

The impact of FDA and EMA guidances regarding Patient Reported Outcomes (PRO) on the drug development and approval process

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## Table of contents

Table of contents.....	I
List of abbreviations .....	IV
1 Introduction: The increasing role of patient reported outcome measures in drug development.....	1
1.1 Incorporating the patients' perspective in health care .....	1
1.2 Patient reported outcomes in drug development .....	3
2 Relevant guidances on PROs.....	4
2.1 EMA guidances .....	5
2.2 FDA guidances.....	6
3 Labeling claims based on PRO instruments .....	7
4 Study endpoints.....	8
4.1 Study endpoints assessed by PRO instruments .....	9
4.1.1 Single-item PRO instruments .....	10
4.1.2 Multi-item, mono-dimensional PRO instruments.....	10
4.1.3 Multi-item, multi-dimensional PRO instruments .....	10
4.1.4 Health-related quality of life (HRQL) instruments.....	10
4.2 Endpoint model .....	14
4.2.1 Documentation of endpoints - recommendations by FDA.....	14
4.2.2 Documentation of endpoints - recommendations by EMA .....	15
5 Selection of a PRO instrument .....	16
5.1 Choice between existing, modified or newly developed PRO instrument.....	16
5.2 Reasons for inadequate PRO instruments .....	17
6 Development of a PRO instrument .....	18
6.1 Conceptual framework .....	18
6.2 Content validity.....	20
6.2.1 Item generation .....	21
6.2.2 Data collection method and instrument administration mode.....	22
6.2.3 Recall period .....	24

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6.2.4	Response options .....	24
6.2.5	Instrument format, instructions, and training.....	25
6.2.6	Patient understanding .....	25
6.2.7	Scoring of items and domains .....	26
6.2.8	Respondent and administrator burden .....	26
6.2.9	Good research practices on content validation of PRO instruments .....	27
6.3	Reliability, construct validity, and ability to detect changes.....	28
6.3.1	Reliability.....	28
6.3.2	Construct validity.....	28
6.3.3	Ability to detect change .....	29
6.4	Translation and cultural adaption of PRO instruments.....	29
6.5	Timing of PRO instrument development.....	31
7	Implementation of PROs in clinical trials.....	32
7.1	Trial design .....	33
7.1.1	Blinding and randomization .....	33
7.1.2	Trial duration.....	33
7.1.3	Recall periods and frequency of assessment .....	34
7.1.4	Country allocation .....	34
7.2	Quality control .....	34
7.2.1	Trainings on the use of PRO instruments in clinical trials .....	35
7.2.2	Handling missing data.....	36
8	Regulatory Interactions.....	36
8.1	Consultation with the regulatory agencies during PRO instrument development ....	36
8.1.1	Parallel scientific advice at EMA and FDA.....	37
8.1.2	Scientific advice .....	37
8.1.3	Qualification procedure .....	39
8.2	Documentation of PRO instrument properties for submission to the regulatory authorities.....	41
8.2.1	PRO Evidence Dossier.....	41
8.2.2	Documents for Scientific Advice .....	42

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8.2.3	Documents for qualification procedure .....	43
8.2.4	Documents for New Drug Application and Marketing Authorization Application.....	43
8.3	Review Procedures of PRO documents .....	44
8.3.1	FDA review procedure.....	44
8.3.2	EMA review procedure .....	45
8.4	Reasons for the rejection of PRO label claims.....	45
9	Discussion.....	46
9.1	EMA versus FDA guidances: Similarities and differences.....	46
9.1.1	Similarities and differences regarding study endpoints and label claims.....	46
9.1.2	Similarities and differences regarding development of PRO instruments.....	47
9.1.3	Similarities and differences regarding implementation of PRO instruments in clinical trials.....	48
9.1.4	Similarities and differences regarding documentation and regulatory interactions.....	49
9.2	Increased harmonization between EMA and FDA .....	49
10	Conclusion and outlook.....	50
10.1	The impact of FDA and EMA guidances on the drug development and approval process.....	50
10.2	Future trends in patient reported outcomes assessment .....	52
11	Summary .....	53
12	References .....	55
13	Appendix: PRO instruments.....	66

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## List of abbreviations

BLA:	Biologics License Application
CDER:	Center for Drug Evaluation and Research
CHMP:	Committee for Medicinal Products for Human Use
ClinRO:	Clinician Reported Outcome
COPD:	Chronic Obstructive Pulmonary Disease
C-Path:	Critical Path Institute
CRA:	Clinical Research Associate
CRQ:	Chronic Respiratory Questionnaire
CTD:	Common Technical Document
DDT:	Drug Development Tool
EMA:	European Medicines Agency
ERIQA:	European Regulatory Issues on Quality of Life Assessment
FDA:	U.S. Food and Drug Administration
HRQL:	Health-Related Quality of Life
IND:	Investigational New Drug
IRT:	Item Response Theory
ISPOR:	International Society for Pharmacoeconomics and Outcomes Research
IVRS:	Interactive Voice Response System
MAA:	Marketing Authorization Application
MID:	Minimal Important Difference
NDA:	New Drug Application
NPS:	Neuropathic Pain Scale
NRS:	Numerical Rating Scale
ObsRO:	Observer Reported Outcome
OLGA:	Online Guide to Quality of Life Assessment
PI-NRS:	Pain Intensity Numerical Rating Scale
PGR:	Patient Global Rating
PRO:	Patient Reported Outcome
PROM:	Patient Reported Outcome Measure
PROMIS:	Patient Reported Outcomes Measurement Information System
PROQOLID:	Patient Reported Outcomes and Quality of Life Instrument Database
QOL:	QOL
SAP:	Statistical Analysis Plan
SEALD:	Study Endpoints and Labeling Claims Development
SF-36:	Medical Outcomes Study 36-Item Short Form Health Survey
SmPC:	Summary of Product Characteristics
VAS:	Visual Analogue Scale
WHO:	World Health Organization

# 1 Introduction: The increasing role of patient reported outcome measures in drug development

## 1.1 Incorporating the patients' perspective in health care

One of the most important developments in health care in the last decade is the growing interest in the patients' perspective on their illness and treatment [1]. The World Health Organization (WHO) claims that patient involvement in their health care is a social, economic and technical necessity [2] [3].

Nowadays all stakeholders in the health care system acknowledge the central role of the patient [4] [5].

- Patients and patient advocacy organizations
- Physicians, health care professionals and their professional associations
- Institutional health care providers, such as hospitals
- Government agencies, e.g., the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA)
- Health care industry, e.g., pharmaceutical and medical device companies
- Payers, e.g., public and private insurers
- Health care policymakers

The relevant stakeholders for this master thesis are the pharmaceutical companies and the regulatory agencies EMA and FDA.

Indications that pharmaceutical companies adopt patient and people centered strategies are seen in the statements that can be found on the company websites. Statements from five top pharmaceutical companies [6] include:

- Pfizer - Mission: "We will become the world's most valued company to patients, customers, colleagues, investors, business partners, and the communities where we work and live [7]."
- Novartis - Statement Corporate Citizenship: "Novartis Pharmaceuticals Corporation puts patients first [8]."
- Sanofi-Aventis – Commitment: We work to protect the health of the earth's 7 billion inhabitants, improve their quality of life and respond to their potential needs [9].

- Merck – Vision: Our vision is to make a difference in the lives of people globally through our innovative medicines, vaccines, biologic therapies, consumer health and animal products [10].
- Roche - Statement of CEO Severin Schwan: Today our Diagnostics and Pharma Divisions contribute on a broad range of fronts to improving people's health and quality of life [11].

The regulatory authorities EMA and FDA share the view that the patients' perspective is important during the development and approval process for new drugs [12].

The EMA Human Scientific Committees' Working Party with Patients' and Consumers' Organization gives recommendations to the EMA and its committees in the interest of patients regarding medicinal products [13]. Furthermore the EMA encourages patients' and consumers' organizations to get involved in agency activities [14].

The FDA supports programs developed to assure that the patient's point of view is reflected in the regulatory decision-making process [15]. Examples for patient participation programs in FDA regulatory issues are the Patient Focused Drug Development Initiative, the Patient Representative Program Drug Development, and the Patient Consultant Program [16].

The demand of the regulatory agencies for patient-focused drug development can be observed in the fact that since 2005 the EMA and the FDA have published a large number of guidance documents, recommending the inclusion of patient reported outcome (PRO) endpoints in clinical trials. The regulatory agencies published between 1 January 2006 and 15 November 2010 following therapy area-specific guidance documents with PRO endpoints [17]:

- EMA: 34 documents (35,8% of all therapy area-specific guidance documents)
- FDA: 15 documents (39,5% of all therapy area-specific guidance documents)

Apart from the need for patient-focused drug development, there are other reasons for a pharmaceutical company to use PROs in clinical research.

One reason is that the efficacy of a new drug is best assessed by the patient himself (e.g., improvement of pain, effect on health-related quality of life).

Another reason is that rising treatment costs focus attention on the patient's perspective regarding the benefits of a treatment. Health care decision-makers and payers condition the reimbursement of a pharmaceutical product on clinical improvement on how patients survive, function and feel [18].

## 1.2 Patient reported outcomes in drug development

The term "patient reported outcome" (PRO) was established in 2001 by the Patient Reported Outcome (PRO) Harmonization group as an umbrella term to describe a broad spectrum of disease and treatment outcomes based on data provided by the patient himself [12] [19].

The term PRO was quickly adopted by the regulatory agencies.

The EMA defines PRO as "any outcome evaluated directly by the patient himself and based on patient's perception of a disease and its treatment(s)" [20].

The FDA gives following definition:

PRO is "a measurement based on a report that comes directly from the patient (i.e., study subject) about the status of a patient's health condition without amendment or interpretation of the patient's response by a clinician or anyone else [21]."

During the development process of new drugs, PRO data are collected in clinical trials via questionnaires, which are completed by the patient. Less common PRO data may be obtained during an interview, provided that the interviewer records only the patient's response [21] [22]. These questionnaires, which can be variously designed, are called PRO instruments or PRO measures (PROMs) [23].

PRO instruments are used to examine specific concepts (constructs), such as symptoms (e.g., pain), functioning (e.g., activity limitations), health-related quality of life (HRQL), patient global rating of change, patient satisfaction, compliance, or treatment preferences [2] [22].

Not all concepts that are measured by a PRO instrument are suitable to support labeling claims. Only concepts, which are specific measures of treatment benefits, such as symptoms, functioning, HRQL, and patient global rating, can lead to PRO labeling claims granted by EMA and FDA [24] [25].

The concept being measured is one of the characteristics of PRO instruments that are reviewed by the regulatory authorities. The other characteristics relevant for review are [21]:

- Number of items
- Conceptual framework of the instrument
- Medical condition for intended use
- Population for intended use
- Data collection method
- Administration mode
- Response options
- Recall period
- Scoring
- Weighting of items or domains
- Format
- Respondent burden
- Translation or cultural adaptation availability

The characteristics of PRO instruments and their relevance for EMA and FDA in the review process will be discussed in detail in sections 6 (Development of a PRO instrument) and 8 (Regulatory interactions).

## **2 Relevant guidances on PROs**

In the light of patient-centered development of new drugs, the EMA and the FDA are very interested to have PRO data from clinical trials included in marketing authorization applications respectively in new drug applications [2].

Both key regulatory agencies produced several guidance documents on the use of PROs to support label claims.

The most relevant guidance documents on PRO for this master thesis will be presented in this section. The guidance documents and their impact on the drug development and submission process will be discussed in the following sections.

## 2.1 EMA guidances

***European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP). Reflection Paper on the Regulatory Guidance for the Use of Health-Related Quality of Life (HRQL) Measures in the Evaluation of Medicinal Products; 27 July 2005. [20]***

In July 2005 the EMA released this Reflection Paper with broad recommendations on the use of Health-Related Quality of Life (HRQL), a specific PRO concept. The document applies only to HRQL and not to other PROs. It is not conceived as a guidance document regarding the methodology of HRQL, but describes how HRQL can be integrated in clinical trials and HRQL data can be used in a submission to support label claims [2] [26].

The understanding of the EMA is that symptoms of a disease assessed by the patient himself are well established primary and secondary endpoints in clinical trials and a formal guidance document on the use of PROs that measure symptoms is not needed. These PRO endpoints are assessed by the EMA like any other clinical endpoint [20] [27] [28].

For specific diseases, the EMA recommends the inclusion of PRO endpoints in clinical trials. In 34 of 95 (35.8 %) disease specific guidance documents, which were released between January 2006 and November 2010, recommendations for PRO endpoints (mostly symptoms and HRQL) are included. The 34 guidance documents were released for following disease areas: infectious diseases, diseases of the respiratory system, mental and behavioral disorders, pain, cancer, musculoskeletal, gastrointestinal, cardiovascular, metabolic, and allergic diseases [17]. An example is the guideline regarding Osteoarthritis.

***Guideline on Clinical Investigation of Medicinal Products in the Treatment of Osteoarthritis; 20 January 2010. [29]***

In this guidance document for clinical trials a range of PRO concepts (symptom pain, functional disability, HRQL, patient global assessment of disease activity) and PRO instruments (pain: visual analogue scales, numerical rating scale; functional disability: validated disease specific and joint specific instruments) are recommended.

***Qualification of novel methodologies for drug development: guidance to applicants; 09 January 2012. [30]***

This guidance document describes a new and voluntary process for pharmaceutical companies to obtain qualification opinion from the EMA on the acceptability of the use of novel methodologies. The guidance document is also applicable for novel HRQL/PRO instruments [28] [31].

## 2.2 FDA guidances

***US Department of Health and Human Services, US Food and Drug Administration: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. December 2009. [21]***

The FDA issued this formal guidance on the use of PRO measures (PROMs) to support labeling claims in December 2009. The FDA expects that all instruments that measure PRO and generate data for label claim submission (e.g., symptoms, HRQL) meet the criteria determined in the guidance document. The adequacy of any PRO instrument has to be demonstrated in a PRO Evidence Dossier [2] [27].

The FDA has also produced several disease-specific guidance documents with the recommendation to include PRO endpoints. 15 of 38 (39.5 %) disease specific guidance documents that were released between January 2006 and November 2010 recommend including PRO endpoints in clinical trials. The guidance documents were released for several disease areas: diseases of the respiratory system, infectious diseases, mental disorders, cancer, metabolic and gastrointestinal diseases, and dermatology [17]. An example is the guideline regarding Chronic Obstructive Pulmonary Disease (COPD).

***Guidance for Industry: Chronic Obstructive Pulmonary Disease: Developing Drugs for Treatment. Draft Guidance. November 2007. [32]***

In this guidance for industry the FDA recommends a range of PRO concepts (COPD symptoms, activity, HRQL) and PRO instruments (COPD symptoms: categorical, visual, or numeric scales; activity: Medical Research Council dyspnoea score, Borg scale, Beck depression inventory; HRQL: chronic respiratory questionnaire, patient diaries) for clinical trials.

***US Department of Health and Human Services, US Food and Drug Administration: Qualification Process for Drug Development Tools. Draft October 2010. [33]***

This draft guidance includes background informations and procedures regarding the qualification process for new drug development tools such as new PRO instruments. The proposed qualification process for a new PRO instrument includes two stages. Stage 1: Consultation and Advice; Stage 2: Review for Qualification Decision [34] [35].

