INTERNATIONAL RARE DISEASES RESEARCH CONSORTIUM

Patient-Centered Outcome Measures Initiatives in the Field of Rare Diseases

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Table of Contents

The IRDiRC Task Force
General Background on Outcome Measures
Introduction
Patient-Centered Outcome Measures
Definition of Outcomes7
Qualitative Research for Outcomes9
Selecting Outcomes for Use in Clinical Trials9
Designing Outcome Measures11
Outcome Measures Initiatives12
Regulation and Guidance on Patient-Centered Outcome Measures12
European Medicines Agency13
US Food and Drug Administration14
Patient-Centered Outcome Measures in Rare Diseases
Biomarkers and Surrogate Outcome Measures17
Developing Outcome Measures for Rare Diseases18
ISPOR and Outcome Measures in the Field of Rare Disease Trials19
Lists of Core Outcomes Developed for Rare Diseases19
Conclusions and Recommendations21
First IRDiRC Task Force Workshop on Patient-Centered Outcome Measures
Bibliography



Notes

Disclaimer:

This document contains information concerning outcome measures issues and a description of initiatives to develop and standardize outcome measures for common diseases, which are potentially of relevance for rare diseases. It also includes an overview of the need in the field of rare diseases and of the questions to be debated to advance the field. The findings, conclusions and recommendations in this report are those of the contributors, who are responsible for the contents; the findings, conclusions and recommendations do not necessarily represent the views of the European Commission or members of the International Rare Diseases Research Consortium (IRDiRC). Therefore, no statement in this report should be construed as an official position of the European Commission or a member of IRDiRC.

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Acronyms

CDER	Center for Drug Evaluation and Research
CER	Comparative effectiveness research
COA	Clinical outcome assessments
COI	Concept of interest
CONSORT	CONsolidated Standards of Reporting Trials
COS	Core outcome set
COSMIN	COnsensus-based Standards for the selection of health Measurement INstruments
COU	Context of use
ClinRO	Clinician-reported outcomes
CYPHOF	Children and Young People Health Outcomes Forum
E5-QD	EQ-5D is a standardized instrument for use as a measure of health outcome
EMA	European Medicine Agency
FDA	Food and Drug Administration (USA)
FDASIA	FDA Safety and Innovation Act
HRQL	Health-related quality of life
HTA	Health technology assessment
IRDiRC	International Rare Diseases Research Consortium
ISOQOL	International Society for Quality of Life Research
ISPOR	International Society for Pharmaeconomics and Outcomes Research
NIH	National Institutes of Health (USA)
NHS	National Health Services (UK)
NQF	National Quality Forum
OBsRO	Observer-reported outcomes
PCOM	Patient-centered outcome measures
PerfO	Performance outcomes
PRO	Patient-reported outcomes
PROM	Patient-reported outcome measures
PROMIS	Patient-Reported Outcome Measurement Information System
RDCRC	Rare Disease Clinical Research Consortia
RDCRN	Rare Diseases Clinical Research Network
SEALD	Study Endpoints and Labeling Development
SLEDAI	Systemic Lupus Erythematosus Disease Activity Index
SLICC/ACR	Systemic Lupus International Collaborative Clinics/American College of Rheumatology



The IRDiRC Task Force

The International Rare Diseases Research Consortium (IRDiRC) was set up to maximize scarce resources and coordinate research efforts in the rare diseases field, with the clear goal to boost the research and development process to help deliver effective therapies as soon as possible. IRDiRC aims to stimulate and coordinate basic and clinical research by promoting links between existing resources, fostering the molecular and clinical characterization of rare diseases, and encouraging translational, preclinical and clinical research.

IRDiRC has adopted a set of policies and recommendations explaining a commitment to develop patient relevant outcome measures:

- Policy 1: Rare diseases research should be collaborative. Resources, data and results should be shared among IRDiRC research projects and made publicly available to the broader community, and duplication should be avoided.
- Policy 2: Rare diseases research should involve patients and/or their representatives in all relevant aspects of the research.
- Guideline 1: The impact of research on people living with a rare disease should be a key consideration for each project. Best ethical practices for ensuring the interest of the individuals living with rare disease should be applied.

In addition, the Therapies Scientific Committee of IRDiRC has issued recommendations on essential actions selected for their high leverage effect to unlock the potential of rare disease therapy development. Among them, the Therapies Scientific Committee recommends:

- Encouraging, supporting and establishing early and continuous dialogue on clinical development strategy and wide evidence generation (e.g. natural history, registry, clinical trial design, clinical endpoints, surrogate endpoints, patient relevant outcomes, regulatory strategy, medical practice, public health strategy) with all relevant stakeholders such as patients' representatives, medical experts, researchers, scientific societies, regulators, health technology assessors, payers and sponsors when appropriate. This could be done through dedicated workshops, safe harbors where knowledge could be shared in a non-competitive manner.
- Encouraging, supporting and developing patient focused/relevant outcomes (e.g. exploring the use of appropriate surrogate endpoints). This is an essential step to gather more successful outcomes at the time of benefit-risk assessment.

In order to take a decisive step to reach these objectives, the IRDiRC Executive Committee established a Task Force on Patient-Centered Outcome Measures in the field of rare diseases in May 2015. The Task Force was requested to draft this document and organize a workshop between relevant stakeholders to discuss possible actions to accelerate the development and validation of patient relevant outcome measures for rare diseases. This document also contains the conclusions of the discussions and the list of items for action agreed on by the workshop participants. This document was drafted by the Scientific Secretariat of the IRDiRC, which is supported, since 2012, by a European FP7 contract, "SUPPORT-IRDIRC" (N° 305207).



