Hepatol* 2004;2:164-74.
- [19] Razvi S, McMillan CV, Weaver JU. Instruments used in measuring symptoms, health status and quality of life in hypothyroidism: a systematic qualitative review. *Clin Endocrinol (Oxf)* 2005;63:617-24.
- [20] Stephensen D, Drechsler WI, Scott OM. Outcome measures monitoring physical function in children with haemophilia: a systematic review. *Haemophilia* 2014;20:306-21.
- [21] Szende A, Schramm W, Flood E, Larson P, Gorina E, Rentz AM, et al. Health-related quality of life assessment in adult haemophilia patients: a systematic review and evaluation of instruments. *Haemophilia* 2003;9:678-87.

All systematic articles of outcome measurement instruments which may be of indirect relevance to rare diseases (n=26)

- [22] Auld M, Boyd R, Moseley GL, Johnston L. Seeing the gaps: a systematic review of visual perception tools for children with hemiplegia. *Disabil Rehabil* 2011;33:1854-65.
- [23] Benfer KA, Weir KA, Boyd RN. Clinimetrics of measures of oropharyngeal dysphagia for preschool children with cerebral palsy and neurodevelopmental disabilities: a systematic review. *Dev Med Child Neurol* 2012;54:784-95.
- [24] Branski RC, Cukier-Blaj S, Pusic A, Cano SJ, Klassen A, Mener D, et al. Measuring Quality of Life in Dysphonic Patients: A Systematic Review of Content Development in Patient-Reported Outcomes Measures. *J Voice* 2009.
- [25] Cagney KA, Wu AW, Fink NE, Jenckes MW, Meyer KB, Bass EB, et al. Formal literature review of quality-of-life instruments used in end-stage renal disease. *Am J Kidney Dis* 2000;36:327-36.
- [26] Castrejon I, Silva-Fernandez L, Bombardier C, Carmona L. Clinical composite measures of disease activity for diagnosis and followup of undifferentiated peripheral inflammatory arthritis: a systematic review. *J Rheumatol Suppl* 2011;87:48-53.
- [27] Che HJ, Burr JM, Ramsay CR, zuara-Blanco A, Prior M. Choosing appropriate patient-reported outcomes instrument for glaucoma research: a systematic review of vision instruments. *Qual Life Res* 2011;20:1141-58.
- [28] Chow MY, Morrow AM, Cooper Robbins SC, Leask J. Condition-specific quality of life questionnaires for caregivers of children with pediatric conditions: a systematic review. *Qual Life Res* 2013;22:2183-200.
- [29] Cleemput I, Dobbels F. Measuring patient-reported outcomes in solid organ transplant recipients: an overview of instruments developed to date. *Pharmacoeconomics* 2007;25:269-86.

- [30] Colosimo C, Martinez-Martin P, Fabbrini G, Hauser RA, Merello M, Miyasaki J, et al. Task force report on scales to assess dyskinesia in Parkinson's disease: critique and recommendations. *Mov Disord* 2010;25:1131-42.
- [31] Cummins RA. Self-rated quality of life scales for people with an intellectual disability: A review. *Journal of Applied Research in Intellectual Disabilities* 1997;10:199-216.
- [32] de Boer MR, Moll AC, de Vet HC, Terwee CB, Volker-Dieben HJ, van Rens GH. Psychometric properties of vision-related quality of life questionnaires: a systematic review. *Ophthalmic Physiol Opt* 2004;24:257-73.
- [33] Deighton J, Croudace T, Fonagy P, Brown J, Patalay P, Wolpert M. Measuring mental health and wellbeing outcomes for children and adolescents to inform practice and policy: a review of child self-report measures. *Child Adolesc Psychiatry Ment Health* 2014;8:14.
- [34] Englbrecht M, Tarner IH, van der Heijde DM, Manger B, Bombardier C, Muller-Ladner U. Measuring pain and efficacy of pain treatment in inflammatory arthritis: a systematic literature review. *J Rheumatol Suppl* 2012;90:3-10.
- [35] Ettema TP, Droes RM, Lange JD, Mellenbergh GJ, Ribbe MW. A review of quality of life instruments used in dementia. *Qual Life Res* 2005;14:675-86.
- [36] Field D, Livingstone R. Clinical tools that measure sitting posture, seated postural control or functional abilities in children with motor impairments: a systematic review. *Clin Rehabil* 2013;27:994-1004.
- [37] Harvey K, Catty J, Langman A, Winfield H, Clement S, Burns E, et al. A review of instruments developed to measure outcomes for carers of people with mental health problems. *Acta Psychiatr Scand* 2008;117:164-76.
- [38] Heffernan C, Jenkinson C. Measuring outcomes for neurological disorders: a review of disease-specific health status instruments for three degenerative neurological conditions. *Chronic Illn* 2005;1:131-42.
- [39] Heineman KR, Hadders-Algra M. Evaluation of neuromotor function in infancy-A systematic review of available methods. *J Dev Behav Pediatr* 2008;29:315-23.
- [40] Ikeda E, Hinckson E, Krageloh C. Assessment of quality of life in children and youth with autism spectrum disorder: a critical review. *Qual Life Res* 2014;23:1069-85.
- [41] Leone MA, Beghi E, Righini C, Apolone G, Mosconi P. Epilepsy and quality of life in adults: a review of instruments. *Epilepsy Res* 2005;66:23-44.
- [42] Millard RW, Beattie PF, Jones RH. A comprehensive review of questionnaires to evaluate chronic pain-related disability. *Crit Rev Phys Rehabil Med* 1997;9:35-52.
- [43] Quittner AL, Modi A, Cruz I. Systematic review of health-related quality of life measures for children with respiratory conditions. *Paediatr Respir Rev* 2008;9:220-32.
- [44] Salek SS, Walker MD, Bayer AJ. A review of quality of life in Alzheimer's disease. Part 2: Issues in assessing drug effects. *Pharmacoeconomics* 1998;14:613-27.
- [45] Silva PF, Quintino LF, Franco J, Faria CD. Measurement properties and feasibility of clinical tests to assess sit-to-stand/stand-to-sit tasks in subjects with neurological disease: a systematic review. *Braz J Phys Ther* 2014;18:99-110.
- [46] Townsend-White C, Pham AN, Vassos MV. A systematic review of quality of life measures for people with intellectual disabilities and challenging behaviours. *J Intellect Disabil Res* 2011.
- [47] Tyson S, Connell L. The psychometric properties and clinical utility of measures of walking and mobility in neurological conditions: a systematic review. *Clin Rehabil* 2009;23:1018-33.