### 3 Labeling claims based on PRO instruments

In the last two decades and specifically since 2006, after the EMA HRQL Reflection Paper in July 2005 and the FDA PRO Draft Guidance in February 2006 were published, the use of PROs in clinical trials to support labeling claims has increased [36] [37]. The FDA defines a labeling claim as a statement of treatment benefit, which can appear in any section of a medical product labeling [21].

Marquis et al. (2011) [17] and Gnanasakthy et al. (2012) [24] have reviewed the extent to which PROs have played a role in drug labeling between 2006 and 2010. EMA and FDA decisions on PRO labeling claims were compared. Here are the results:

Marquis et al. (2011) [17]:

- For 54 (22 %) out of 248 approved pharmaceutical products the EMA granted one or more labeling claims.
  - 48 products (89 % of all products with a PRO claim) with symptoms in label.
  - 16 products (30 % of all products with a PRO claim) with HRQL in label.
- For 93 (22 %) out of 432 approved pharmaceutical products the FDA granted one or more labeling claims.
  - 79 products (85 % of all products with a PRO claim) with symptoms in label.
  - 8 products (9 % of all products with a PRO claim) with HRQL in label.

Gnanasakthy et al. (2012) [24]:

75 new pharmaceutical products (generic products were not considered) were approved by both the EMA and the FDA between 2006 and 2010.

Of these 75 pharmaceutical products

- 35 products (47%) obtained one or more PRO claim from the EMA.
  - 19 products (54 %) with symptoms in label.
  - 9 products (26 %) with functioning in label.
  - 13 products (37 %) with HRQL in label.
  - 5 products (14 %) with patient global rating in label.
- 14 products (19%) obtained one or more PRO claim from the FDA.
  - 12 products (86 %) with symptoms in label.
  - 5 products (35 %) with functioning in label.
  - 2 products (14 %) with HRQL in label.
  - 3 products (21 %) with patient global rating in label.

Despite the differences in the scientific approach of the two reviews, it is possible to conclude as follows:

- The patient's perspective in clinical research is important for the EMA and the FDA. A considerable number of PRO labeling claims are granted for new pharmaceutical products.
- The most labeling claims in Europe and USA are for symptoms. HRQL claims are playing a smaller role.
- The EMA granted significantly more HRQL claims than the FDA, which rarely grants HRQL label claims.

Another review by Caron and Emery (2010) [38] assessed for which indications pharmaceutical products with PROs as primary endpoint were approved. The most frequent indications for the relevant 282 products approved by the EMA and the FDA between 1995 and 2010 were: pain (25 products), rheumatoid arthritis (25), menopause (18), Parkinson's disease (17), epilepsy (15), migraine disorder (13), sleep disorder (12), allergic rhinitis (12), and ankylosing spondylitis (10).

These results show that symptoms (e.g., pain), which can only be measured by patients, are still the common PROs. More sophisticated PROs, such as HRQL, are used less often.

In the USA, the PRO label claims granted by the FDA can be used for direct-to-consumer advertising. Direct-to-consumer advertising is not allowed in Europe, but the PRO label claims granted by the EMA can be used to inform physicians about the efficacy of a drug and their additional value for the patient [37].

## 4 Study endpoints

According to EMA HRQL Reflection Paper [20] and the FDA PRO Guidance [21] HRQLs and PROs can be used as primary or key secondary study endpoints to support label claims on condition that validated instruments are used in controlled, well-designed clinical trials.

A study endpoint is defined by the FDA as "the measurement that will be statistically compared among treatment groups to assess the effect of treatment and that corresponds with the clinical trial's objectives, design, and data analysis." [21]

### Primary endpoints:

A primary endpoint typically assesses the core symptom(s) of the disease to evaluate whether the treatment resulted in symptomatic relief or not [25]. If there are two or more primary endpoints considered equally important, they are called co-primary endpoints [39].

### Key secondary PRO endpoint:

A key secondary endpoint provides additional information to evaluate the effect of the treatment on the primary endpoint [25].

Only primary or key secondary endpoints in a clinical trial can support a label claim [25].

The assessment of study endpoints can be classified in the following way [18]:

- Record-based assessments (e.g., death)
- Biological & anthropomorphic assessments
  - Vital signs (e.g., weight, height, pulse, blood pressure, temperature)
  - Analysis of tissue samples
  - Data from medical or imaging devices
  - Machine-assessed functioning (e.g., treadmill tests)
- Subjective assessments
  - Measurements based on patient self-report (PROs)
  - Clinician reported outcomes (ClinROs)
  - Observer reported outcomes (e.g., technicians, family, friends, teachers of the patient) (ObsROs)

## **4.1 Study endpoints assessed by PRO instruments**

The EMA defines PRO instruments as a large set of patient-assessed measures ranging from single-item to multi-item instruments. Multi-item PRO instruments can be mono-dimensional measuring a single well-defined concept or multi-dimensional questionnaires measuring broad concepts. PRO instruments provide information on the patient's perspective of a disease and its treatment [40].

#### **4.1.1 Single-item PRO instruments**

A single-item PRO instrument measures one single item.

Examples for a single-item PRO instrument measuring pain are the Pain Visual Analogue Scale (Pain VAS) and the 11-point pain intensity numerical rating scale (PI-NRS). The scales can be found in Appendix, PRO instruments 1 – 2.

#### **4.1.2 Multi-item, mono-dimensional PRO instruments**

A multi-item, mono-dimensional PRO instrument measures a single construct (e.g., physical functioning, fatigue, sexual function) with a series of items [40].

An example for a multi-item, mono-dimensional PRO instrument measuring fatigue is the Fatigue Severity Scale, which can be found in Appendix, PRO instrument 3.

#### **4.1.3 Multi-item, multi-dimensional PRO instruments**

A multi-item, multi-dimensional PRO instrument measures broad concepts such as psychological function, satisfaction, well-being or health-related quality of life (HRQL) [41].

An example for a multi-item, multi-dimensional PRO instrument measuring psychological function is the Neuropathic Pain Scale (NPS) (see Appendix, PRO instrument 4).

#### **4.1.4 Health-related quality of life (HRQL) instruments**

Health related quality of life (HRQL) is one of the most complex concepts that can be measured by a PRO instrument [42].

The EMA HRQL Reflection Paper defines health-related quality of life as a “broad concept which can be defined as the patient’s subjective perception of the impact of his disease and its treatment(s) on his daily life, physical, psychological and social functioning and well-being.” [20]

The definition of the FDA, given in the FDA PRO Guidance, is very similar: “HRQL is a multi-domain concept that represents the patient’s general perception of the effect of illness and treatment on physical, psychological, and social aspects of life.” [21]

In order to measure a combination of symptoms and functioning to obtain information on physical, psychological, and social aspects of life HRQL Instruments have to be composed of multi-items and multi-domains. HRQL instruments usually assess several domains and provide a profile of scores [22].

A HRQL instrument may be generic or disease-specific. A generic instrument is designed to be used in a wide range of disease populations and interventions. Disease-specific HRQL instruments are intended to be used in a certain disease population (e.g., patients with COPD) or for particular interventions [22].

#### Generic HRQL instrument

The most commonly used generic HRQL instrument is the Medical Outcomes Study 36-Item Short Form (SF-36) health survey [43]. A schematic diagram of SF-36 is shown in Figure 1, the complete SF-36 questionnaire can be found in Appendix, PRO instrument 5A and 5B.

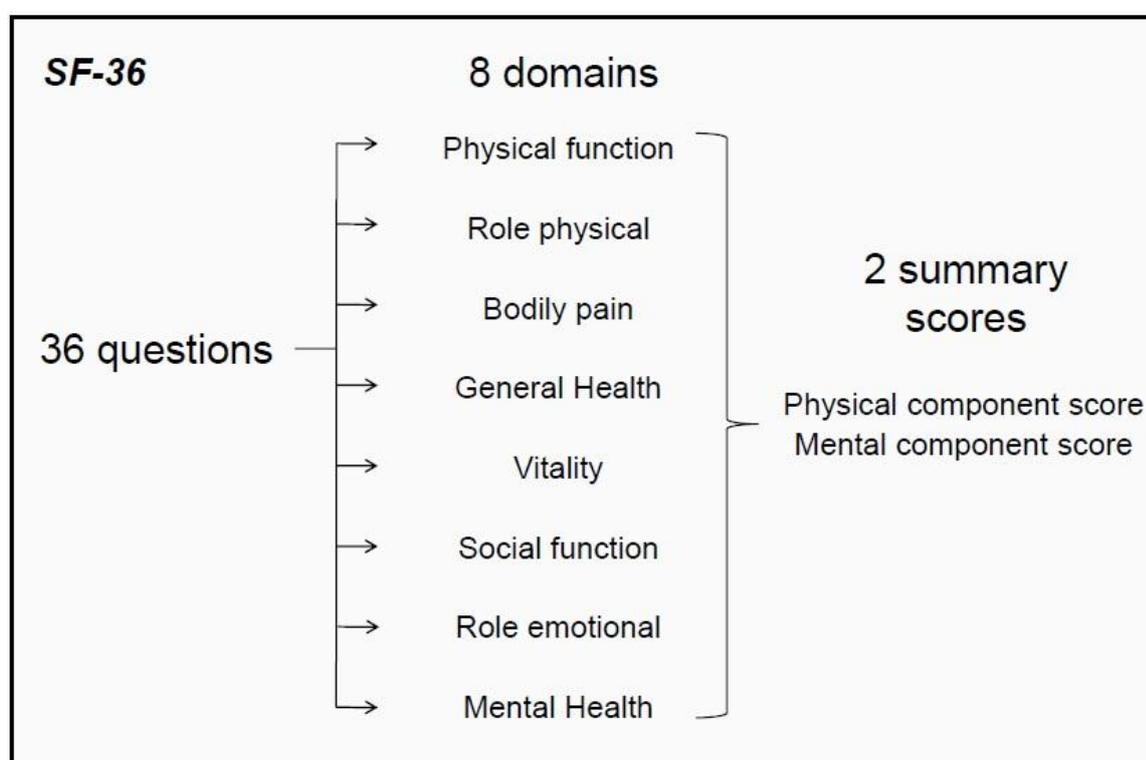


Figure 1: Schematic diagram of SF-36 (taken from [44])

The SF-36 questionnaire measures, on the basis of 36 items (questions) and 8 multi-item scales (domains) the physical component score and the mental component score. The scores are transformed to a 0 to 100 scale, in which higher scores indicate better health [43].

### Disease-specific HRQL instrument

An example for a disease-specific HRQL questionnaire is the Chronic Respiratory Questionnaire (CRQ). Figure 2 shows a schematic diagram of CRQ. In Appendix, PRO instrument 6, examples of Chronic Respiratory Questionnaire (CRQ) questions are displayed.

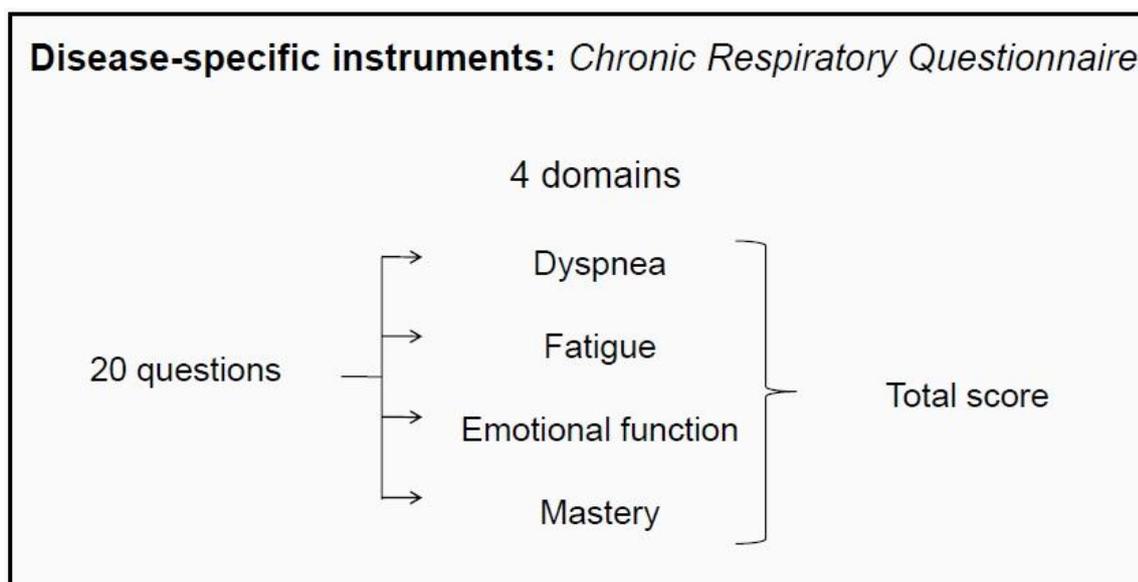


Figure 2: Schematic diagram of CRQ (taken from [44])

If a pharmaceutical company aims for a label claim “improvement of health-related quality of life”, following statement regarding HRQL instruments in the guidance documents of both regulatory agencies have to be considered.

### EMA HRQL Reflection Paper [20] [29]:

- HRQL should be clearly differentiated from the core symptoms of a disease, as core symptoms are well-accepted primary and secondary efficacy endpoints in registration trials.
- A PRO instrument should be chosen that is designed to explore the domains relevant for the disease and its treatment.
- Generic and disease specific questionnaires may be used, but it is very important to choose the questionnaire which is most suitable to explore the domains relevant for the disease and its treatment(s).
- A claim regarding improvement in HRQL needs to be supported by data collected by validated instruments.

- A HRQL instrument should be validated in therapeutic exploratory (Phase 2) trials by testing and documenting validity, reliability, responsiveness and interpretability for the specific condition/setting before it is implemented in therapeutic confirmatory (Phase 3) trials. Instruments should not be validated using data from the same pivotal clinical trials that are used to test the HRQL endpoint.
- Evidence of the cultural adaptation and/or translation of an HRQL instrument is needed (if applicable).

#### FDA PRO Guidance [21]:

- The HRQL instrument has to measure all HRQL domains that are important for interpreting change in how the clinical trial's population feels or functions as a result of the targeted disease and its treatment.
- PRO instruments that measure a simple concept are not adequate to measure a complex, multi-domain concept such as HRQL.
- A complex, multi-domain claim (such as improvement of HRQL) cannot be substantiated by instruments that do not adequately measure the individual component domain concepts.

In disease-specific guidance documents issued between January 2006 and November 2010 the inclusion of HRQL as primary or secondary endpoint was recommended by the EMA in 22 of the 34 guidances (65%). The FDA recommends improvement of HRQL only in 3 of the 15 guidances (20%) and only as secondary endpoints [17].

This facts show that the EMA's receptivity to HRQL endpoints is greater than the FDA's and that HRQL endpoints are playing a minor role in label claims granted by the FDA.