Introduction

Clinical trials aim to evaluate the effectiveness and safety for patients of a medical intervention, based on comparable results. To determine and compare clinical safety and efficacy, clinical trial results must reflect relevant "outcome measures", also referred to as "endpoints" or "outcomes".¹ Outcomes should reflect what must be measured and reported in clinical trials in specific disease areas. They may be broad or specific depending on the disease area, on aspects of health benefits or disease progression.

While clinical trial outcome measures and reports are essential for decision- and policy-makers to introduce appropriate recommendations, outcomes in randomized trials have been widely heterogeneous and cause biased findings, resulting in inconsistent evaluation of treatments and recommendations.

Regulatory agencies, standards organizations and international societies have issued a number of guidance documents on outcomes, but many trials, on rare diseases in particular, still do not include standardized outcomes in clinical data. Overall, insufficient attention to the selection of clinical trial outcomes has led, too frequently, to a waste of generated data, research efforts, and inefficiencies in drug development and in regulatory review processes.

Outcomes applied in clinical trials and used in medical product labeling are also often disease-specific. For many indications however, reliable outcomes have not yet been developed. Some outcomes, on the other hand, have been developed to measure concepts that span several diseases.

Patient-Centered Outcome Measures

Clinical trials, involving a number of audiences, do not always and systematically measure outcomes that patients consider important or relevant, resulting in inconsistent outcome information in approved drug labeling and difficulties for payers to appraise the value of a new indication. What patients consider relevant is an important criterion, and as such patient perspectives on other aspects of their disease/ treatment experience that are of importance to other stakeholders should not be ignored.

As a relatively new concept, Patient-Centered Outcome Measures (PCOM) aim to place patients, their families and carers at the heart of decisions concerning the most valuable criteria in health assessment, rather than leaving assessments solely to clinicians. While it is accurate to say that patients are the best reporters of their experience across a broad range of criteria, what is important to them is not always what is most important to all. It is important, therefore, to characterize the use of PCOM. Patient-centered outcome measurements should provide evidence on the impact of the disease and treatment on patients.² Their identification and validation require rigorous planning, methodology and partnership between investigators and patient organizations.



While it is expensive, resource-intensive and time consuming due to extensive research and testing processes, outcomes' standardization is essential to combine and compare data from different studies and data sets.³ Data sets from relevant studies, but generated using heterogeneous outcome measures, cannot therefore systematically be included into meta-analyses.⁴

Definition of Outcomes

An **outcome** is what should be measured and reported in all trials in a specific area.⁵

An **outcome measurement instrument** is a tool that is being used to measure the outcome. Outcome measurement instrument should be selected according to their reliability, validity and responsiveness.⁶

- Reliability: do outcome measures remain constant from one test or study to another and across different investigators?
- Validity: to what degree do outcome measures assess what they are intended to measure?
- Responsiveness: if an outcome measure is used to evaluate changes in patients over time, are the measures able to detect these changes?
- Interpretability: how interpretable are the scores of the instrument?
- Feasibility: is the instrument easy to administer and process?

Surrogate outcomes, sometimes used instead of, or in addition to, clinical outcomes, aim to detect the effects of an intervention before clinical changes actually occur.⁷ They may be an assumed or established risk factor that impacts on disease progression and serve as a measure of intermediate health status to predict future health status.⁸ Validation criteria should be fulfilled before a surrogate outcome can be used instead of a definitive clinical outcome in clinical trials.⁹

Clinical outcomes are a common category of outcomes to be considered in, but should not be limited to, comparative effectiveness research (CER) studies.¹⁰ Medical treatments must demonstrate efficacy in pre-approval clinical trials to:

- prevent the occurrence of undesirable outcomes;
- delay disease progression;
- hasten recovery or improve survival from disease;
- manage or reduce the burden of chronic diseases.

Post-approval observational comparative effectiveness research (CER) studies are necessary to:

- compare newer treatments with standards of care;
- obtain real-world data on effectiveness of treatments used in a variety of medical situations and patient populations;
- increase understanding of the relative treatment benefits and risks through measures of quality of life, cost and safety outcomes, besides clinical benefits.

A **clinical outcome assessment (COA)** measures patient symptoms, mental state or the effects of a disease on patient functions. A COA can be used to determine whether or not a drug has been demonstrated to provide treatment benefit (i.e. a benefit compared with other treatments).



Five types of COA measures are:

- Patient-reported outcomes (PRO): measurements based on data provided by patients, or proxies, regarding their health condition. The Food and Drug Administration (FDA) describes a PRO as "a measurement based on a report that comes directly from the patient about the status of a patient's health condition without amendment or interpretation of the patient's response by a clinician or anyone else. A PRO can be measured by self-report or by interview provided the interviewer records only the patient's response."
- Clinician-reported outcomes (ClinRO): based on a trained health-care professional's report following observation of a patient's health condition. According to the FDA, "a ClinRO measure involves a clinical judgment or interpretation of the observable signs, behaviors, or other physical manifestations thought to be related to a disease or condition. ClinRO measures cannot directly assess symptoms that are known only to the patient (e.g. pain intensity)."
- Observer-reported outcomes (ObsRO): the FDA defines ObsRO as "measurements based on an observation by someone other than the patient or a health professional who is in a position to regularly observe and report on a specific aspect of the patient's health. An ObsRO measure does not include medical judgment or interpretation. Generally, ObsROs are reported by a parent, caregiver, or someone who observes the patient in daily life. For patients who cannot respond for themselves, it is recommended to include only those events or behaviors that can be observed."
- Performance outcomes (PerfO): define by the FDA as "measurements based on a task performed by a patient according to instructions administered by a health care professional. Performance outcomes require patient cooperation and motivation. These include measures of gait speed, memory recall, or other cognitive testing."
- Biomarkers: "physiologic, pathologic or anatomic patient characteristics measured by an automated process or algorithm as an indicator of normal biologic processes, pathologic processes, or biological responses to a therapeutic intervention".¹¹ Appropriate biomarkers should indicate disease progression and disease activity linked to a biological process and should assess any effects of therapeutic intervention.^{12,13} They can be used at all stages of drug development, from dose response to clinical efficacy endpoints, surrogate endpoints and long term drug response.¹⁴ Biomarkers may predict disease outcome, risk of complications and survival. Patient-selection biomarkers help investigators identify patients who respond to therapeutic success.¹⁵