Bibliography

- ¹ Zbrozek A, Hebert J *et al.* Validation of electronic systems to collect patient-reported outcome (PRO) data - Recommendations for clinical trial teams: Report of the ISPOR ePRO systems validation good research practices task force. *Value Health* 2013; 16:480-9.
- ² Cella D, Nowinski C, Peterman A *et al.* The Neurology Quality of Life Measurement Initiative. *Arch Phys Med Rehabil.* 2011; 92(10 Suppl):S28-S36.
- ³ Victorson D, Cavazos JE, Holmes GL *et al.* Validity of the Neurology Quality-of-Life (Neuro-QoL) measurement system in adult epilepsy. *Epilepsy & Behavior* 2014; 31:77-84.
- ⁴ Gershon RC, Lai JS, Bode R *et al.* Neuro-QOL: quality of life item banks for adults with neurological disorders: item development and calibrations based upon clinical and general population testing. *Quality of Life Research* 2012; 21(3):475-486.
- ⁵ Neuro-QoL Reports and Manuals: National Institute of Neurological Disorders and Stroke (NINDS). User Manual for the Quality of Life in Neurological Disorders (Neuro-QOL) Measures. Version 2.0, March, 2015. <http://www.neuroqol.org/Resources/Neuro-QolReports-Manuals/Pages/default.aspx> (accessed 20 July 2015).
- ⁶ Cella D *et al.* The Patient-Reported Outcomes Measurement Information System (PROMIS): Progress of an NIH Roadmap Cooperative Group During its First Two Years. *Medical Care* 2007; 45(5):S3_S11.
- ⁷ Cella D *et al.* on behalf of the PROMIS Cooperative Group. Initial adult health item banks and first wave testing of the patient-reported outcomes measurement information system (PROMIS™) Network: 2005–2008. *Journal of Clinical Epidemiology* 2010; 63(11):1179-94.
- ⁸ Alonso J, Bartlett SJ *et al.* The case for an international patient-reported outcomes measurement information system (PROMIS) initiative. *Health and Quality of Life Outcomes* 2013; 11:210.
- ⁹ Serrano-Aguilar P, Linertová R, *et al.*, BURQOL-RD Research Network. Recruitment procedures for descriptive socioeconomic studies in rare diseases. The BURQOL-RD project. *Expert Opinion on Orphan Drugs.* 2015;3(7):759-65.
- ¹⁰ Linertová R, Serrano-Aguilar P, *et al.* Delphi approach to select rare diseases for a European representative survey. The BURQOL-RD study. *Health Policy.* 2012;108:19–26.
- ¹¹ Calvert M, Blazeby J *et al.* Reporting quality of life in clinical trials: a CONSORT extension. *The Lancet* 2011; 378(9804): 1684-5.
- ¹² Brundage M, Blazeby J *et al.* Patient-reported outcomes in randomized clinical trials: development of ISOQOL reporting standards. *Quality of Life Research* 2013; 22(6):1161-75.
- ¹³ Calvert M, Blazeby J *et al.* Reporting of patient-reported outcomes in randomized trials: the CONSORT-PRO extension. *Journal of the American Medical Association* 2013; 309(8):814-22.
- ¹⁴ Calvert M, Brundage M *et al.* The CONSORT Patient-Reported Outcome (PRO) extension: implications for clinical trials and practice. *Health Qual Life Outcomes* 2013; 11:184.
- ¹⁵ Rouette J, Blazeby J *et al.* Integrating health-related quality of life findings from randomized clinical trials into practice: an international study of oncologists' perspectives. *Quality of Life Research* 2015; 24(6):1317-25.
- ¹⁶ Calvert M, Kyte D *et al.* Patient-reported outcome (PRO) assessment in clinical trials: a systematic review of guidance for trial protocol writers. *PLoS One* 2014; 9(10):e110216.
- ¹⁷ Kyte D, Duffy H *et al.* Systematic evaluation of the patient-reported outcome (PRO) content of clinical trial protocols. *PLoS One* 2014; 9(10):e110229.
- ¹⁸ Calvert M, Kyte D *et al.* Putting patients at the heart of health-care research. *Lancet* 2015; 21:385(9973):1073-4
- ¹⁹ Kyte D, Draper H *et al.* Patient-reported outcome alerts: ethical and logistical considerations in clinical trials. *Journal of American Medical Association* 2013; 310(12):1229-30.