An example for a medicinal product that obtained approval for HRQL label claims from both agencies is Soliris (eculizumab). Soliris is a monoclonal antibody developed for the treatment of primary nocturnal hemoglobinuria, an orphan disease, and is in the moment the world's most expensive drug (treatment costs \$ 409,500 per year) [18]. In the USA and Europe a label statement reads: "After 3 weeks of Soliris treatment, patients reported less fatigue and improved health-related quality of life." [17]

## 4.2 Endpoint model

For study endpoints used in clinical trials that are intended to support label claims the EMA and the FDA advise that sponsors document the hierarchy of the endpoints, the relationship between different endpoints (PRO and non-PRO), and the value of the endpoints [27].

### 4.2.1 Documentation of endpoints - recommendations by FDA

The FDA recommends sponsors to show the relationship between different endpoints, both PRO and non-PRO, in an endpoint model [27].

In the PRO Guidance the FDA defines an endpoint model as

- a clear statement on the role a PRO endpoint intends to play in the clinical trial, and
- a diagram of the hierarchy of relationships among all clinical trial endpoints [21].

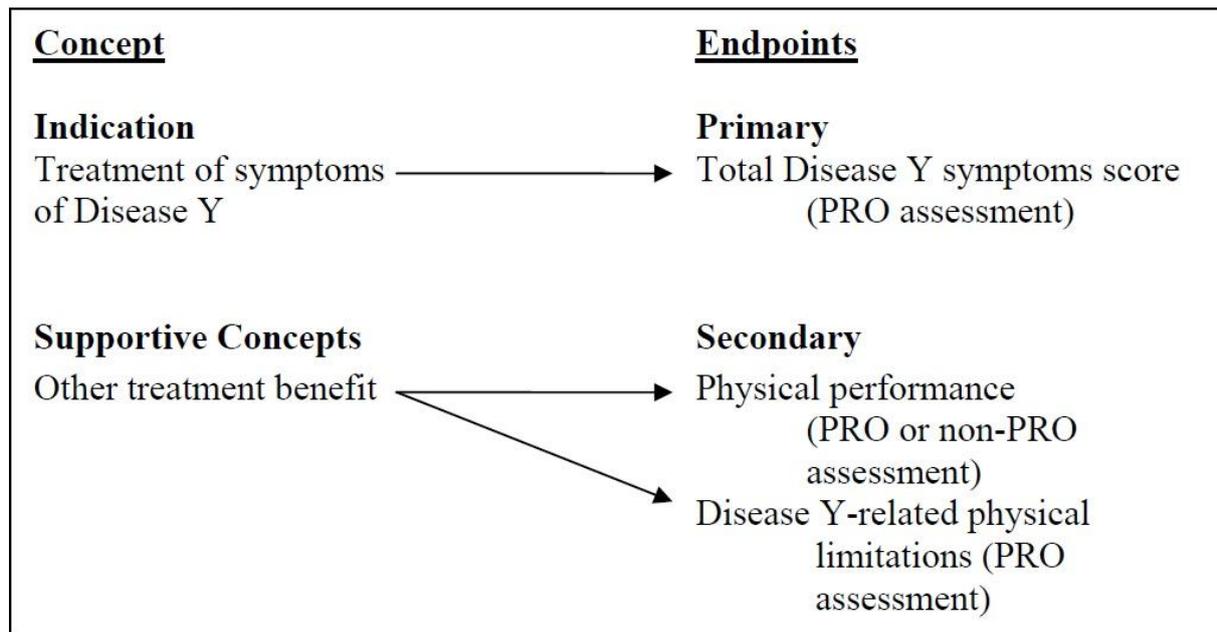


Figure 3: Endpoint Model (taken from FDA PRO Guidance [21])

Figure 1 shows an example of an endpoint model, taken from the FDA PRO Guidance [21]. The PRO symptom assessment is the primary endpoint intended to support an indication for the treatment of symptoms associated with Disease Y. The physical performance and limitation measures would be the key secondary endpoints.

The FDA recommends that for all PRO and non-PRO endpoints, which are intended to support a labeling claim, an endpoint model is developed, documented and submitted in the PRO Evidence Dossier [21].

#### 4.2.2 Documentation of endpoints - recommendations by EMA

The EMA does not specifically recommend the use of an endpoint model to demonstrate relationships between endpoints, but states that clear definitions of all endpoints, hierarchy and expected claims are always required for all new applications [28].

In disease specific guidance documents, the EMA suggests specific primary and secondary endpoints for most therapeutic fields [27].

An example is the EMA Guideline on Clinical Investigation of Medicinal Products in the Treatment of Osteoarthritis [29]. In chapter 5.1 primary, co-primary and secondary endpoints are recommended:

Primary endpoint: Pain attributable to the target joint (measured with visual analogue scales or numeric rating scales)

Co-primary endpoint: Functional disability (measured by disease-specific and joint-specific instruments)

Secondary endpoints (should be chosen in line with the pharmacological characteristics of the drug and the claimed indication): pain intensity (additional measurement time point); patient's global assessment of disease activity; treatment response; percentage of patients having reached the patients acceptable symptom state; percentage of patients achieving an improvement > minimal clinically important improvement; Osteoarthritis Research Society International set of responder criteria; physician's global assessment of disease activity; total osteoarthritis questionnaire; quality of life (e.g., including mood, sleep, disability); consumption of rescue medication.

If a novel PRO can be used as a primary endpoint the EMA will decide on a case by case basis. A clear and detailed justification for the use of the PRO is needed.

The use of a new PRO as a secondary endpoint is acceptable when the expected claim and the relation to other endpoints are plausible [28].

## **5 Selection of a PRO instrument**

PRO data, which are intended to support a label claim, must be generated in a scientific way. This includes the choosing of appropriate endpoints for the clinical trials, the selection or development of adequate and valid PRO instruments, and scientifically sound data collection, analysis and interpretation [42].

### **5.1 Choice between existing, modified or newly developed PRO instrument**

If a pharmaceutical company plans to use PRO instruments during the medical product development, the FDA encourages the company to determine early in the development process if an appropriate PRO instrument exists to measure the concept of interest. If the existing instruments are not adequate, the FDA recommends that a new PRO instrument be developed from scratch or that an existing instrument be modified for the purpose [21].

The FDA states that the adequacy of an existing, modified or newly developed PRO instrument as a measure to support medical product labeling claims depends on whether its measurement properties are satisfactory. The measurement properties that have to be verified are content validity, construct validity, reliability, ability to detect change, conceptual framework, and the instrument characteristics. The pharmaceutical company has to provide the required information on the measurement properties in the PRO Evidence Dossier [21].

The EMA recommends that PRO instruments, which are composed of multi-items and multi-domains (e.g., HRQL instruments), are validated in therapeutic exploratory trials before their implementation in therapeutic confirmatory trials. The PRO instrument should be validated by testing and documenting validity, reliability, responsiveness and interpretability for the specific condition/setting [20].

It is recommended that a pharmaceutical company relies on specialists to select and develop appropriate PRO instruments [22]. There are various service companies that can be hired to advise or assist the pharmaceutical company regarding selection, validation, development, and licensing of PRO instruments.

Research for existing PRO instruments can be done in several data bases. Examples are as follows:

- Patient Reported Outcomes Measurement Information System (PROMIS)  
PROMIS was funded by the National Institutes of Health and is a system of highly reliable, valid, flexible, precise, and responsive assessment tools that measure patient reported health status [45] [46].
- Patient Reported Outcomes and Quality of Life Instrument database (PROQOLID)  
PROQOLID was developed and is managed by MAPI Research Trust and aims to identify and describe PRO and QOL instruments to help researchers and companies to choose appropriate instruments and facilitate the access to them [47] [48].
- The Online Guide to Quality of Life Assessment (OLGA)  
OLGA is a source of information about questionnaires, rating scales and other tools for assessing psychosocial effectiveness in clinical trials [2] [49].

## 5.2 Reasons for inadequate PRO instruments

The pharmaceutical companies do not always use the most appropriate or efficient instruments. The reasons are as follows [2] [22]:

- PRO instrument selection is often based on availability or familiarity rather than on considerations of instrument relevance or validity.
- The instruments are selected ahead of more appropriate instruments, because they are considered to be the standard instrument in that disease area, they are used by a competitor or they are available in a wide range of languages.
- Due to a limited budget or aggressive timelines too little money or time is spent on the selection and development of the most suitable PRO instrument for the target population and indication of a new medicinal product.

The use of inappropriate PRO instruments and missing verification of the measurement properties of PRO instruments implemented in clinical trials are often reasons for rejection of PRO label claims [50].

## 6 Development of a PRO instrument

As Figure 4 “Development of a PRO Instrument” illustrates, the development of a PRO instrument is a complex and time consuming process that is divided in several steps.

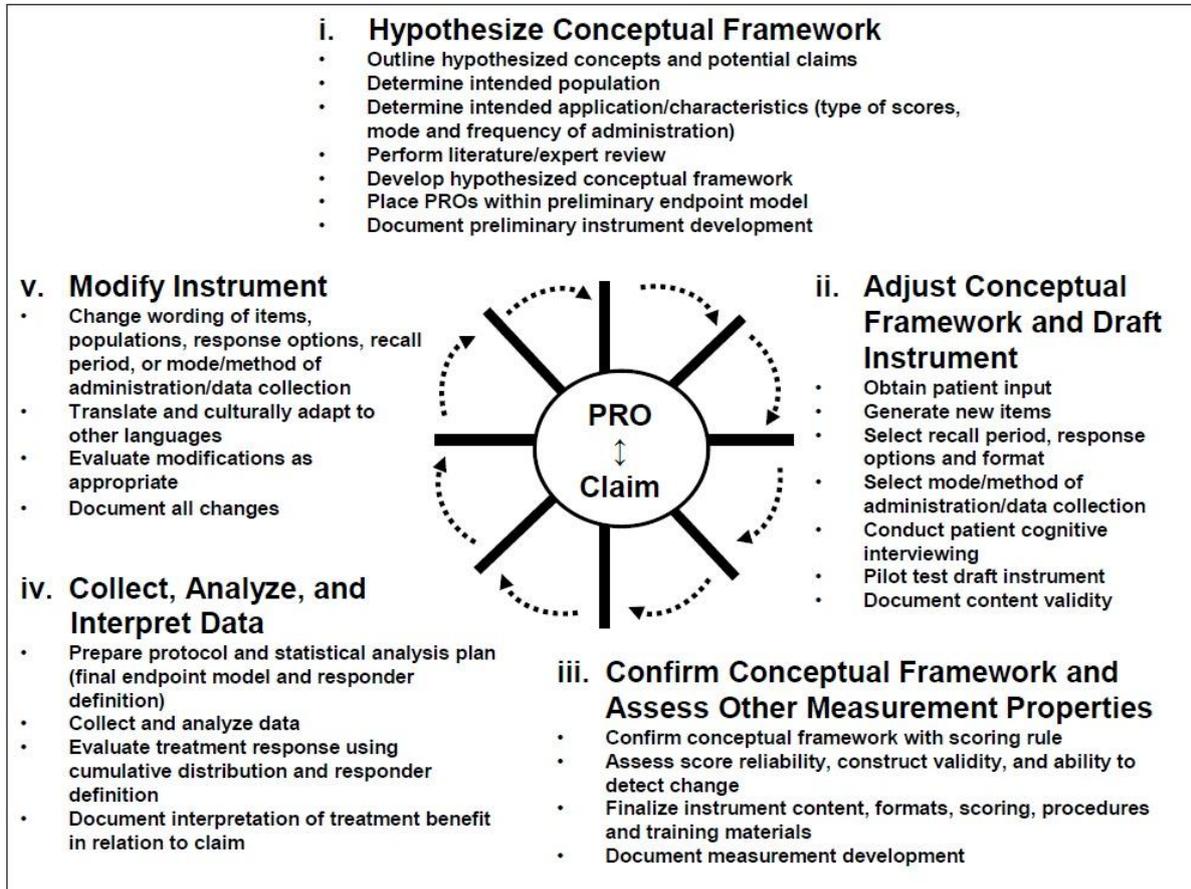


Figure 4: Development of a PRO Instrument in 5 steps (taken from the FDA PRO Guidance [20])

### 6.1 Conceptual framework

The first step during the development of a PRO instrument is to hypothesize the conceptual framework, which will be adjusted and confirmed during the next development steps [41].

The conceptual framework of a PRO instrument, by FDA definition, is “an explicit description or diagram of the relationships between the questionnaire or items in a PRO instrument and the concepts measured. The conceptual framework of a PRO instrument evolves over the course of instrument development as empiric evidence is gathered to support item grouping and scores.” [21]

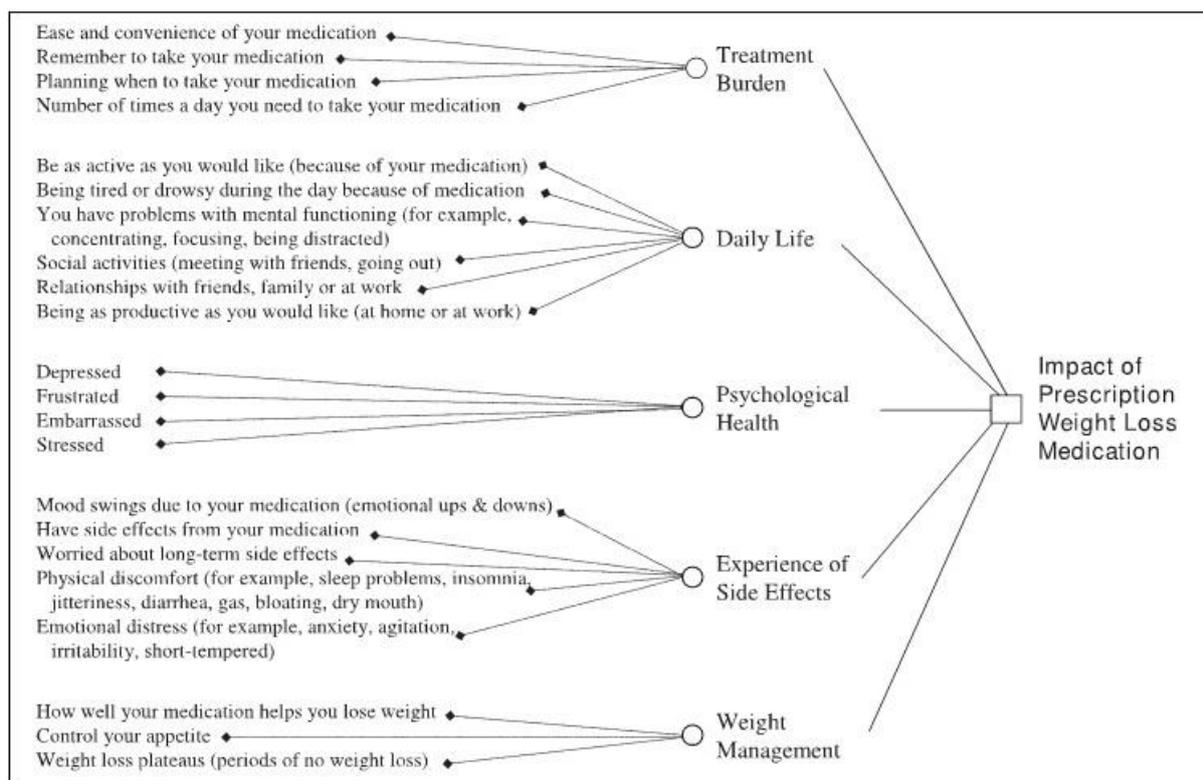


Figure 5: Diagram of the Conceptual Framework of a PRO instrument that measures the impact of weight loss medication (taken from [51])

Figure 5 shows an example of a conceptual framework of a PRO instrument. The diagram shows the relationships between items (e.g., ease and convenience of medication), domains (e.g., about treatment burden) and the general concept (impact of prescription weight loss medication) measured by the PRO instrument.