Qualitative Research for Outcomes

Qualitative research is key to identify what are the main "concepts" of interest to patients (in terms of symptoms or functioning – the proximal dimensions –, and in terms of impact of the disease – the distal dimensions) and is essential to conceptualize treatment benefit from their view point. According to the FDA, benefit can be defined as how patients feel, function and survive. Qualitative research could address critical challenges of outcome measurement in rare diseases and orphan drug development, among which: complexity, variability, individualization, lack of background knowledge, small sample sizes, etc. There should be an iterative process of qualitative research before quantitative exercise may be considered.

This qualitative research is needed to clarify issues to be considered. They should be followed by mixedmethods approach for COA (see Figure 1), which allow the review of potential items and scales before moving on to quantitative exercises.¹⁶



Figure 1: Overview of instrument development steps using mixed-methods. Adapted from James Stansbury, 2013.

From a regulatory perspective, the FDA highlights in its guidance document the need to understand the "concepts of interest" and to define upfront what we need to measure.¹⁷ Although the FDA has previously indicated that "qualitative research alone remains acceptable" for establishing content validity of PROs used to support drug approval and product labeling, they increasingly encourage the mixed methods approach as depicted in Figure 1.

Selecting Outcomes for Use in Clinical Trials

When selecting outcomes for clinical trials, the definition of what needs to be measured have to come first, before checking existing instruments to see if these cover the issues, or deciding on the development of new instruments. Inappropriate selection of outcome and outcome measurements can result in inadequate use of resources, misleading data and misinterpretation of the potential benefits of an intervention.¹⁸ The choice of outcome must therefore be adapted to the studied population (adult or



pediatric) and the disease or group of diseases in order to reflect disease pathogenesis, clinical features and natural history.

Selecting outcomes to include in CER studies must take into consideration the stakeholders involved and the intended use of the study results, i.e. "the generation and synthesis of evidence that compares the benefits and harms of alternative methods (...) to assist consumers, clinicians, purchasers, and policy makers to make informed decisions that will improve health care at both the individual and population levels".¹⁹

Depending on the disease natural history, on whether the condition is chronic, acute, transient and/or episodic, and on the treatment mechanism and desired effect, the clinical outcomes to be identified will be either incident (whether the condition is newly diagnosed), prevalent (for an existing disease) or recurrent (recurrence or worsening of a condition in a patient). In the absence of standard history databases or measurement tools, it is typically challenging to choose outcomes to design clinical trials for rare diseases with episodic symptoms for instance.²⁰

Measures such as health-related quality of life (HRQL) data are of importance. They can provide investigators with significant data to justify disease management strategies and treatments that effectively improve patient outcomes and HRQL.²¹

One of the best known models of HRQL is the Wilson & Cleary model that provides a classification scheme for different measures of health outcome. The model consists of five different classes of measures: biological and physiological factors, symptoms, functioning, general health perceptions, and overall quality of life (See Figure 2).²² These outcome measures are classified and linked with traditional clinical variables to measures of HRQL, with additionally interlinked causal relationships indicated.



Figure 2: Relationships among measures of patient outcome in a health-related quality of life conceptual model. Adapted from Wilson & Cleary, 1995.

However, in a reflection paper on the use of PRO measures in oncology studies, it was concluded that longitudinal HRQL data have rarely been informative from a licensure perspective.²³ This was mainly due to the absence of demonstrated difference between the study arms. It is not known whether this is related to poor sensitivity of the instruments, high attrition rates and informative censoring, or simply reflects the resilience and dynamics of the individual's perception of HRQL during the course



of disease. Additionally, consensus is often missing regarding what amount of difference is clinically relevant.

Designing Outcome Measures

To design outcome sets, researchers must assess potential impact of methodological decisions on the final results: group composition, questioning technique, information participants receive to inform their answers, response anonymity, group participants' interaction with or influence of each other, the place of interaction, attrition bias, methods of analysis and weighting of outcomes, and how consensus is reached.²⁴ A wide selection of stakeholders should represent the consensus panel to agree on outcome measures. Accordingly, investigators should take into account the selection of stakeholders and methods to develop these measures (e.g. structured consensus techniques, Delphi technique, involvements of patients, families and clinicians, etc.).

Developing guidelines for core sets of outcomes with standardized backbones for different conditions would improve the quality of clinical studies and increase homogeneity between clinical trials.²⁵ Where numerous clinical aspects may be observed or where there is uncertainty about which outcomes are most relevant to patients and other stakeholders, several measures may be necessary to obtain relevant data. For instance, in the case of Systemic Lupus Erythematosus, researchers may use the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), to measure changes in disease activity, or they can use the Systemic Lupus International Collaborative Clinics/American College of Rheumatology (SLICC/ACR) damage index to assess accumulated damage since disease onset.^{26,27,28}

Short-term measures of disease activity, symptom burden, functional status, long-term consequences of disease, overall well-being and healthcare resource use must all be considered. All criteria will not be weighted equally, depending on the questions asked. Researchers must therefore select outcomes that would best represent each of the investigated disease or patient well-being characteristics. Investigators must also take into account and balance outcome feasibility and patient acceptability.²⁹

Healthcare professionals will usually asses and analyze objective clinical outcomes. Many measures typically collected in clinical trials from healthcare professionals are, however, also subjective in nature. Objective outcomes should be "reliably measured across patients in a study, by different health care providers, and over time."³⁰ The focus is now on more subjective outcomes such as HRQL, social health, pain, and patient satisfaction which are subjective concepts. Their assessment relies on scales which have to be proved as reliable and valid, exactly as for the objective outcome measures.

Experts recommend developing "core outcome sets" to avoid significant outcomes being overlooked and avoid researchers measuring outcomes in a non-uniform way, making comparisons between and aggregation of results from trials impossible for meta-analyses.³¹ Investigators should ensure that the core outcome set they use is relevant to and compatible with their trial (e.g. age group, disease or condition). As trials progress, any necessary modifications in outcomes, context and methodology must be documented, justified and explained in final reports.



Outcome Measures Initiatives

A number of organizations and industrial players have increased their efforts to develop relevant outcome measures for common disease studies or make recommendations on ways to improve patient-relevant outcome measures used in patient-centered outcome research. In Annex 1, an inventory list of a number of initiatives is given, which may not be fully comprehensive. This list does not include for-profit initiatives.

Organizations that have produced guidance documents to propose standards to develop, assess, implement and analyze PRO in diseases in general include the publishing standards organization CONsolidated Standards of Reporting Trials (CONSORT), the quality standards organization National Quality Forum (NQF), the professional association International Society for Quality of Life Research (ISOQOL), COnsensus-based Standards for the selection of health Measurement Instruments (COSMIN) and the International Society for Pharmacoeconomics and Outcomes Research (ISPOR).³²

In the field of rare diseases, the EveryLife Foundation conducted a workshop in 2011 on Clinical Evaluation of Rare Disease Treatments, featuring a practical, in-depth review of methods to select and adapt PRO for rare disease clinical trials. PCORI began funding research in December 2012 and have a sizeable and growing portfolio of projects designed to improve patient care and outcomes through patient-centered comparative clinical effectiveness research. The US National Institutes of Health (NIH) established the Rare Disease Clinical Research Consortia (RDCRC) in 2013, as part of the Rare Diseases Research Network (RDCRN), and the Patient Reported Outcomes Measurement Information System (PROMIS)³³ to improve research in rare diseases. The COMET³⁴ database lists disease areas addressed in some way by 300 published and ongoing core outcome studies; this list includes 22 rare diseases or groups of rare diseases. The Mapi Trust PROQOLID database maintains a database of PROMs that have been used by FDA and EMA to support labeling claims (PROLabels)³⁵.

Regulation and Guidance on Patient-Centered Outcome Measures

In order to meet regulatory approval, early discussions should be conducted with the relevant agencies to ensure that appropriate outcome measures are applied and compatible with regulatory standards. The European Medicines Agency (EMA) and the FDA have released guidelines for the assessment of PROs (see related sections below).

While the EMA suggests that guidelines relating to common diseases may be applied to rare diseases, the ISPOR Task Force Group on PRO and OBsRO Measurements in Rare Disease Clinical Trials demonstrated the difficulties to apply existing guidelines on outcomes for rare diseases during their 19th Annual International Meeting in June 2014.³⁶ ISPOR strongly recommends that regulatory agencies become fully involved with manufacturers to ensure rigorous planning of orphan drug development programs, whilst optimizing rare disease patient recruitment in clinical trials.

Standardized guidance provides greater transparency and the ability to generate comparative data in clinical trials, thus reducing the number of special cases dealt with in rare diseases. To establish standards however, the research community must reach consensus on objectives and project



leadership. It must ensure that guidance and standards are then adopted by all stakeholders involved, including regulators, manufacturers, payers and providers.

- Regulators must be able to assess clinical study results and evidence according to a roadmap and based on rare disease-specific limitations;
- Manufacturers must be able to generate evidence on unmet needs and new therapy costeffectiveness according to a clear pathway;
- Payers must be better equipped to evaluate novel orphan medicinal products and technologies and provide access to patients who would benefit from the treatment;
- Providers must have a clearer and larger view of clinical evidence, allowing them to make the right therapeutic choices for their patients.

European Medicines Agency

The EMA provides recommendations for patient reported outcome measures (PROM) assessment. The Agency highlights the importance of measurements concerning HRQL,³⁷ i.e. the "state of complete physical, mental, and social well-being and not merely the absence of disease,"³⁸ and states that PROM should cover single and multi-dimension measures of symptoms, health status, adherence to treatment and satisfaction with treatment.

HRQL instrument validation should be completed prior to use in clinical trials and the same study should not be applied to test both the HRQL instrument and HRQL changes. If further validation is required, the instrument can still be used in exploratory trials and adjusted accordingly for confirmatory trials.

Where multiple outcomes are assessed, efficacy outcomes should be prioritized. If efficacy is significant, HRQL can be assessed; if efficacy is not significant, then HRQL need not be tested and no further testing is conducted. In severe, life-threatening diseases, HRQL benefit must be achieved without reduction in efficacy.

The EMA published a Guideline on Clinical Trials in Small Populations in 2006, in which the agency outlines criteria for choice of outcomes (or endpoints).³⁹ While the EMA states that no particular methods exist to design, conduct or analyze clinical trials in small populations, approaches do exist to increase the efficiency of clinical trials. Clinically relevant and interpretable results should be prioritized.

For example, in a rare disease such as Fabry's, a clinical outcome like renal failure will be relevant because it severely reduces a patient's well-being and survival potential. In this case, multiple outcomes should be assessed, taking into account the patient's preferences and well-being, in addition to the impact of the treatment on disease progression. In cases where demonstrating outcomes would take too long, the EMA may consider applying validated and justified surrogate outcomes as substitutes, provided they are reasonably likely to predict effectiveness, to avoid further harm to patients.