The development of a conceptual framework is based on the targeted claim, the intended population and application, a review of disease-specific literature, and input from experts, physicians and patients. It is an iterative process of item reduction and validation using psychometric procedures. A thoroughly generated conceptual framework is important, as it supports the rationale for PRO instrument development in relation to a specific product claim [52].

The FDA reviews the alignment of the final conceptual framework with the objectives, design, patient population, and analysis plan of the clinical trials and the proposed label claim during the PRO instrument review [21].

The EMA reviews the conceptual framework during the validation of (multi-item, multi-dimensional) PRO instruments to verify its functional performance [28].

## 6.2 Content validity

A PRO instrument, its items, domains, and scores, has to reflect what patients consider the most important outcomes of the disease and its treatment. This is called the content validity of the PRO instrument [53].

Definitions and statements from the FDA regarding content validity are given in the FDA PRO Guidance [21].

- Content validity is the extent to which the instrument measures the concept of interest for the intended population and use.
- Content validity is supported by evidence from qualitative studies that the items and domains of an instrument are appropriate and comprehensive.
- Content validity is specific to the population, condition, and treatment to be studied.
- Documentation of patient input in item generation and evaluation of patient understanding through cognitive interviewing can contribute to evidence of content validity.

To prove content validity, the sponsor has to test the instrument in the target patient population and in a context, which is similar to the setting the clinical trial will eventually be performed in [53]. The evidence of the content validity of a PRO instrument should be based on a systematic process of collecting qualitative data to show the link between the opinions and concerns of the patients and the items and structure of the PRO instrument [54]. Quantitative data can contribute to content validity evidence, but are not sufficient on their own [55].

Qualitative and quantitative data to evidence content validity can be collected in different ways [21] [56] [55].

- Literature review and expert opinion on concept, disease, and existing instrument.
- Patient input obtained through focus group testing or open-ended patient interviews.
- Testing of draft PRO instruments using cognitive patient interviews.

The data collection should be guided by qualitative research protocols and an analysis plan [56]. The statistical exploration of the data can be done with the help of text analysis software, factor analysis, Rasch analyses, or item response analysis [41].

Both regulatory agencies, the FDA and the EMA, evaluate the content validity to assess if a PRO instrument is suitable for the clinical trial target patient population and for the target indication of a new medicinal product [37]. The FDA PRO Guidance gives detailed recommendations on the information that should be provided by the sponsor to document the content validity of a new PRO instrument. The EMA HRQL Reflection Paper does not include specific guidances on the documentation of content validity, but it is recommended by the EMA to rely on the FDA PRO Guidance [28].

In the FDA PRO Evidence Dossier the adequacy of a PRO instrument's content validity should be documented by the following development processes and instruments attributes, which will be outlined on the next pages:

item generation; data collection method and instrument administration mode; recall period; response options; instrument format, instructions, and training; patient understanding; scoring of items and domains; respondent and administrator burden [21].

### **6.2.1 Item generation**

According to the FDA PRO Guidance, following should be considered when generating items (questions) for PRO instruments [21]:

- Items should be derived from interviews with relevant patients. (Thirty to thirty-five interviews are usually sufficient to generate items [22].)
- The input of a wide range of patients with the condition of interest is important to reflect variations in disease severity and in population characteristics (age, sex, ethnicity, and language groups).
- The interviewed patients will help generate item wording, evaluate the completeness of item coverage, and perform initial assessment of clarity and readability.
- PRO instrument items can also be generated from literature reviews, transcripts from focus groups, clinicians, family members or researchers, but patient interviews are always required.
- When using multi-item instruments, it is important that all items be relevant to most of the patients in the clinical trial.

Documentation provided to the FDA to support content validity should include all item generation techniques used, including any theoretical approach; the populations studied; source of items; selection, editing, and reduction of items; cognitive interview summaries or transcripts; pilot testing; importance ratings; and quantitative techniques for item evaluation [21].

### 6.2.2 Data collection method and instrument administration mode

The data collection method and the instrument administration mode of a PRO instrument are other attributes that are reviewed by the regulatory authorities to verify content validity of the instrument.

There are two different instrument administration modes [21] [57]:

- Self administration:
  - PRO data are collected via questionnaires, which are completed by the patient himself.
  - Advantages: cost-effective, patient can answer questionnaire at own pace
  - Disadvantages: risk of missing data, requires simple design of instrument
- Interviewer administration:
  - PRO data are obtained by interview. The interviewer records only the patient's response without any interpretation.
  - Advantages: more complex questionnaires possible, useful for patient with reading or vision difficulties
  - Disadvantages: interviewer costs, potential for bias (e.g., interviewer bias, social desirability bias)

The following data collection methods are possible for PRO instruments [21] [57]:

- Paper-based assessment
  - Examples: questionnaires, diaries
  - Advantages: cost-effective
  - Disadvantages: risk of data entry errors, data entry and scoring are time-consuming
- Telephone based assessment
  - Examples: Interactive Voice Response System (IVRS)
  - Advantages/Disadvantages: see computer-assisted assessment
- Computer-assisted assessment (electronic PRO instruments)
  - Examples: laptop computers, touch-screen computers, web-based systems, web-enabled mobile phones.
  - Advantages: interactive, practical, minimizes risk of data entry errors, immediate scoring feedback, possible real-time PRO data transfer, ability to time stamp records
  - Disadvantages: cost-intensive (software and/or devices), potential discomfort with technology, potential problems with accessibility

The FDA will review data quality control procedures specific for the data collection method or instrument administration mode. The sponsor has to provide copies or screen shots of the PRO instruments, of the case report forms, and of the instructions to patient and/or interviewers [21]. An example for an ePRO instrument (touch-screen computer) can be found in Appendix, PRO instrument 7.

#### Considerations regarding electronic PRO instruments

The collection of patient data by ePRO instruments has become an important and widespread methodology in clinical trials during the last decade. The reason for this development are the advantages of ePRO use, for instance the transfer of PRO data in real-time to the clinical trial team, data management and investigators, the possibility to time stamp records (e.g., in electronic patient diaries), and the minimization of data entry errors [36] [58].

The FDA reacted to the increased use of ePRO instruments by implementing specific requirements regarding ePRO instruments in the FDA PRO Guidance to ensure that the electronic systems are valid and reliable, and that obtained data are protected from manipulation and disclosure to unauthorized third parties [21] [59]. In addition the FDA Guidances for Industry “Part 11, Electronic Records; Electronic Signatures - Scope and Application” [60] and “Computerized Systems Used in Clinical Investigations” [61] are applicable for ePRO instruments.

In Europe the EMA “Reflection paper on expectations for electronic source data and data transcribed to electronic data collection tools in clinical trials” [62] provides guidance on the implementation and use of ePRO instruments in clinical trials.

For the development of ePRO instruments, pharmaceutical companies can seek advice through the following organizations.

- C-Path Electronic Patient-Reported Outcome (ePRO) Consortium

The C-Path ePRO Consortium was established by the Critical Path Institute (C-Path). C-Path is a nonprofit, public-private partnership under the auspices of the FDA's Critical Path Initiative program. The ePRO Consortium provides methodological guidance on measurement issues related to ePRO applications [63] [64].

- ISPOR ePRO Good Research Practices Task Force

The International Society for Pharmacoeconomics and Outcomes Research (ISPOR), an international non-profit public organization, promotes the science of pharmacoeconomics and outcomes research. The ISPOR ePRO Good Research Practices Task Force develops principles of good practice surrounding the migration of paper-based PRO instruments to ePRO instruments and assist companies in assessing ePRO data collection systems [65] [66].

### 6.2.3 Recall period

The recall period is defined in the FDA PRO Guidance [21] as “period of time patients are asked to consider in responding to a PRO item or question. Recall can be momentary (real time) or retrospective of varying lengths.” The selection of the most appropriate recall period for a PRO instrument depends on the instrument’s purpose and intended use, the patient population, the disease, the tested treatment, and the clinical trial design. Patient burden and patient understanding of the recall period should also be considered [21] [67].

The FDA assumes that recall periods longer than 7 days could cause recall bias, as the response can be affected by the patient’s state at the time of recall or the patient averages responses over a period of time. As recall bias could negatively affect the content validity of a PRO instrument, the choice of recall periods longer than 7 days should be justified based on qualitative and quantitative data [21] [67].

The FDA recommends including short recall periods that ask patients about their current or recent state, their best or worst experience over the recall period, or the use of a diary. For symptom endpoints (e.g., pain intensity) the FDA favors the use of a daily diary, preferably an electronic diary to secure a time stamp of completion [27] [68]. The EMA has no specific requirements for PRO instrument regarding the recall period or the method of data collection [37].

### 6.2.4 Response options

Different types of item response options for PRO instruments are available. A table with response option types can be found in the FDA PRO guidance (page 15) [21]. Examples for types of response options are: Visual analogue scale (e.g., Pain VAS, see Appendix, PRO instrument 1), numeric rating scale (e.g., PI-NRS, see Appendix, PRO instrument 2), pictorial scale (e.g., pictorial scale for pain assessment, see Appendix, PRO instrument 8).

Item response options are considered appropriate by the FDA when [21]:

- Wording is clear and appropriate.
- Options are suitable for the intended patient population, purpose, and intended use.
- Responses offer a clear distinction between choices.
- Number of response options is justified by qualitative research.
- Responses are appropriately ordered, represent similar intervals and avoid ceiling or floor effects.
- Responses do not bias the direction of responses.

### **6.2.5 Instrument format, instructions, and training**

The format of the PRO instrument (i.e., the exact appearance of the questionnaire, diary, or interview script) used in the clinical trials has to be consistent with the format used during the PRO instrument development [21].

The user manual for a PRO instrument should contain [21] [56]:

- Exact version of the PRO instrument
- Screen shots of electronic format
- Patient training and instructions to patients
- Instruction to investigators/interviewers
- Investigator/interviewer training methods and materials
- Instrument administration guidelines
- Scoring algorithm

### **6.2.6 Patient understanding**

The FDA encourages sponsors to examine if the drafted PRO instruments are comprehensive and understandable to the targeted patient population.

The examination should include documentation

- that the concepts (i.e., the specific measurement goals) of the instrument are confirmed,
- that the patients understand how to complete the instrument,
- that the recall periods are appropriately comprehended,
- and that the instrument's readability is adequate for the intended population [21].

Patient understanding can be assessed by conducting usability test, readability test and cognitive interviews. Based on the results of the cognitive interviews and/or pilot tests the sponsor should adjust the PRO instrument, e.g., by deleting or modifying items, response scales, or patient instructions [21] [55].

### 6.2.7 Scoring of items and domains

The FDA PRO guidance contains the following recommendations for scoring of items and domains [21]:

- Numerical scores should be assigned to each item based on the most appropriate scale of measurement for the item (e.g., nominal, ordinal, interval, or ratio scales).
- A scoring algorithm has to be developed to create a single score from multiple items (e.g., to create a domain score).
- Sponsors should justify the method chosen to combine items to create a score or to combine domain scores to create a general score. Qualitative research or defined statistical techniques can be used for justification of the method.

### 6.2.8 Respondent and administrator burden

Physical, emotional, or cognitive burden on patients generally decreases the quality and completeness of PRO data. Factors affecting respondent burden include the following [21] [69]:

- Length of questionnaire or interview
- Inadequate time to complete questionnaires or interviews
- Poor formatting and appearance of questionnaire, e.g., font size too small to read easily
- New instructions for each item
- Requirement that patients consult records to complete responses
- Lack of privacy for the patient during questionnaire completion
- Literacy level too high for patient population
- Questions that patients are unwilling to answer
- Need for physical help in responding (e.g., assistance with a telephone or computer keyboard)

The degree of patient burden that is tolerable for PRO instruments in clinical trials depends on the frequency and timing of PRO assessments in a clinical trial protocol and on patient cognition, illness severity, or treatment toxicity [21].

## 6.2.9 Good research practices on content validation of PRO instruments

As outlined in the previous pages, establishing, evaluating and documenting content validity for new developed PRO instruments is a complex, demanding and time-consuming process. The ISPOR PRO Task Force [70] developed good research practice documents regarding establishing and reporting content validity of newly developed PRO instruments in 2011. In two documents, the PRO Task Force suggests specific methodological practices involved in designing studies to gather evidence of content validity and methods for evaluating and documenting content validity.

Patrick et al. (2011) *Content validity - Establishing and reporting the evidence in newly-developed patient-reported outcomes (PRO) instruments for medical product evaluation: ISPOR PRO good research practices task force report:*

- *Part 1 - Eliciting concepts for a new PRO instrument* [41].
- *Part 2 – Assessing respondent understanding* [55].

For existing and modified PRO instruments the adequacy of the content validity has to be documented as well. Additional validation studies may be needed to confirm the adequacy of the modified instrument's measurement properties. Examples for modifications are [21]:

- Changing the application to a different setting, population, or condition
- Changing an instrument from paper to electronic format
- Changing the timing of procedures for PRO instrument administration
- Changing the order of items, item wording, response options, or recall period or deleting portions of a questionnaire
- Changing the instructions or the placement of instructions within the PRO instrument

The ISPOR PRO Task Force [70] developed a good research practice document for evaluating and documenting content validity for the use of existing and modified PRO instruments.

Rothman et al. (2009) *Use of Existing Patient-Reported Outcome (PRO) Instruments and Their Modification: The ISPOR Good Research Practices for Evaluating and Documenting Content Validity for The Use of Existing Instruments and Their Modification PRO Task Force Report* [71].

## 6.3 Reliability, construct validity, and ability to detect changes

Once the content validity has been verified by the regulatory authorities, additional measurement properties of a PRO instrument will be reviewed. The other relevant measurement properties are reliability, construct validity, and ability to detect change [21].

### 6.3.1 Reliability

Reliability is the ability of a PRO instrument to yield the same score each time it is administered given that the concept being measured (e.g., change of symptom intensity) has not changed [72].

The reliability of a PRO instrument can be estimated in three ways [21] [53] [72]:

- Test-retest or intra-interviewer reliability confirms that the PRO instrument produces the same result at multiple time points if the patient's condition has not changed.
- Internal consistency reliability is estimated by assessing whether several items that intend to measure the same general construct yield similar scores.
- Inter-interviewer reliability is determined by assessing the grade of agreement among responses when the PRO instrument is administered by different interviewers.

### 6.3.2 Construct validity

The construct validity assesses to what extent a PRO instrument measures the construct it is supposed to measure [73].

Construct validity includes convergent, discriminant, and known groups validity [21] [68] [74]:

- Convergent validity is the degree to which scores of a PRO instrument are related to scores of other instruments that are designed to assess the same construct.
- Discriminant validity is the degree to which scores of a PRO instrument do not correlate with scores from instruments that are not designed to assess the same construct.
- Known group validity is the ability of the PRO instrument to differentiate between clinical distinct groups of patients.