While the EMA has not published further guidance on patient relevant outcome measures, some EU countries are increasing their efforts to develop PCOMs in certain therapeutic areas. In the UK, the National Health Services (NHS) announced in February 2015 that children and young adults would becoming increasingly involved in deciding which mental health outcomes are most important to them.



Seven sites across the UK have chosen to develop PCOMs for children and young adults in several therapeutic areas, such as asthma, complex respiratory conditions, palliative care, use of wheelchairs and posture services.

The UK's Children and Young People Health Outcomes Forum (CYPHOF) was established in 2012 as an independent expert advisory group of professionals and representatives in the pediatric sector to advise on ways to improve health outcomes in that patient population.⁴⁰ The Forum published an initial report in 2012, providing 78 recommendations to health system organizations to improve children and young people's health outcomes. In response, the UK government launched the "Better health outcomes for children and young people pledge" in 2013. In 2014, the Forum examined progress in the field and outlined a series of challenges to the health system.

In June 2014, the EMA published a draft reflection paper on the use of patient reported outcome measures in oncology studies.⁴¹ Its consultation period ended in November 2014. In this paper, the term "patient-reported outcome measure" covers "health status, symptoms HRQL, adherence to treatment, satisfaction with treatment, etc with the emphasis placed upon the patient's judgment". However, "this reflection paper covers general aspects of the use of PRO endpoints in oncology studies such as the designing and carrying out of clinical studies, the acceptability of instruments and the clinically important differences and added value. This reflection paper does not cover the validation of instruments nor does it make specific recommendations regarding the instrument to select". While this reflection paper addresses only the field of oncology, it aims to further develop a patient focused assessment of disease burden and impact and aims to understand the impact of novel treatments on patient functioning.

US Food and Drug Administration

The FDA has strongly influenced industry-funded PROM research since it published a guidance document in 2009.⁴² The guidance provides an overview of PROM development, application and evaluation for medical product development.⁴³ According to the guidance, in order to support claims in medical product labeling, a PROM instrument must consider the following criteria:

- the population enrolled in the clinical trial;
- the clinical trial objectives and design;
- the PROM instrument's conceptual framework;
- the PROM instrument's measurement properties.

The FDA guidance states that a PROM must capture a patient's experience using an instrument adapted to the target patient population. Sponsors should therefore provide documented evidence of patient input in the development of appropriate instruments. The FDA supports the use of existing instruments provided they are adapted to the studied population and the study outcome objectives.

The FDA proposes an iterative process to develop a PROM instrument to apply in clinical trials, as illustrated in the following diagram:





Figure 3: The COA Wheel and Spokes diagram (above) identifies the key components of the documentation submitted to Center for Drug Evaluation and Research (CDER) to support COA qualification. The Wheel and Spokes diagram also represents the general iterative process used in developing a COA for qualification. Source: FDA, 2013.

In April 2015, the FDA held a public workshop entitled "Clinical Outcomes Assessment Development and Implementation: Opportunities and Challenges". The aim of the workshop was to provide updates on accomplishments, challenges and ongoing efforts in the use of clinical outcome assessments (COAs), and plan the development of COA and application in drug development.

A COA measures patients' symptoms, overall mental state, or the effects of a disease or condition on how the patients function. The workshop focused on identifying and measuring outcomes that are meaningful to patients and explored ways to incorporate these patients' views in drug development. Optimized use of well-defined and reliable PROM will enable progress towards a more patient-centered approach to drug development. The workshop also discussed standards for COA use and collaborative processes for COA development and dissemination.

The FDA has conducted several other patient-focused drug development meetings, but has yet to demonstrate how it intends to use the information in drug review processes. The agency has proposed steps to develop and improve patient-centered drug development by increasing patient input and providing FDA guidance to patient organizations and drug developers.

While the FDA's 2009 Patient-Reported Outcome guidance was essential to recommend a more systematic approach to outcome measure instrument development, the agency is now pursuing a more



flexible and innovation oriented approach. These efforts aim to improve the development and incorporation of patient-centered clinical outcomes into regulatory assessments.

During the FDA's April 2015 public workshop on COAs, officials from CDER's Clinical Outcome Assessments Staff (formerly Study Endpoints and Labeling Development (SEALD) staff) announced the development of a compendium of COA tools by therapeutic area. The mission of the Clinical Outcome Assessments Staff is to "promote the development and implementation of patient-focused endpoint measures in medical product development to describe clinical benefit in labeling." The compendium will aim to increase collaboration between stakeholders to identify assessment gaps in disease areas needing outcome measures to accelerate drug development. A clear path for patient organizations, regulators, research and industry to work together must be established to achieve patient-centered drug development.

The following roadmap was developed for Patient-Focused Outcome measurement in clinical trials:

Roadmap to **PATIENT-FOCUSED OUTCOME MEASUREMENT** in Clinical Trials



Figure 4: Roadmap to Patient-Focused Outcome Measurement in Clinical Trials. Source: FDA, 2013.



Patient-Centered Outcome Measures in Rare Diseases

Appropriate and validated PCOMs of disease activity or disease progression do not exist for most of the 7,000 rare diseases as they previously were not targets for the development of therapies. Due to the rarity of each individual disease, these niche markets were not attractive enough as to generate investments in research and development.

The situation changed with the adoption of the Orphan Drug Act in the USA in 1983, followed by similar decisions in several regions of the world, including Europe in 1999. Since then, the development of medicinal products for rare diseases with totally unmet needs has increased year after year. In Annex 2, some figures on the products already on the market in Europe or in the USA are given, as well as a list of rare diseases for which these products have an indication.

Two of the characteristics of research and development for rare diseases which are linked to the difficulty to define potential outcomes and to insufficient/inappropriate outcome measurement instruments are: (1) the attrition rate of products which is higher than for common diseases, and (2) the difficulty to appraise the medical added-value of new products due to extensive use of biomarkers or surrogate markers.

Biomarkers and Surrogate Outcome Measures

Outcome measurement instruments currently used in rare disease clinical trials are mostly biomarkers and surrogate outcome measures. The challenge of developing innovative therapeutic approaches for rare diseases has been recognized by all stakeholders who endorse the need for flexibility in the regulatory review process for novel therapeutics to treat rare diseases.

In the United States, the best expression of this flexibility was the creation of the Accelerated Approval (AA) pathway. The AA pathway is critically important for the development of treatments for diseases with high unmet medical need. In 2012, the AA provisions were amended to enhance the application of the AA pathway to expedite the development of drugs for rare disorders under the FDA Safety and Innovation Act (FDASIA). FDASIA, among many provisions, requires the development of a more relevant FDA guidance on the types of evidence that may be acceptable in support of using a novel surrogate endpoint. The application of AA to rare diseases requires more predictability to drive greater access to appropriate use of AA for more rare disease treatments that might not be developed otherwise.

A scientific framework has been recently proposed for assessing biomarker endpoints to enhance the development of novel therapeutics for rare and devastating diseases currently without adequate treatment.⁴⁴ It is based on the opinions of experts in drug development and rare disease patient groups. Specific recommendations include: (1) establishing regulatory rationale for increased AA access in rare disease programs; (2) implementing a Biomarker Qualification Request Process to provide the opportunity for an early determination of biomarker acceptance; and (3) a proposed scientific framework for qualifying biomarkers as primary endpoints.



However, it should also be emphasized that using biomarkers in biomedical research has several limitations as they may or may not be correlated with clinical outcomes. The use of biomarkers to accelerate the development process is very feasible and appropriate for some portion of the development process. For example, the use of biomarkers as a proof of concept is helpful in early development. Nonetheless, using biomarkers as a surrogate end-point is a difficult proposition for regulatory agencies and health technology assessment (HTA) bodies. In efficacy trials, it is necessary to show that the biomarker is adequately useful, under what circumstances and in which diseases. The implication is thus very disease-specific. It is why, in parallel to efforts to qualify new biomarkers, it is essential to develop also PCOMs in the field of rare diseases.

Developing Outcome Measures for Rare Diseases

Although the task seems enormous as there are over 7,000 identified rare diseases so far, in fact the needs are more restricted as (1) there are clusters of diseases with close expression which may be monitored using same indicators, and (2) only a subset of rare diseases are amenable to interventions requiring the development of outcome measures for their assessment (see Annex 2). So far, there are 450 rare diseases for which a drug has been already marketed in the USA or in Europe.

Data on rare diseases are provided by Orphanet, which is the reference portal for information on rare diseases and orphan drugs. Orphanet offers a range of freely accessible services of interest to identify the needs in the field of outcome measures:

- an inventory of rare diseases and a classification of diseases elaborated using existing published expert classifications;
- an encyclopedia of rare diseases in English and French, progressively translated into the other languages of the website;
- an inventory of orphan drugs at all stages of development;
- a directory of expert resources, providing information on expert clinics, medical laboratories, ongoing research projects, clinical trials, registries, networks, technological platforms and patient organizations, in the field of rare diseases in each country in the Orphanet's consortium;
- a collection of thematic reports, the Orphanet Reports Series, focusing on overarching themes, directly downloadable from the website.

Half of the companies involved in the development of therapies for rare diseases are small- and medium-sized biotechnology companies which do not have the capacity to develop and validate new sets of PCOMs as this is too labor-intensive.

In addition, the rare disease community has a low awareness of methods to define new outcome measures and certainly lacks experience in this domain. This situation suggests that a shared approach to the problem would be a pre-competitive effort likely to meet the needs of the community.

The focus of this document is on clinical outcome measures to be used in clinical trials. However careful thought should also be given to if, and how, these clinical measures used in a trial, could be also used in observational studies, especially in prospective observational studies and to inform economic evaluation.



ISPOR and Outcome Measures in the Field of Rare Disease Trials

ISPOR has a Task Force on outcome measures which has already discussed the specificities of clinical outcome measurement in Rare Disease Clinical Trial. Their main conclusions are summarized below as the report from ISPOR is not yet available.

The Task Force concluded that it is important to remember that each rare disease drug-development program presents different challenges for selecting, developing and implementing outcome measures. No one solution will fit all diverse challenges and only possible solutions can be proposed. The problems raised in rare diseases are the same as for common diseases but magnified due to the small size of the patient population and the multi-systemic and heterogeneous nature of most rare diseases. Heterogeneity impacts the ability to measure across the disease spectrum with small samples.

The first challenge is the yet incomplete understanding of rare diseases. To overcome this difficulty, it is recommended to use all available sources, even in non-traditional approaches, to engage with the rare diseases community, to partner with patient organizations and to collaborate with experts in the field. The second challenge is to define the clinical expression elements. The solution is to focus on the core symptoms, the ones which really impact patients' life and which are likely to be impacted by the treatment. The third challenge is due to the evolutive dimension of most rare diseases, which very often delays the diagnosis. It is important to consider the treatment at different stages of the trajectory and to understand the timeframe from first disease symptoms to diagnosis well. The fourth challenge is the diversity of disease presentation and patient experience. It is why it is recommended to identify the common outcomes associated across phenotypes. The fifth challenge is the impossibility in practice to develop specific outcome measures for every rare disease. The recommendation may be to use previously-validated measures when possible, to adapt measures from similar rare diseases using qualitative and quantitative methods, and to consider including generic or domain-specific instruments when sensitive enough for the treatment. It is also advisable to consider the use of a multi-concept instrument or battery customized to symptom profile with skip patterns. Of course new measures will have to be developed but unfortunately standard methods may not be applicable because of small sample sizes.