### 6.3.3 Ability to detect change

If the following statements are true, the PRO instrument has the ability to detect change over time (responsiveness):

The scores of the instrument change in a predicted direction when there has been a notable change in the patient's state.

The scores of the instrument are stable when there is no change in the patient's state [68].

The ability to detect change of a PRO instrument influences the number of clinical trial patients that are needed to evaluate the effectiveness of a treatment [21].

## 6.4 Translation and cultural adaption of PRO instruments

As a result of the internationalization of clinical research and the increasing number of countries participating in multinational clinical trials, it is necessary to have multiple translations and cultural adaptations of a PRO instrument [75]. Most PRO instruments are developed in English-speaking countries and need to be translated into other languages and adapted to their cultures [76]. Another possibility is to develop a new PRO instrument concurrently in multiple cultures or languages [21].

It is challenging to develop PRO instrument versions for different countries that are equivalent in meaning, interpretation, valuation and relevance. The reasons for the complexity of translation and cultural adaptation are [2] [75] [77]:

- Limitation of language
  - Example: Response options, such as “quite a bit” or “somewhat likely” do not translate easily in different languages
- Cultural differences among countries in terms of values, expectations, experiences, and attitude toward health
  - Example: Questions concerning sexual health that are considered suitable for Western Europe may be considered offensive in Southeast Asia or the Middle East
- Varying relevance of the content of the PRO instrument to the culture, the lifestyle, and the living conditions in a country
  - Example: There is the risk that assessments of functional status that use the wording “ability to walk several blocks” may find that “blocks” have a different or no meaning at all in some countries.

Regarding translations and cultural adaptations of PRO instruments, the FDA and the EMA acknowledge the use of a methodology similar to that outlined in the ISPOR Task Force guidelines [37].

The ISPOR Task Force for Translation and Cultural Adaption has published two guidelines on translation and cultural adaption of PRO instruments. The task force developed a 10-step process to translate and cultural adapt PRO instruments [78] and provided recommendations on the selection of languages for specific countries and on translation methods for 'same language' versions used in multiple countries (e.g., Spanish speaking countries in South America) [76].

For translated and cultural adapted PRO/HRQL instruments, the FDA PRO Guidance and the EMA HRQL Reflection Paper recommend that sponsors provide evidence that the content validity and other measurement properties for the various versions of the instrument show similar adequacy [20] [21].

The measurement properties of each translation and cultural adaption should be established before the start of the phase 3 trials, e.g., in phase 2 trials. If this is not possible for all countries (e.g., for countries not participating in phase 2 trials), separate studies have to be conducted to confirm the measurement properties of the concerned PRO instrument versions [79]. The adequacy of the measurement properties of the different language versions should be assessed by conducting cognitive interviewing and test-retest surveys [21] [22].

According to the FDA PRO Guidance, documentation provided to the FDA to support adequacy of all language and cultural versions of the PRO instrument should include [21]:

- Process used to translate and culturally adapt the instrument
- Description of patient testing, language- or culture-specific concerns, and rationale for decisions made to create new versions
- Copies of translated or adapted versions
- Evidence that content validity and other measurement properties are comparable between the original and new instruments

The EMA requires the same information for language and cultural versions of PRO instruments to verify the measurement properties, but does not request a specific format [37].

## 6.5 Timing of PRO instrument development

Laurie Burke, Associate Director for Study Endpoints and Labeling (CDER) at the FDA, discussed in her presentation at the FDA Workshop “Measurement in Clinical Trials: Review and Qualification of Clinical Outcome Assessments” (October 2011) the timing and planning of the development of PRO (and other clinical outcomes) instruments [80] [81]. Figure 6, which displays the timelines for PRO development during drug development, is based on a slide shown during the presentation.

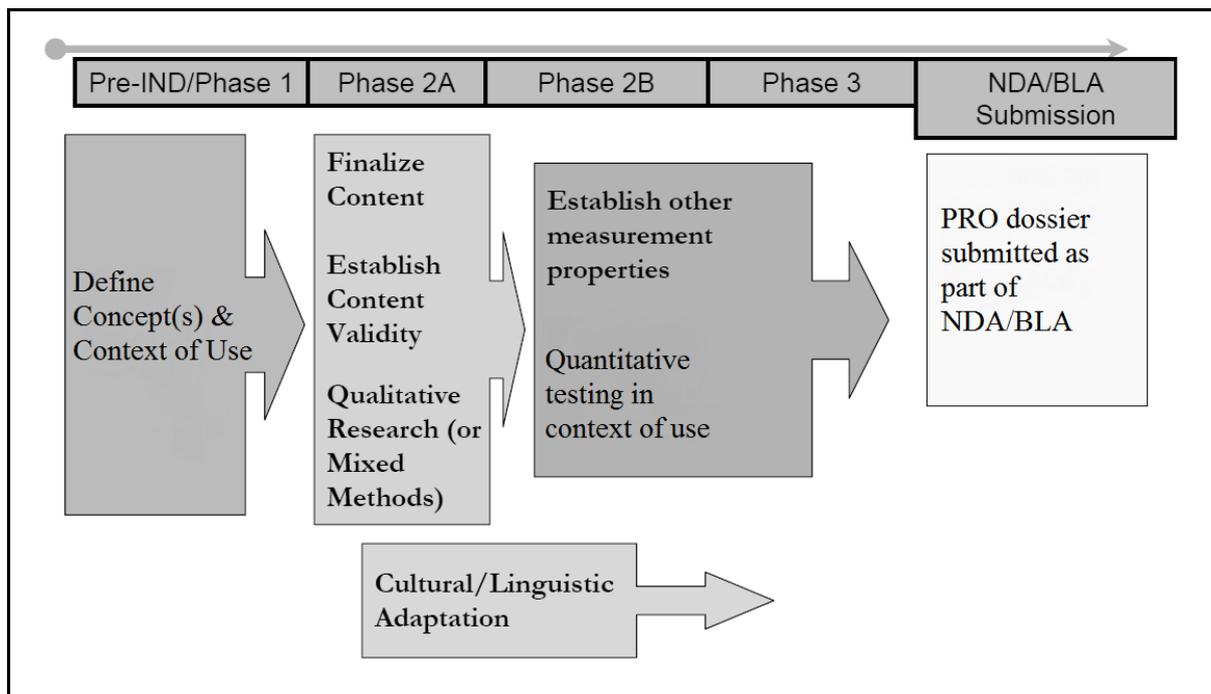


Figure 6: Timelines for PRO instrument development during drug development (adapted from [80]) IND: investigational new drug, NDA: new drug application, BLA: biologics license application

Laurie Burke recommends in her presentation [80] to begin with the PRO development even before the first in human clinical trials start. As soon as the potential therapeutic area of a new medicinal product is considered, the sponsor should define the context of use and the concept of the planned PRO instrument. The context of use refers to what the clinical outcome assessment is intended to be used for. The statement should contain information regarding the targeted patient population, the clinical trial endpoint model, and the proposed claim wording [33].

Subsequently, the PRO instrument has to be developed and the content validity has to be established and verified. The content validity should be demonstrated during the phase 2A trials by performing qualitative (and quantitative) research.

The other measurement properties (reliability, construct validity, and ability to detect change) should be established at the end of phase 2B.

In the case that translation and cultural adaptation of a PRO instrument is needed, this should be completed at the end of phase 2B, too.

If all measurement properties have been established at the time the End-of-Phase 2 meeting is held, the FDA is able to agree with the sponsor that the PRO instrument is appropriate for the use in the phase 3 trials. When a PRO instrument cannot be reviewed and accepted by the FDA at the end of phase 2, the appropriate measurement properties have to be established throughout phase 3. In that case, there is the risk that if the PRO instrument is not accepted by the FDA during the NDA process, the claim based on the PRO cannot be granted [80].

The EMA recommends in the HRQL Reflection Paper that the validation of a HRQL instrument should be completed before the start of the phase 3 trials [20]. According to Maria Isaac, a member of the Scientific Advice team at the EMA, scientific advice and PRO instrument qualification can be requested by pharmaceutical companies in parallel from the EMA and the FDA [82].

The timing of PRO instrument development, as shown in Figure 6, is also applicable for Europe.

## **7 Implementation of PROs in clinical trials**

It was discussed in section 6 that PRO instruments are implemented in Phase 2 trials to test them in the target patient population in order to confirm the adequacy of the instrument's measurement properties (validity, reliability, ability to detect changes) and the validity of cultural adaptation/translation.

In this section the implementation of PRO instruments in phase 3 trials will be addressed.

The use of PRO instruments in clinical trials is not widespread, but significant. Scoggins et al. (2009) have analyzed the usage of PRO instruments in interventional clinical trials that were registered with ClinicalTrials.gov between September 2004 and September 2007. In about 12% of the interventional trials registered by pharmaceutical companies and in more than 15% of the non-industry sponsored clinical trials PRO instruments were used [83]

## 7.1 Trial design

If the PRO instrument is used to assess primary or key secondary study endpoints to support a label claim, this should be reflected in the objectives of the clinical trial protocol [21].

The EMA recommends for clinical trials, which uses a HRQL instrument, to incorporate efficacy and HRQL endpoints in the trial. If the assessment of HRQL is only performed in a subset of the clinical trial patient population, this has to be justified by the sponsor. For medicinal products that have already obtained marketing authorization, it is possible to test HRQL change as the only endpoint in a clinical trial [20].

The FDA prefers placebo controlled clinical trials, whereas the EMA accepts active comparator and/or placebo-controlled clinical trials [20] [21].

### 7.1.1 Blinding and randomization

The EMA and the FDA state that only blinded clinical trials are adequate to obtain PRO/HRQL data used to support label claims. Both regulatory agencies assume that patients who are aware that they receive active treatment are biased as they may overestimate the benefit of the treatment.

It is strongly recommended by both agencies to use PRO/HRQL instruments only in randomized, double-blind clinical trials to avoid any bias (of patient or investigator) [20] [21].

In situations, where for clinical trials with PRO instruments blinding is not possible or where there is no acceptable control group, the FDA recommends that the sponsor requests scientific advice.

### 7.1.2 Trial duration

The EMA HRQL Reflection Paper gives specific statements regarding duration of clinical trials with HRQL endpoints. In order to assess HRQL change, the EMA recommends for conditions with relapsing or remitting symptoms (e.g. depression) and for chronic diseases (e.g. rheumatoid arthritis) long-term trials with duration from 3 – 6 months or more. Short-term trials with duration up to 1 month are discouraged as a change in HRQL cannot be assessed in such a short period [20].

The FDA PRO Guidance states that the clinical trial duration should be adequate to support the proposed PRO claim and assess a durable outcome in the disease [21].

### **7.1.3 Recall periods and frequency of assessment**

The recall period is an important aspect of a PRO instrument. It should match the clinical trial schedule and the duration of the treatment [84].

The FDA recommends short recall periods not longer than 7 days and the use of daily diaries for symptom assessment.

The EMA has no specific requirements for HRQL instruments regarding the recall period or the method of data collection [37]. For further information please refer to section 6.2.3.

The frequency of PRO assessment should be based on the targeted labeling claim (PRO endpoint), the disease characteristics, the durability of treatment effects, the duration of the trial, and the burden for the patient (depending on the number and the length of the questionnaires). At least at baseline and at the end of study an assessment with the PRO instrument has to be performed [21] [73].

### **7.1.4 Country allocation**

One of the criteria for selection of participating countries in multinational clinical trials should be the availability of valid translated and cultural adapted versions of the PRO/HRQL instruments.

If a clinical trial is allocated to a country for which at trial start a validated adapted PRO instrument is not available, the instrument has to be translated and adapted just before the start of the trial. As this instrument could not be validated by the regulatory agency before the start of the study, there is the risk that the agency does not accept the belatedly translated and adapted PRO instrument and the PRO data from that country cannot be used to support the label claim [76].

## **7.2 Quality control**

Procedures have to be specified in the trial protocol that minimize inconsistency regarding data collection among different patients, investigators, trial sites, and trials countries.

The FDA PRO Guidance recommends including the following standardized instructions and processes in the trial protocol when PRO instruments are used [21]:

- A standardized order for the administration of PRO instruments and other clinical assessments
- Training and instructions
  - for patients, if self-administered PRO instruments are used
  - for interviewer, if PRO instruments in an interview format are administered
- Instructions for the clinical investigators regarding
  - patient supervision
  - timing and order of questionnaire administration
  - processes and rules for questionnaire review for completeness
  - documentation of how and when data are filed, stored, and transmitted
- Plans for confirmation of the PRO instrument's measurement properties

Additional strategies to ensure quality of the collected PRO data are as follows: Accurately planned logistics of PRO data collection and transfer, ongoing monitoring of PRO data collected at the sites, proactive communication with sites on issues regarding PRO instruments, and quick remediation of problems with PRO instruments [42].

### **7.2.1 Trainings on the use of PRO instruments in clinical trials**

The training material, which is provided to patients, interviewers and investigators has to be comprehensive and effective. The training material has to be validated along with the PRO instrument during the development process [73] [85].

Examples for trainings are [85]:

- Training for investigators and site staff on the influence of the disease on the PRO reporting
- Training for investigators, interviewers, and site staff on the PRO instrument and the patient training material
  - Trainings for investigator and site staff can be conducted at the investigator meeting or by a clinical research associate (CRA) during the trial initiation visit
- Patient training on the PRO instrument
  - Patient training should be conducted by the investigator or site personnel during patient's first PRO assessment. When the patients have problems with PRO instrument completion, ongoing training by site personnel is recommended.

### **7.2.2 Handling missing data**

As missing PRO data can introduce bias in a clinical trial they are a major challenge to the interpretation of a clinical trial. Reasons for missing PRO data are that patients miss study visits, forget to complete questions or the entire PRO questionnaire, or prematurely withdraw from a clinical trial [21].

Trial protocols have to describe how missing data can be avoided during the clinical trial and how missing data will be handled in the data analysis [21]. The reasons for missing data or patients' withdrawals from treatment should be recorded in a timely manner to gather information on a potential pattern for why data are missing [53] [73]. Missing data due to premature withdrawal from treatment can be avoided by establishing a process that these patients can remain in the clinical trial and can continue completing PRO questionnaires [21].

## **8 Regulatory Interactions**

### **8.1 Consultation with the regulatory agencies during PRO instrument development**

As outlined in the previous sections, the validation of a PRO instrument regarding its measurement properties should be completed before the start of the phase 3 trials. It is essential that the sponsor obtains scientific advice from the regulatory authorities if the PRO instrument is used to generate data to support a labeling claim. The authorities have to review during the scientific advice if the instrument is adequate and can be used for the pivotal trials in phase 3. It is recommended to stay in contact with the regulatory authorities during the entire development process of PRO instruments [22] [42].

The opinion or the advice regarding the adequacy of a PRO instrument from the EMA and the FDA can be sought by a sponsor in 2 different types of procedures: The scientific advice procedure and the qualification process [28].

When requesting a scientific or qualification advice, the sponsor has to provide a detailed briefing package for the EMA and/or the FDA that includes all relevant information on the measurement properties of a PRO instrument [22].