Lists of Core Outcomes Developed for Rare Diseases

Currently, no complete database of outcome measures exists, and it is unlikely one will come to existence in the future. Therefore it is more efficient to highlights outcome measures developed for rare diseases in existing databases. The development of a PCOM for rare diseases can be supported by using PROMIS (see annex 1). An example of the development of outcome measures for rare diseases is described by Revicki *et al.*⁴⁵

Additionally, COMET has established a database of the clinical conditions for which either a published core outcome set (COS) exists, or where one is in development. COS are defined by consensus methods, such as Delphi studies, and published COS were found through an earlier systematic review and a recent update.^{46,47} Ongoing COS were identified opportunistically. However, no quality assessment of the published studies has been undertaken to date due to the lack of a well-developed validated quality assessment tool. A list of the COS is provided in Annex 3; rare diseases are highlighted in green, and



conditions highlighted in yellow include some rare diseases or are conditions which can be found in some rare diseases.

COSMIN systematically collects reviews of existing outcome measurement instruments, published in PubMed or Embase. Such systematic reviews could be important tools for the selection of outcome measurement instruments for research and clinical practice and for identifying gaps in knowledge on the quality of outcome measurement instruments, i.e. their measurement properties. A list of articles that are directly or indirectly linked to a rare disease or a group or rare diseases can be found in Annex 4.



Conclusions and Recommendations

Developing patient-centered outcome measures (PCOM) for rare diseases is a necessity. PCOM are the instruments that can be used to measure real benefits for patients and from their perspective. PCOM's insertion into the design of rare diseases registries is necessary to fully evaluate their natural history. However, the process must be done carefully and thoughtfully.

- PCOM need to be relevant, useful and feasible for health care providers in clinical practice
- PCOM should be usable not only to monitor/ evaluate trials results but also for evaluation by regulators and by HTA bodies
- PCOM development for rare diseases should respect the core principles established by PROMIS⁴⁸, COMET⁴⁹ and related initiatives.
- Clear definition of:
 - What to measure, based on qualitative research
 - Why we measure, for what purpose
 - Where measuring takes place
 - Who is qualified to measure (a critical element)
 - How to measure (instrument, scale, etc)
- The Wilson and Cleary model⁵⁰ should be kept in mind, which integrates biological and psychological aspects of health outcomes; it documents consequences of a defective function in a cascade of events from bodily dysfunction to Quality of Life perception.

The first step (i.e. what to measure) can be informed through interviews/focus groups with key stakeholder groups (including clinicians, patients, carers and policy makers). The discussion should start with general questions around the impact of disease and treatment, followed by more detailed questioning regarding outcomes. During the interview stage, attention should be paid to identify both the benefits and harms which patients experience. According to the FDA, benefits are defined as "how patients feel, function and survive."

It is important to keep in mind that qualitative interviewing requires adequate training; without such training the quality and validity of interview data cannot be ensured. The interview process should lead to the development of a conceptual framework of patient concerns as well as data that can be used to identify an item pool to populate a set of scales to measure patients concerns.

Finding already validated instruments is not a trivial task. Databases such as COMET, COSMIN, PROMIS, and PROQOLID are, nonetheless, available and seek to track this information. However, without substantial and continuous funding, maintenance of updated databases is very difficult, especially if the database includes information on the quality of the tools.

COSMIN has published guidelines to assess the quality of instruments.⁵¹ COMET and COSMIN should add a feature to their database to ease the selection of outcome measures developed for rare diseases.



Many rare diseases are complex, multi-systemic diseases. It would be advisable to stratify them into groups sharing the same functional disabilities to facilitate the use of instruments already developed for another disease.

Whenever possible, adaptation of existing tools to the specificities of a rare disease is preferable over the development of a new tool. The most important consideration in tool adaptation is to ensure content validity through qualitative research.

While working in disease-specific silos tends to be the rule in research on common diseases, where large numbers of patients suffer from the same condition, the situation in rare diseases is different: small patient numbers and other factors make international collaboration across diseases and institutions a crucial condition for disease research. The rare diseases community comprises of a network of health professionals, researchers, patients and industry working closely together with personal relationships. Moreover, patients with rare diseases are typically very engaged and invested in research in the area of their condition.

The question of whether it will be necessary to re-validate the instrument for a new rare disease remains open and should be discussed with regulatory authorities at time of scientific advice. Again, if existing measures are used, qualitative efforts to establish content validity is crucial to ensure that patient' most pressing concerns are properly captured. Additional effort will remain necessary for the adoption of instruments developed in another rare disease.

Most rare diseases evolve rapidly over time and require a dynamic model of PCOM. What matters most to patients is often not to lose the functions they still have; stabilization is thus a meaningful outcome to evaluate for severe evolutive rare diseases.

A process that is faster and less expensive to implement is needed. An early strategy is also needed to combine the view of industry, regulatory bodies, HTA and those of patients.

Qualitative research could address critical challenges of outcome measurement in rare diseases, among which: complexity, variability, individualization, lack of background knowledge, small sample sizes, etc. The use of Goal Attainment Scales should also be explored.

If a PCOM used within a rare disease does not measure the concerns that matter to patients, it may appear that a new treatment or intervention has little to no benefit. Engagement of patients in the identification of issues that matter to them, and using their stories to develop or adapt PCOM for us will help to ensure content validity.

PROMIS item banks may serve as a starting point if there is a need to measure generic concepts (e.g. fatigue) in specific rare disease conditions. It is of note that the PROMIS item banks are generic rather than condition-specific and may therefore not measure the concerns that matter the most to particular patient groups. Qualitative research is necessary to ensure that such scales have content validity for patients with rare disease.