### **8.1.1 Parallel scientific advice at EMA and FDA**

The EMA and the FDA have initiated a program to provide parallel scientific advice and in July 2009 both agencies have agreed on general principles regarding these procedures and have published the document “General Principles of the EMA-FDA Parallel Scientific Advice” [86] on their websites. The goal of the parallel scientific advice program “is to provide a mechanism for EMA and FDA assessors and sponsors to exchange their views on scientific issues during the development phase of new medicinal products” [86]. Advantages of the program are, among others, an increased dialogue between the two agencies and sponsors and the opportunity to harmonize the qualification procedures for new methodologies of both agencies [82] [86].

Parallel scientific advice procedures are voluntary and are normally initiated at the request of the sponsor. Both agencies have to agree to conduct the parallel scientific advice procedure, as the number of parallel scientific advice meetings per year is limited and the procedure is only applicable for specific products (e.g., oncological products, vaccines, orphan drugs, advanced therapies) [86] [87]. Sponsors can submit a similar briefing packages and the same questions to both agencies [82].

The scientific advice timelines of the two agencies are in essence similar: FDA Type C meeting should be scheduled in 75 days and EMA scientific advices should be scheduled in most cases in 70 days [88] [89].

During the parallel scientific advice procedure both agencies communicate among themselves and meet with the sponsor together. Sponsors have to be aware that the intention of the parallel advice is not to harmonize scientific advice from the EMA and the FDA regarding a drug development issues. The authorities will provide their independent advice to the sponsor according to their usual procedures and timelines [86].

The parallel scientific advice procedure is also applicable for the assessment of PRO instruments and sponsors are encouraged to seek parallel scientific advice regarding the qualification of a new PRO instrument [28].

### **8.1.2 Scientific advice**

It is also possible to request separate scientific advice from the EMA or from the FDA.

It is recommended to ask for scientific advice regarding a new PRO instrument before the start of the first in human trials. In the Pre-IND meeting, it should be discussed with the

regulatory agencies if the context of use and the concept of the planned PRO instrument are appropriate for the intended use of the medicinal product (indication and patient population) [42].

Most important is the scientific advice that is scheduled before the start of phase 3 in an End-of-Phase 2 meeting. At the end of phase 2 all measurement properties of a PRO instrument (conceptual framework, validity, reliability, ability to detect change, and translation and cultural adaption) should be established and documented in a briefing package. The regulatory agencies is thereby able to assess if the PRO instrument is adequate and appropriate for the use in the phase 3 trials to support the targeted label claim [27] [80].

An additional scientific advice is recommended at the end of phase 2A for complex PRO instruments if the content validity has been established and tested by performing qualitative research. Content validity is the most significant measurement property for the review of the PRO instrument by the authorities. If content validity is not established, the other measurement properties cannot be assessed [41] [55].

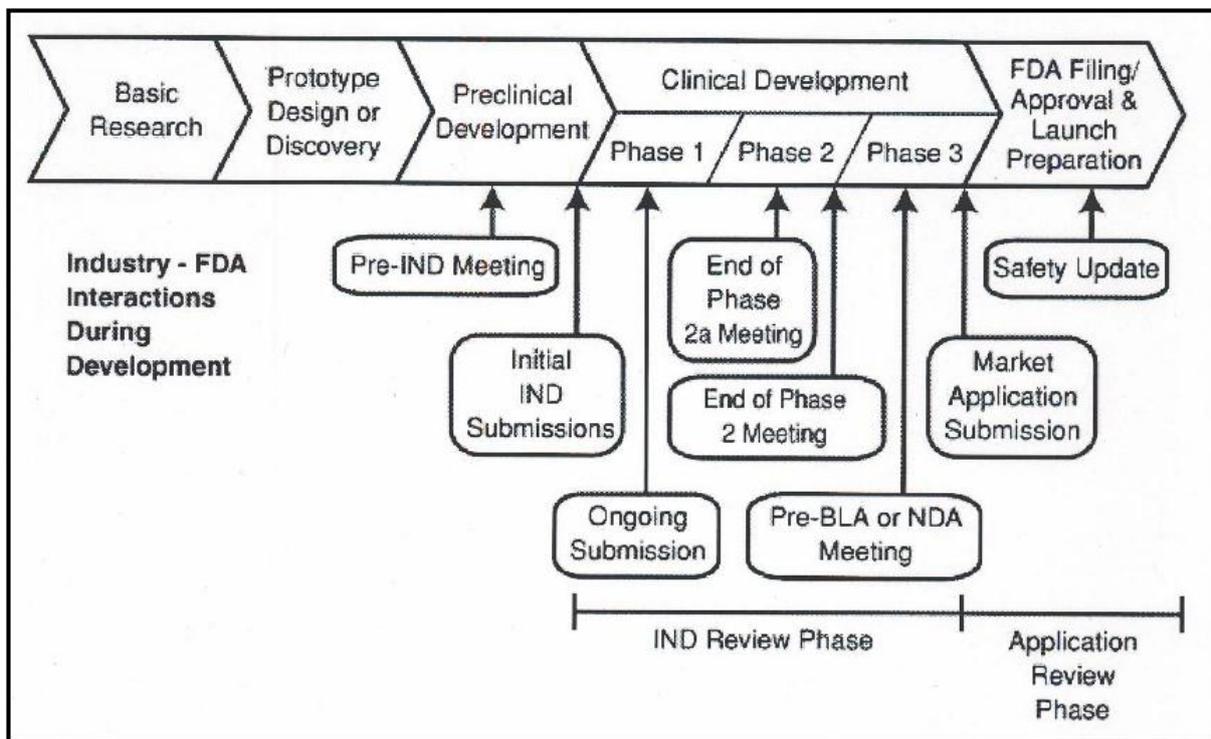


Figure 7: Interactions between the sponsor and the FDA during drug development (taken from [90])

Figure 7 illustrates the possible interactions between sponsors and the FDA during drug development and PRO instrument development. The timing of interactions between sponsors and the EMA are comparable [37].

If scientific advice is requested from the EMA, the FDA, or from both agencies, the following has to be considered:

- The respective procedures and timelines of the EMA and the FDA regarding scientific advice have to be regarded (even if parallel scientific advice is sought) [86].
- Communication with regulatory agency should start as early as possible.
- Scientific advice should additionally be coordinated with advice sought in other regions than Europe or the USA [91].
- Scientific advice can cover more topics than the assessment of PRO instruments (e.g., development questions, deviation from guidances, scientific issues regarding clinical aspects) [91].
- Scientific advice requests require diligent preparation of questions and briefing documents.
- Fees for scientific advice have to be taken into account.

### **8.1.3 Qualification procedure**

The qualification process for drug development tools (DDT) is applicable for PRO instruments. Both regulatory agencies, the FDA and the EMA, developed and published a DDT Qualification Guidance in the last years [30] [33].

#### **EMA Qualification Procedure**

***European Medicines Agency: Qualification of novel methodologies for drug development: guidance to applicants; 09 January 2012.*** [30]

The EMA qualification process is a optional, scientific pathway, which leads to either a CHMP Qualification Opinion or a CHMP Qualification Advice regarding innovative methods and tools (e.g., novel PRO instruments) developed by the pharmaceutical industry or consortia [30].

#### **CHMP Qualification Opinion:**

If a DDT qualification procedure for a PRO instrument leads to a binding CHMP Qualification Opinion, the proposed method (e.g., PRO instrument) is acceptable for a specific use in a research and development context (e.g., clinical trials), based on the assessment of the submitted data [30]. The PRO instrument with a Qualification Opinion is considered by the EMA as an acceptable regulatory standard for the claimed use in a defined context for drug development. The CHMP Qualification Opinion will be made publicly available on the EMA website [30].

### CHMP Qualification Advice:

If a new tool is not accepted for qualification, the procedure will turn into a scientific advice regarding future studies, which should be performed in order to generate the data required to support the proposed use of the tool in drug development. When the new data is generated, the applicant may request a Qualification Opinion. The CHMP Qualification Advice is confidential [30].

### Required documents for Qualification Procedure can be:

Protocols, study reports, primary data, published articles, expert statements and expert summaries [30] [31].

### FDA Qualification Procedure

***US Department of Health and Human Services, US Food and Drug Administration: Qualification Process for Drug Development Tools. Draft October 2010. [33]***

The FDA qualification process is an optional submission process for drug development tools (DDT), such as PRO instruments, intended for use in multiple drug development programs [33] [35]. The qualification process includes two stages. Stage 1: Consultation and Advice; Stage 2: Review for Qualification Decision [34].

If a DDT (e.g., a novel PRO instrument) is qualified for a specific context of use, the pharmaceutical industry can use the DDT for the qualified purpose during drug development. CDER reviewers can be confident in applying the DDT for the qualified use without the need to reconfirm the DDT's utility [33]. The term "context of use" for a qualified PRO instrument describes all important criteria regarding the circumstances under which the DDT is qualified and defines the boundaries within which the available data justify the use of the instrument [33].

The FDA (CDER) makes the information about qualified DDTs available in the Federal Register and on the FDA DDT website [33] [35].

### Required documents for Qualification Procedure:

Comprehensive dossier of the PRO instrument's qualitative development and validation work

### Parallel Qualification Procedure:

Applicants are encouraged to apply for qualification advice in parallel to the EMA and FDA and get the opportunity to meet simultaneously with both agencies. This will maximize the chance for scientific consensus [30] [82].

## 8.2 Documentation of PRO instrument properties for submission to the regulatory authorities

### 8.2.1 PRO Evidence Dossier

The key document used to submit the required information on the PRO instrument to the regulatory agencies is the PRO Evidence Dossier. In the appendix of the FDA PRO Guidance [21], the FDA gives recommendations on the content and structure of the document. It contains the relevant information provided to the FDA for review of a PRO instrument. This document is referred to as “PRO Evidence Dossier” [92].

The EMA has no specific recommendations regarding the structure of the required documentation of HRQL instrument characteristics and properties, but it is recommended to rely on the FDA PRO Guidance and use a dossier similar to the PRO Evidence Dossier [28] [93].

The PRO Evidence Dossier can be considered as a living document that records the key elements regarding PRO instrument development, adaption and assessment [92].

The structure and content of the PRO Evidence Dossier can be outlined as follows [21]:

- Exact version of the PRO instrument and prior versions, if relevant
- Instructions for use of the instrument
- Proposed label claim
- Endpoint model
- Conceptual framework
- Content validity documentation
  - Including literature review, expert input, documentation of item development, item content, response options, recall period, scoring, summary of qualitative and quantitative research
- Assessment of other measurement properties
  - Reliability, construct validity, ability to detect change
- Interpretation of scores
- Translation and cultural adaption (if applicable)
- Data collection method
- Modifications (if applicable)
- Clinical trial protocol
- Statistical analysis plan

## 8.2.2 Documents for Scientific Advice

### **The PRO instrument briefing package**

The briefing package should be based on the PRO Evidence Dossier containing the relevant and available information for the scientific advice. If a parallel scientific advice from both agencies is sought, the same briefing package and the same questions should be submitted to the agencies [82].

### **FDA scientific advice briefing documents:**

If a sponsor is interested in a scientific advice meeting with the FDA regarding assessment of a PRO instrument (Type C meeting [27]) the following documents have to be submitted [88]:

- Written request (i.e., letter or fax) for a meeting
- Information packages
  - Package should contain
    - Product name, chemical name and structure, proposed indication(s)
    - Brief statement of the purpose of the meeting
    - List of the specific objectives/outcomes expected from the meeting
    - Proposed agenda, agenda items and designated speakers
    - List of specific questions
- PRO instrument briefing package

### **EMA scientific advice briefing documents:**

If scientific advice regarding HRQL instrument assessment is requested, the following documents have to be submitted to the EMA [89]:

- Letter of intend
  - The letter has to be sent approximately 1 month before the planned start of the scientific advice procedure.
- Table of contents and request
- Briefing document including the questions, the company's positions, and the HRQL instrument briefing package

**Parallel scientific advice briefing documents:**

If a parallel scientific advice regarding PRO instrument assessment is requested, the following documents have to be submitted to the EMA and the FDA [86]:

- Request for parallel scientific advice letter
  - Letter should contain
    - Explanation why a discussion with both agencies would be beneficial for the product development
    - Specific question to be clarified
    - Authorization regarding the exchange of information between EMA and FDA
- PRO instrument briefing package

**8.2.3 Documents for qualification procedure**

The EMA proposes in detail a format for the request for CHMP Qualification Opinion in the EMA DDT Qualification Guidance [30].

In the FDA DDT Qualification Guidance, the FDA recommends a specific structure for a briefing document for PRO instrument qualification [33].

If a sponsor applies for a DDT qualification procedure for a PRO instrument in parallel to the EMA and FDA, the same documents should be submitted to both agencies [82].

**8.2.4 Documents for New Drug Application and Marketing Authorization Application****PRO instrument documents for New Drug Application to the FDA**

The FDA PRO Guidance [21] contains the following statement regarding the submission of the New Drug Application (NDA):

“The adequacy of any PRO instrument, whether existing, modified, or newly developed, as a measure to support medical product labeling claims depends on whether its characteristics, conceptual framework, content validity, and other measurement properties are satisfactory. The FDA will review documentation of PRO instrument development and testing in conjunction with clinical trial results to determine whether a labeling claim is substantiated.” [21]

The requirements regarding the documentation of PRO instrument properties, development, and testing, and submission of the information can be found in the appendix of the FDA PRO Guidance [21]. The PRO instrument information for review by the FDA during the NDA review process should be submitted in the PRO Evidence Dossier electronically in the section 5.3.5.3 “Reports of Analyses of Data from More than One Study” of the electronic Common Technical Document (eCTD).

### **PRO instrument documents for Marketing Authorization Application to the EMA**

The EMA HRQL Reflection Paper [20] gives the following statement regarding the documentation of the PRO instrument properties in the Common Technical Document (CTD): “The claim in the SmPC with the respect to HRQL will always be considered depending on the strength of the evidence and the relevance (pertinence and importance) of the finding. The strength of the evidence should be based on the rationale for HRQL assessment in the context of the disease/medicinal product, the justification of the choice of the HRQL questionnaire(s), the objectives of HRQL assessment and the hypotheses of HRQL changes, the evidence of validation (and of cultural adaptation/translation if applicable) of the HRQL questionnaire(s), the adequacy of the statistical analysis plan, and the relevance of observed changes.” [20]

The HRQL Reflection Paper [20] gives no specific recommendations regarding the structure of the required documentation of HRQL instrument characteristics and properties. As the EMA recommends relying on the FDA PRO Guidance [21] the required HRQL instrument information should be submitted to the EMA for MAA review in a HRQL (PRO) Evidence Dossier placed in section 5.3.5.3 of the eCDT [28].

## **8.3 Review Procedures of PRO documents**

### **8.3.1 FDA review procedure**

The Study Endpoints and Labeling Claims Development (SEALD) group is responsible for the review of the PRO Evidence Dossiers at the FDA. The SEALD group provides its advice regarding the adequacy of the PRO instrument to support the targeted labeling claim to the reviewing divisions of the FDA [27] [94].

### 8.3.2 EMA review procedure

As the EMA has no internal experts for HRQL instrument assessment, the agency requests review of the HRQL Evidence Dossiers from selected academic or clinical experts in different countries. As the dossiers are reviewed by a large number of different experts, there is a risk of heterogeneity of advices regarding the adequacy of HRQL instruments within the EMA [17] [27].

## 8.4 Reasons for the rejection of PRO label claims

DeMuro et al. (2012) [95] have reviewed 116 New Drug Applications and Biological License Applications that were approved by the FDA between 2006 and 2010. The objective of the review was to explore the reasons why PRO label claims were rejected by the FDA. Here are the results:

- 52 products included PROs in the pivotal trials
- Only 28 products received a label claim based on PRO
- For 24 products the targeted PRO label claims was rejected by the FDA

Important reasons for the denial of the PRO label claims were as follows:

- Evidence to support measurement properties of the PRO instruments (e.g., content validation, ability to detect change) were not sufficiently established and documented
- Missing evidence to support validation of translation and cultural adaption
- PRO data were not interpretable due to issues of potential bias (unblinded trials), inappropriate recall periods, or poor compliance of patients
- Lack of link between concept and targeted label claim
- Incomplete documentation (e.g., copy of PRO instrument not provided to the FDA)
- PRO instrument data did not support treatment benefit

The reasons for the rejection of PRO claims shows how important a thorough development, validation, and implementation of PRO instruments, and close interaction with the regulatory authorities are to obtain a targeted PRO label claim.

## 9 Discussion

### 9.1 EMA versus FDA guidances: Similarities and differences

In the previous sections the development, properties, and application of PRO instruments with the aim to obtain a label claim based on patient reported outcomes were discussed in detail. A number of similarities between the EMA and FDA regarding assessment of PRO/HRQL instruments were identified, but also specific differences could be noticed.

In this section the relevant similarities and differences regarding patient reported outcomes measures between the two regulatory agencies will be summarized.

#### 9.1.1 Similarities and differences regarding study endpoints and label claims

##### Similarities

An important consensus between EMA and FDA is the opinion that only **primary and key secondary PRO endpoints** can be used to support a label claim. Both agencies require the development of an **endpoint model** to document the value, hierarchy and relationship among all endpoints (PRO and non-PRO endpoints). An endpoint model defines the role a PRO endpoint plays in the clinical trials [27] [28].

Both regulatory agencies recommend **PRO/HRQL endpoints in disease specific guidances**, as for example in the guidance documents for COPD [32] [37] [96].

##### Differences

An obvious difference between the EMA HRQL Reflection Paper [20] and the FDA PRO Guidance [21] is the fact that the **EMA Reflection Paper provides guidance specifically for HRQL-related label claims** (e.g., improvement in health-related quality of life), but is not applicable for simple PRO-related claims (e.g., improvement of symptoms), whereas the **FDA PRO Guidance covers all PRO-related claims** [37] [42].

The **EMA Reflection Paper gives broad recommendations** on the use of HRQL in clinical trials, but is not a formal guidance regarding the methodology of HRQL. The FDA, on the other hand, issued a **formal FDA PRO Guidance on the use of PRO instruments** to support labeling claims [2]. The **FDA PRO Guidance is also applicable for clinician reported outcome (ClinRO) and observer reported outcome (ObsRO)** [35].

A review of authorization of medicinal products from 2006 – 2010 showed that the **EMA granted significantly more HRQL claims than the FDA**. The FDA grants HRQL label claims rarely [17].

### 9.1.2 Similarities and differences regarding development of PRO instruments

#### Similarities

The EMA as well as the FDA **evaluate the content validity to assess if a PRO instrument is appropriate** for the patient population and the target indication of a new medicinal product [25] [37]. The **adequacy of the content validity** of a PRO instrument will be assessed based on the **documentation of the following development processes and instrument attributes**: item generation; data collection method and instrument administration mode; recall period; response options; instrument format, instructions, and training; patient understanding; scoring of items and domains; respondent and administrator burden [21].

Both agencies ask for evidence that the PRO instrument used in a clinical trial **is reliable, valid, and able to detect change** over time [25] [37] .

The **adequacy of translated and cultural adapted PRO instruments** will be assessed by both regulatory agencies based on data from cognitive interviewing of patients and test-retest surveys [2] [22].

If **all measurement properties of a PRO instrument have been established at the end of Phase 2**, the EMA and the FDA are able to agree with the sponsor that the PRO instrument is appropriate for the use in the phase 3 trials. This ensures that in the pivotal trials valid PRO data that can support the targeted label claim are obtained [37] [42].

## **Differences**

The **FDA recommends short recall periods** for PRO instruments (24 – 48 h). For symptom endpoints (e.g., pain intensity) the FDA favors the **use of a daily diary** [27] [68]. The **EMA has no specific requirements regarding the recall period** for PRO instruments [37].

The FDA implemented **specific requirements regarding electronic PRO instruments in the FDA PRO Guidance** to ensure that the electronic systems are valid and reliable, and the obtained data are protected from manipulation and disclosure to unauthorized third parties [59]. The FDA recommends for daily assessment of symptoms an electronic patient diary to secure a time stamp of completion [21] [18]. The **EMA HRQL Reflection Paper gives no recommendations regarding the use of ePROs**.

### **9.1.3 Similarities and differences regarding implementation of PRO instruments in clinical trials**

#### **Similarities**

Both regulatory agencies strongly **recommend using PRO instruments only in randomized, double-blind clinical trials** to avoid bias [20] [21].

#### **Differences**

The **FDA prefers placebo controlled** clinical trials, whereas the **EMA accepts active comparator and/or placebo-controlled** clinical trials [20] [21].

In the HRQL Reflection Paper, the **EMA recommends long-term trials** (duration 3 – 6 months or more) for conditions with remitting symptoms and for chronic diseases. The EMA **discourages short-term trials** with duration up to 1 month [20]. The **FDA PRO Guidance recommends no specific trial duration**, but states that the trial duration should be adequate to support the targeted PRO label claim [21].

#### **9.1.4 Similarities and differences regarding documentation and regulatory interactions**

##### **Similarities**

The FDA provides in the **FDA PRO guidance a detailed template for the PRO Evidence Dossier** [21]. The EMA has no specific recommendations regarding the documentation of PRO instrument properties, but it is recommended by the **EMA to use a dossier similar to the PRO Evidence Dossier** [28].

Sponsors can seek **parallel scientific advice or individual scientific advice from the regulatory agency** in order to address questions regarding PRO instruments [86]. EMA and FDA recommend sponsors requesting scientific advice early on [37].

**Both agencies issued qualification guidances** for drug development tools, which are applicable for PRO instruments [22]. Sponsors are encouraged to apply in parallel to the EMA and the FDA for qualification advice [30] [82].

##### **Differences**

Within the FDA, the **SEALD group is responsible for the review** of PRO Evidence Dossiers. The EMA requests **review of the HRQL Evidence Dossier from external academic or clinical experts** [27].

## **9.2 Increased harmonization between EMA and FDA**

The interactions between the EMA and the FDA, based on the EMA-FDA confidentiality arrangements, have increased in the last years. The EMA-FDA interactions, which will be continued in the next years, are aimed to lead to more consistency and predictability in the regulatory interactions between the sponsors and both regulatory agencies [97]. This could result in more similarities between the EMA and the FDA regarding the assessment of PRO instruments, e.g., by harmonizing the EMA HRQL Reflection Paper and the FDA PRO Guidance [26].

## 10 Conclusion and outlook

The increased interest of the FDA and the EMA in the patients' perspective during the drug development and approval process is reflected by the number of guidance documents regarding patient reported outcomes (PRO) that were issued by both regulatory agencies. The FDA PRO Guidance, the EMA HRQL Reflection Paper, the DDT Qualification Guidances published by the EMA and the FDA, and the various disease-specific guidance documents of both agencies, had substantial effects on the pharmaceutical industry and the health care sector. This final section summarizes the observed impact of PRO-related guidances and discusses the possible future trends regarding patient reported outcomes.

### 10.1 The impact of FDA and EMA guidances on the drug development and approval process

- Pharmaceutical companies have to start early with the determination of PRO endpoints and the development of PRO instruments even before the start of the phase 1 clinical trials. As soon as the potential therapeutical area of a new medicinal product is considered, the PRO selection and development process have to begin. The used PRO instrument has to be valid and adequate at the beginning of the phase 3 trials to ensure that the PRO data can be accepted by the regulatory authorities and can support the targeted label claim [42] [80].
- The development of a new PRO instrument or the modification of an existing PRO instrument is a time-consuming and costly process. Pharmaceutical companies have to plan the timelines and the clinical trial budget accordingly [22].
- Pharmaceutical companies have to be aware that a thorough development and detailed documentation of new or modified PRO instruments are inevitable as the regulatory agencies reject PRO data measured by inadequately developed instruments [50] [95].
- The translation and cultural adaption of PRO instrument to be used in multinational trials should start early as it is time-consuming to establish validity for these instruments. It is recommended that pharmaceutical companies cooperate with the concerned country subsidiaries to ensure that the adapted PRO instruments are suitable for the patient population and culture in the respective countries [22].

- Pharmaceutical companies have to involve highly qualified internal or external specialist in the PRO instrument development, adaption, and validation process to ensure that the PRO data are acceptable by the regulatory agencies and PRO label claims can be granted [22]. Service companies can be hired to counsel or assist the company during PRO instrument development. The outsourcing of the PRO instrument development is also possible, but has to be considered carefully.
- PRO endpoints are replacing partly the assessment of symptoms and functioning by physicians, as PRO instruments measure symptoms directly and effectively [18]. PRO data can reveal additional beneficial effects of a new treatment that was not expected by the researchers during the drug development by the pharmaceutical company.
- Early communication between the pharmaceutical company and the regulatory agencies is required to discuss if the clinical and PRO endpoints are appropriate to support the targeted label claims [25]. As soon as the potential therapeutical area of the new medicinal product is considered, the company should develop a draft endpoint model [80].
- Both regulatory agencies, the EMA and the FDA, encourage pharmaceutical companies to seek parallel scientific advice or parallel DDT qualification advice for new PRO instruments that are used in international trials.
- PRO label claims and other reliable PRO data can help physicians to choose the most beneficial treatment for patients [42].
- Presenting PRO label claims on the company website emphasizes the patient-centered attitude of a pharmaceutical company and can increase the reputation among patients and physicians [2].
- Several working groups were established, where pharmaceutical companies can seek guidance, support and advice regarding patient reported outcomes. Examples are as follows:
  - European Regulatory Issues on Quality of Life Assessment (ERIQA) PRO Harmonization Group
  - International Society for Pharmacoeconomics and Outcomes Research (ISPOR) PRO Task Force
  - Critical Path Institute (C-Path) Patient-Reported Outcome (PRO) Consortium

- The PRO guidance documents have caused much debate in the pharmaceutical industry and the health care sector. International societies have organized workshops on PRO endpoints and instruments and journals published a number of articles on the development and validation of PRO instruments [2] [18].
- In the USA, the PRO label claims granted by the FDA can be used for direct-to-consumer advertising, which is not allowed in Europe [37]. PRO label claims and reliable PRO data can be valuable for health technology assessment in Europe and the USA [98].

## 10.2 Future trends in patient reported outcomes assessment

- Modern PRO instruments, based on state-of-the-art psychometric research, need to be developed to improve the quality of the data obtained by PRO instruments [18] [22]. Discussions between the regulatory agencies, PRO workgroups, and the pharmaceutical industry regarding the most appropriate PRO instruments will lead to a specific number of qualified templates for PRO instruments. Based on this templates adequate disease, product, or trial specific PRO instruments can be developed more quickly [18].
- Electronic PRO instruments will be the norm to obtain PRO data in the future, due to the obvious advantages (e.g., faster data transfer, less missing data). The acceptability of electronic PRO instruments will increase and the technical problems will decrease in the next years. Interactive ePRO instruments (e.g., apps for smart phones) will facilitate the use of PRO instruments for the patients [18].
- The pharmaceutical industry has to look for new modern sales models to demonstrate the value of medicinal products to physicians, patients, and patient advocacy organizations. One option would be to publish scientific articles demonstrating the benefits of a new treatment based on valid PRO data on the internet. If the article is relevant for physicians and patients, it will spread on the internet [2].

## 11 Summary

Patient reported outcome (PRO) is a measurement of the patient's health status that comes directly from the patient himself. PRO data are collected in clinical trials via PRO instruments (e.g., questionnaires or diaries) completed by the patient or completed during an interview, provided that the interviewer records only the patient's response.

In the light of patient-centered drug development, the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) are highly interested that pharmaceutical companies use PRO instruments in clinical trials to support claims in approved medicinal product labeling. Since 2005, the EMA and the FDA have issued several guidance documents regarding patient reported outcomes. The two central guidance documents are the EMA Guidance "Reflection Paper on the Regulatory Guidance for the Use of Health-Related Quality of Life (HRQL) Measures in the Evaluation of Medicinal Products" issued in July 2005 and the FDA Guidance "Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims" issued in December 2009.

This master thesis compares the EMA and the FDA PRO guidances and discusses the impact of the PRO guidance documents on the drug development and approval process.

### Similarities:

Both agencies require the development of an endpoint model to document the hierarchy and relationship among all clinical trial endpoints that are intended to support label claims.

The EMA and the FDA evaluate the measurement properties (content and construct validity, reliability, ability to detect change, conceptual framework, cultural adaptation/translation, and the instrument characteristics) of a PRO instrument to assess if the instrument is appropriate for the clinical trial patient population. The sponsor has to establish and demonstrate the measurement properties by performing qualitative and quantitative research (e.g., cognitive interviewing of patients) and document the adequacy of a PRO instrument in the PRO Evidence Dossier.

Both regulatory agencies recommend the use of PRO instruments only in randomized, double-blind clinical trials to avoid bias.

Sponsors can seek scientific advice or drug development tool (DDT) qualification advice regarding PRO instruments. They are encouraged to apply in parallel to the EMA and the FDA for advice.

**Differences:**

The EMA Reflection Paper provides guidance specifically for HRQL-related label claims, whereas the FDA PRO Guidance covers all PRO-related claims (symptoms, functioning, and HRQL).

The FDA prefers placebo controlled clinical trials, whereas the EMA recommends active comparator and/or placebo-controlled clinical trials with a minimum duration of 3 months.

The FDA recommends short recall periods for PRO instruments (24 – 48 h) and favors the use of daily (electronic) diaries in clinical trials.

Within the FDA, the Study Endpoints and Labeling Claims Development (SEALD) group is responsible for the review of PRO Evidence Dossiers. The EMA requests review of HRQL Evidence Dossiers from external academic or clinical experts.

Pharmaceutical companies have to be aware that a thorough development, validation, and implementation of PRO instruments and close interaction with the regulatory authorities are inevitable to obtain a targeted PRO label claim.

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### 13 Appendix: PRO instruments



PRO instrument 1: Pain Visual Analogue Scale (VAS) (taken from [99])

**Select the number that best describes your neuropathic pain during the past 24 hours. (Circle one number only)**

0    1    2    3    4    5    6    7    8    9    10  
 No pain Worst possible pain

PRO instrument 2: 11-point pain intensity numerical rating scale (PI-NRS) (taken from [100])

### Fatigue Severity Scale (FSS)

Your Name \_\_\_\_\_

Date: \_\_\_\_\_ Date of birth: \_\_\_\_\_

This questionnaire contains nine statements that rate the severity of your fatigue symptoms. Read each statement and circle a number from 1 to 7, based on how accurately it reflects your condition during the past week and the extent to which you agree or disagree that the statement applies to you.