An advantage to developing PCOM based on general item banks is the possibility of use of many domains across populations. This approach is considered more patient-friendly although not yet accepted by the FDA and EMA.

The approach to develop PCOM with ability to use computer-adaptive testing represents a promising and efficient new way of administering PCOM; this makes it possible to administer a subset of items in automatable manner and reduce patient burden. Beyond this, a new, more flexible and adaptive way of capturing what matters to patients should be developed. The need for flexibility is not only on what items should be developed, but also on what matters to them.

Developing outcome measures should start early in the research and development process as it is a time-consuming activity. This process also needs to be conveyed to patient organizations who should be engaged in the research process. Patient engagement in the development of outcome measures is essential.

Information regarding the validity of outcomes used should be reported with the trial results in accordance to the CONSORT-PRO ${\rm Extension.}^{52}$

We also recommend asking clinical trial registries to include a section on outcome measures. In addition, the regulatory bodies should disclose the outcome measures on which they granted marketing authorization (The PCOM measurement used can be found in section 5.1 of the Summary of Product Characteristics (SPC) when a product is authorized. In addition, there is a possibility to request access to documents for additional information).

The problem of small numbers has important consequences when it comes to finding enough patients and clinical experts to develop and validate a new PCOM. The rare diseases community expects companies to develop products in areas where no products are yet available; support for the new development of PCOM would be an incentive for that.

In the development of new outcome measures, regulatory bodies should be involved early on to ensure the outcome measures can be used for benefit-risk assessment. Tools and scientific advice are available at the EMA to validate outcome measures for regulatory use.⁵³

Publication of new tools in peer-review journals is highly recommended.

Developing PCOM for rare diseases has to be considered as a non-competitive activity where both data and expertise should be shared. It is acknowledged that sharing data has a financial cost. Patients should make their participation conditional on the ground that results will be shared.

Regulatory bodies would be very interested to see companies using the same PCOM for the same type of clinical problem. A period of embargo is acceptable if the new tool confers a competitive advantage, but this period should be limited.

Sources of funding for the development of PCOM are scarce. Better resources for the development of PCOM should be made available, as well as a mechanism to foster collaboration. All funders need to



consider how they can support the development of PCOM. PCORI, for example, would be an appropriate organization to fund the development of PCOM.

Awareness of best practices is necessary. All existing guidelines must be highlighted, promoted, and disseminated as a support to the rare disease community. Each guideline should be presented with their strengths and weaknesses.

Searching the literature through PubMed may be difficult for rare diseases that have no well-established name. Orphanet has developed search filters to do so; the use of these Orphacodes should also be promoted.

An identical tool used by various groups would ease and standardize training. Ideally, the same outcome measures would also be used for natural history follow-up in untreated patients.

Summer schools for patient representatives have progressively started to include a session on PCOM, and the programming of these sessions should be encouraged.

Training tools should be developed for both professionals and patients; training material should also be developed for expert patients.

Outcomes for economic evaluation are an important area for future research to assess if treatments for rare diseases require a PCOM other than E5QD (EQ-5D^M is a standardized instrument for use as a measure of health outcome).



First IRDiRC Task Force Workshop on Patient-Centered Outcome Measures

The first workshop on PCOM initiatives in the field of rare diseases was held on November 30, 2015 in Paris, France. This workshop was attended by the following members:

- Annemieke Aartsma-Rus (Leiden University Medical Center/ TREAT-NMD, the Netherlands)
- Benoit Arnould (MAPI, France)
- Ségolène Aymé (Coordinator IRDiRC Scientific Secretariat, France)
- Stephen Joel Coons (Critical Path Institute, USA)
- Steven Hass (Genzyme, USA)
- Virginie Hivert (EURORDIS, France)
- Louise Humphrey (C-Path, UK)
- Yllka Kodra (National Centre for Rare Diseases, Istituto Superiore di Sanità, Italy)
- Valérie Legout (Pfizer, USA)
- Samantha Parker (Lysogene, France)
- Kushang Patel (University of Washington, USA)
- Manuel Posada (Instituto de Salud Carlos III, Spain)
- Barbara Prainsack (King's College London, UK)
- Caroline Terwee (VU University Medical Centre / EMGO Institute of Health and Care Research / COSMIN / COMET / PROMIS, the Netherlands)
- Margaret Vernon (ISPOR / Evidera, UK)
- Paula Williamson (University of Liverpool/ COMET, UK)

In addition to the workshop attendees, the following are members of the IRDiRC's PCOM Task Force:

- Stiina Aarum (EMA, UK)
- Jason Arora (ICHOM, UK)
- Melanie Calvert (Birmingham University, UK)
- Stefan Cano (Modus Outcomes/ ScaleReport, UK)
- David Cella (Northwestern University/ NeuroQOL, PROMIS, USA)
- Simon Denegri (NIHR/ INVOLVE, UK)
- Robert Dworkin (University of Rochester Medical Center/ IMMPACT, USA)
- Rachael Fleurence (PCORI, USA)
- Pat Furlong (Parent Project Muscular Dystrophy, USA)
- Kathleen Gondek (Shire, USA)
- Petra Kaufmann (NIH/NCATS/ORDR, USA)
- Thomas Kelley (ICHOM / UK Foundation Program Office, UK)
- Anne Klassen (McMaster University, Canada)
- Yann Le Cam (EURORDIS, France)
- Thomas Morel (KU Leuven, Belgium)
- Claudia Scala Moy (NIH/NINDS, USA)
- Katherine Payne (Manchester University, UK)
- Marshall Summar (PCORI / Children's National Medical Center, USA)



- Jochen Schmitt (Dresden University Hospital / Harmonizing Outcome Measures for Eczema, Germany)
- Sharon Terry (Genetic Alliance, USA)
- ► James Witter (NIH/NINDS / PROMIS, USA)



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