\*\*\*A low value (e.g. 1) indicates strong disagreement with the statement, whereas a high value (e.g. 7) indicates strong agreement.

<b>During the past week, I have found that:</b>	Disagree ← → Agree
1. My motivation is lower when I am fatigued	1 2 3 4 5 6 7
2. Exercise brings on my fatigue.	1 2 3 4 5 6 7
3. I am easily fatigued.	1 2 3 4 5 6 7
4. Fatigue interferes with my physical functioning.	1 2 3 4 5 6 7
5. Fatigue causes frequent problems for me.	1 2 3 4 5 6 7
6. My fatigue prevents sustained physical functioning.	1 2 3 4 5 6 7
7. Fatigue interferes with carrying out certain duties and responsibilities.	1 2 3 4 5 6 7
8. Fatigue is among my three most disabling symptoms.	1 2 3 4 5 6 7
9. Fatigue interferes with my work, family or social life.	1 2 3 4 5 6 7
<b>Total Score:</b> _____	

PRO instrument 3: Fatigue Severity Scale (taken from [101])

1. Please use the scale below to tell us how **intense** your pain is. Place an "X" through the number that best describes the intensity of your pain.

No pain	0	1	2	3	4	5	6	7	8	9	10	The most intense pain sensation imaginable
---------	---	---	---	---	---	---	---	---	---	---	----	--

2. Please use the scale below to tell us how **sharp** your pain feels. Words used to describe "sharp" feelings include "like a knife," "like a spike," "jabbing" or "like jolts."

Not sharp	0	1	2	3	4	5	6	7	8	9	10	The most sharp sensation imaginable ("like a knife")
-----------	---	---	---	---	---	---	---	---	---	---	----	--

3. Please use the scale below to tell us how **hot** your pain feels. Words used to describe very hot pain include "burning" and "on fire."

Not hot	0	1	2	3	4	5	6	7	8	9	10	The most hot sensation imaginable ("on fire")
---------	---	---	---	---	---	---	---	---	---	---	----	---

4. Please use the scale below to tell us how **dull** your pain feels. Words used to describe very dull pain include "like a dull toothache," "dull pain," "aching" and "like a bruise."

Not dull	0	1	2	3	4	5	6	7	8	9	10	The most dull sensation imaginable
----------	---	---	---	---	---	---	---	---	---	---	----	------------------------------------

5. Please use the scale below to tell us how **cold** your pain feels. Words used to describe very cold pain include "like ice" and "freezing."

Not cold	0	1	2	3	4	5	6	7	8	9	10	The most cold sensation imaginable ("freezing")
----------	---	---	---	---	---	---	---	---	---	---	----	---

6. Please use the scale below to tell us how **sensitive** your skin is to light touch or clothing. Words used to describe sensitive skin include "like sunburned skin" and "raw skin."

Not sensitive	0	1	2	3	4	5	6	7	8	9	10	The most sensitive sensation imaginable ("raw skin")
---------------	---	---	---	---	---	---	---	---	---	---	----	--

7. Please use the scale below to tell us how **itchy** your pain feels. Words used to describe itchy pain include "like poison oak" and "like a mosquito bite."

Not itchy	0	1	2	3	4	5	6	7	8	9	10	The most itchy sensation imaginable ("like poison oak")
-----------	---	---	---	---	---	---	---	---	---	---	----	---

8. Which of the following best describes the **time** quality of your pain? Please check only one answer.

( ) I feel a background pain all of the time and occasional flare-ups (break-through pain) some of the time.

Describe the background pain: \_\_\_\_\_

Describe the flare-up (break-through) pain: \_\_\_\_\_

( ) I feel a single type of pain all the time. Describe this pain: \_\_\_\_\_

( ) I feel a single type of pain only sometimes. Other times, I am pain free.

Describe this occasional pain: \_\_\_\_\_

9. Now that you have told us the different physical aspects of your pain, the different types of sensations, we want you to tell us overall how **unpleasant** your pain is to you. Words used to describe very unpleasant pain include "miserable" and "intolerable." Remember, pain can have a low intensity, but still feel extremely unpleasant, and some kinds of pain can have a high intensity but be very tolerable. With this scale, please tell us how **unpleasant** your pain feels.

Not unpleasant	0	1	2	3	4	5	6	7	8	9	10	The most unpleasant sensation imaginable ("intolerable")
----------------	---	---	---	---	---	---	---	---	---	---	----	--

10. Lastly, we want you to give us an estimate of the severity of your **deep** versus **surface** pain. We want you to rate each location of pain separately. We realize that it can be difficult to make these estimates, and most likely it will be a "best guess," but please give us your best estimate.

**HOW INTENSE IS YOUR DEEP PAIN?**

No deep pain	0	1	2	3	4	5	6	7	8	9	10	The most intense deep pain sensation imaginable
--------------	---	---	---	---	---	---	---	---	---	---	----	---

**HOW INTENSE IS YOUR SURFACE PAIN?**

No surface pain	0	1	2	3	4	5	6	7	8	9	10	The most intense surface pain sensation imaginable
-----------------	---	---	---	---	---	---	---	---	---	---	----	--

PRO instrument 4: Neuropathic Pain Scale (taken from [102])

	excellent	very good	good	fair	poor
1. In general would you say your health is	<input type="checkbox"/>				
	Much better	Somewhat better	About the same	Somewhat worse	Much worse
2. Compared to one year ago, how would you rate your health in general now?	<input type="checkbox"/>				
3. The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?					
	Yes, limited a lot	Yes, limited a little	No, not limited at all		
a Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
b Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
c Lifting or carrying groceries.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
d Climbing several flights of stairs.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
e Climbing one flight of stairs.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
f Bending, kneeling, or stooping.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
g Walking more than one mile.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
h Walking several blocks.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
i Bathing or dressing yourself.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?					
	Yes	No			
a Cut down on the amount of time you spent on work or other activities.	<input type="checkbox"/>	<input type="checkbox"/>			
b Accomplished less than you would like.	<input type="checkbox"/>	<input type="checkbox"/>			
c Were limited in the kind of work or other activities.	<input type="checkbox"/>	<input type="checkbox"/>			
d Had difficulty performing the work or other activities (for example, it took extra effort).	<input type="checkbox"/>	<input type="checkbox"/>			
5. During the past 4 weeks, have you had any of the following problems with your work or other regular activities as a result of any emotional problems (such as feeling depressed or anxious)?					
	Yes	No			
a Cut down on the amount of time you spent on work or other activities.	<input type="checkbox"/>	<input type="checkbox"/>			
b Accomplished less than you would like.	<input type="checkbox"/>	<input type="checkbox"/>			
c Didn't do work or other activities as carefully as usual.	<input type="checkbox"/>	<input type="checkbox"/>			

	Not at all	Slightly	Moderately	Quite a bit	Extremely	
6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?	<input type="checkbox"/>					
	None	Very mild	Mild	Moderate	Severe	Very severe
7. How much bodily pain have you had during the past 4 weeks?	<input type="checkbox"/>					
	Not at all	A little bit	Moderately	Quite a bit	Extremely	
8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?	<input type="checkbox"/>					
9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks:						
	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
a Did you feel full of pep?	<input type="checkbox"/>					
b Have you been a very nervous person?	<input type="checkbox"/>					
c Have you felt so down in the dumps that nothing could cheer you up?	<input type="checkbox"/>					
d Have you felt calm and peaceful?	<input type="checkbox"/>					
e Did you have a lot of energy?	<input type="checkbox"/>					
f Have you felt downhearted and blue?	<input type="checkbox"/>					
g Did you feel worn out?	<input type="checkbox"/>					
h Have you been a happy person?	<input type="checkbox"/>					
i Did you feel tired?	<input type="checkbox"/>					
	All of the time	Most of the time	Some of the time	A little of the time	None of the time	
10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities with friends (like visiting, relatives, etc.)?	<input type="checkbox"/>					
11. How TRUE or FALSE is each of the following statements for you?						
	Definitely true	Mostly true	Don't know	Mostly false	Definitely false	
a I seem to get sick a little easier than other people.	<input type="checkbox"/>					
b I am as healthy as anybody I know.	<input type="checkbox"/>					
c I expect my health to get worse.	<input type="checkbox"/>					
d My health is excellent.	<input type="checkbox"/>					

**CRQ standardized dyspnea (domain) questions**

Below is a list of activities which make some people with lung problems feel short of breath.

For each of the items below, place an "x" in the box that best describes how much shortness of breath you have had while doing that activity during the LAST 2 WEEKS.

The last column has been provided for you to indicate if you have NOT DONE an activity during the last two weeks.  
(Place an "x" in one box on each line)

ACTIVITIES:	Extremely short of breath	Very short of breath	Quite a bit short of breath	Moderate shortness of breath	Some shortness of breath	A little shortness of breath	Not at all short of breath	Not done
1. Feeling emotional such as angry or upset	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. Taking care of your basic needs (bathing, showering, eating or dressing)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. Walking	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. Performing chores (such as housework, shopping for groceries)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. Participating in social activities	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

**Example of CRQ standardized emotional function (domain) questions**

These next questions ask you about your energy in general and how your mood has been during the LAST 2 WEEKS. Please put an "x" in a box, from 1 to 7, that best describes how you have felt.

In general, how much of the time during the LAST 2 WEEKS have you felt frustrated or impatient?

1. All of the time	<input type="checkbox"/>
2. Most of the time	<input type="checkbox"/>
3. A good bit of the time	<input type="checkbox"/>
4. Some of the time	<input type="checkbox"/>
5. A little of the time	<input type="checkbox"/>
6. Hardly any of the time	<input type="checkbox"/>
7. None of the time	<input type="checkbox"/>

(Place an "x" in one box only)

**Example of CRQ standardized mastery (domain) questions**

In the LAST 2 WEEKS, how much of the time did you feel very confident and sure that you could deal with your illness?

1. None of the time	<input type="checkbox"/>
2. A little of the time	<input type="checkbox"/>
3. Some of the time	<input type="checkbox"/>
4. A good bit of the time	<input type="checkbox"/>
5. Most of the time	<input type="checkbox"/>
6. Almost all of the time	<input type="checkbox"/>
7. All of the time	<input type="checkbox"/>

(Place an "x" in one box only)

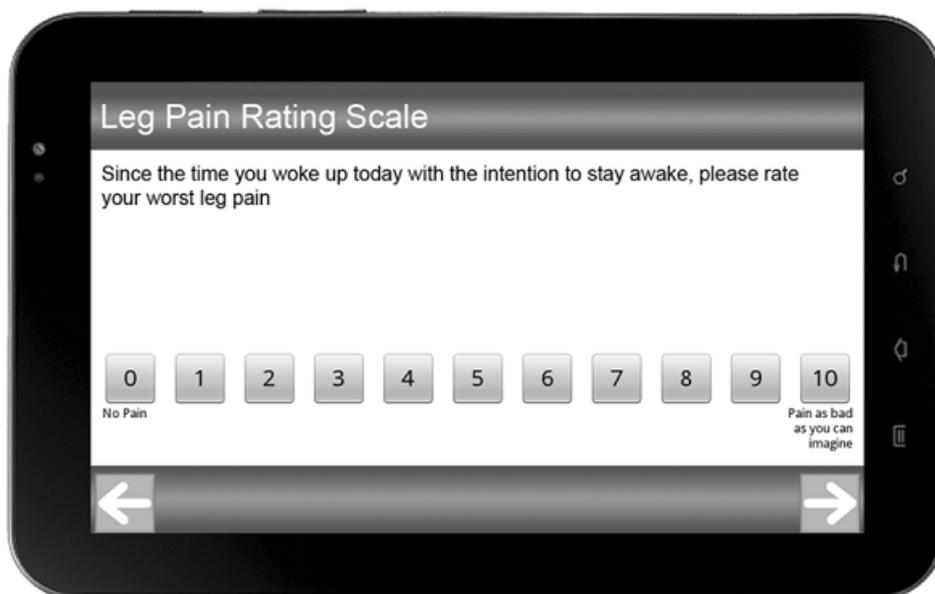
**Example of CRQ standardized fatigue (domain) questions**

What about fatigue? How tired have you felt over the LAST 2 WEEKS?

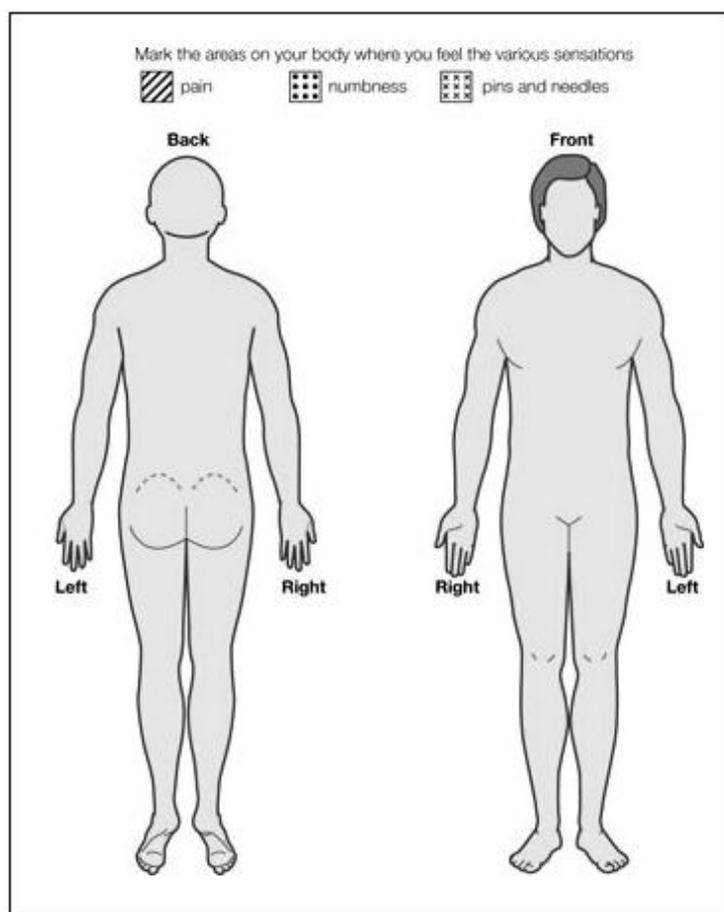
1. Extremely tired	<input type="checkbox"/>
2. Very tired	<input type="checkbox"/>
3. Quite a bit of tiredness	<input type="checkbox"/>
4. Moderately tired	<input type="checkbox"/>
5. Somewhat tired	<input type="checkbox"/>
6. A little tired	<input type="checkbox"/>
7. Not at all tired	<input type="checkbox"/>

(Place an "x" in one box only)

PRO instrument 6: Examples of Chronic Respiratory Questionnaire (CRQ) items (taken from [104])



PRO instrument 7: ePRO instrument (touch-screen computer) (taken from [105])



PRO instrument 8: Pictorial scale for pain assessment (taken from [106])

Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.