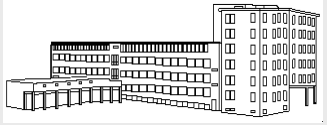
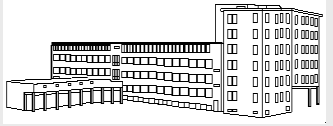


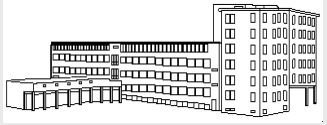
The role of PRO in Clinical Research
EMEA and FDA documents

Giovanni Apolone
Center for Evaluation & Research on Pain
"Mario Negri" Institute
Milan, Italy



Overview

- Outcome: definion and sources
- PROs:definitions and examples
- FDA and EMEA guidances
- The very questions
- An example from the CPOR-SG

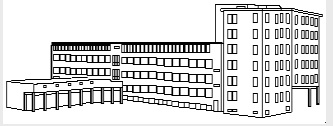


Outcomes

"..what comes out....after applying a medical/health intervention to patients..."

"…a change in patients' current and future health status that can be attributed to health care…" and "...that has meaning for patients and decision-makers..."

A.Donabedian, 1980 and G.Apolone



Outcomes according to the source

OBJECTIVE FINDINGS AND MEASURES

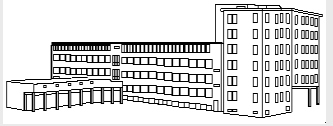
- change in vital status, clinical event, lab results

CRO: Clinician-Reported Outcomes

- Subjective physicians evaluations and ratings

PRO: Subjective Patient-Reported Outcomes

- patient reports
- patient ratings and evaluation



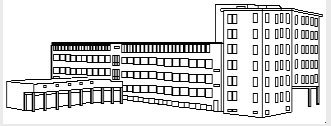
What is a PRO Measure?

PRO is an umbrella term applicable to any health care data reported by the patients

Without interpretation by physicians or anyone, about how they function or feel in relation to a health condition and its therapy

PRO come from diaries, questionnaires, interviews, etc.

PRO are used to assess clinical benefit



WHY PROs?

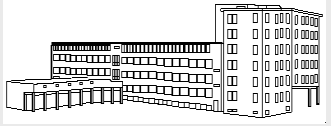
Some treatment effects known only to the patient, i.e. pain, symptoms, feelings

Physiologic measures may not reflect how patient functions or feels

Survival may not be a relevant outcome of interest

Small changes in survival further informed by symptoms, function, and feelings

Well-developed assessment by patients is as reliable (if not more reliable) than global ratings by clinicians



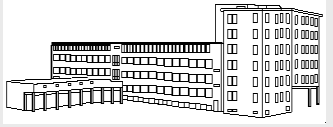
Examples of PROs

HEALTH RELATED

- Symptoms reported and rated by patients
- Global evaluation about an health issue
- Evaluation of functioning or well-being
- HR-QOL, QOL

HEALTH CARE RELATED

- Satisfaction with care
- Compliance/Adherence to therapy

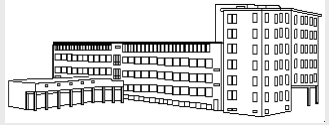


From definition to assessment

PRO Concept: The specific goal of measurement (i.e., the *thing or event* that is to be measured by a PRO instrument)

PRO Instrument: A means to capture data plus all the information and documentation that supports its use (e.g., instructions, mode, scoring and interpretation)

PRO Endpoint: PRO statistical outcome used to compare treatment groups in a particular trial



News from FDA and EMEA

After many attempts, both Agencies have delivered guidance documents

The process was independent but with some coordinations at the very end

FDA: Guidance more exhaustive and technical

EMEA: document more vague and "timid"

FDA

Guidance for Industry

Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims

DRAFT GUIDANCE

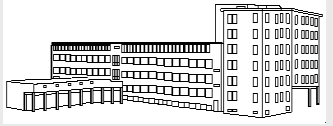
February 2006
www.fda.gov/cder/guidance/5460dft.pdf

EMEA

Reflection paper on the regulatory guidance for the use of health-related quality of life (HRQL) measures in the evaluation of medicinal products

Scope : to discuss the place that HRQL, a specific type of PRO, may have in drug evaluation process and to give some broad recommendations on its use in the **context of already existing guidance documents**.

EMEA/CHMP/EWP/139391/2004
Adoption by CHMP : July 2005
Came into effect : January 2006
www.emea.eu.int



FDA perspective

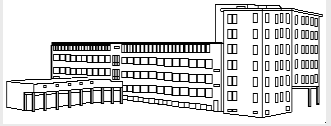
PROs may be an outcome/endpoint to document the treatment benefit

In addition to the usual requirements that are relevant for all the benefit measures, some specific concerns should be considered

These concerns are about the need to document their validity before implementation

FDA recommends to discuss in advance their utilization in trials

NB *Some FDA sections hate subjective measures (Oncology)*



The FDA Guidance

Purpose: provide guidance on FDA's expectations and current thinking about application of federal regulations to the use of PRO measures to support statements in labeling or advertising of regulated products

Topics include:

FDA reviews regarding development, validation, translation, implementation and interpretation of PRO's used to support claims

Outstanding questions FDA seeks input from the scientific and medical community regarding the use of PROs

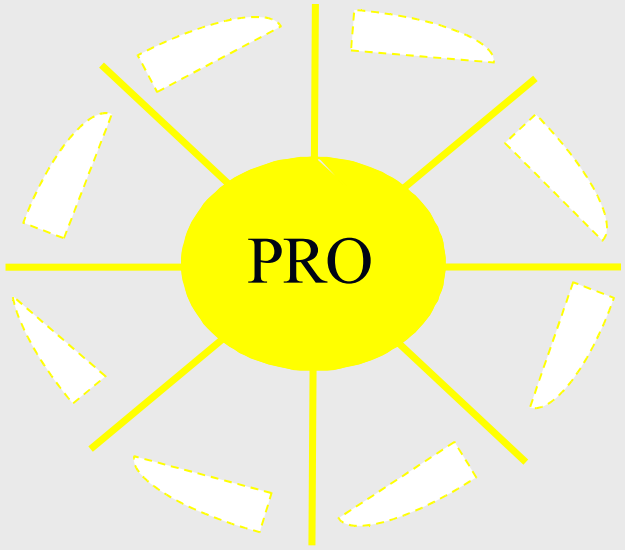
Explanation of how FDA regulations may influence the use and interpretation of PRO data

A. Identify Concepts & Develop Conceptual Framework

Identify concepts and domains.
Identify intended application and population
Hypothesize expected relationships among concepts

D. Modify Instrument

Revise measurement concept
Change application
Change mode of administration
Adapt for culture or language
Other modifications

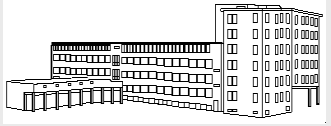


B. Create Instrument

Generate items
Choose data collection method
Choose recall period
Choose response options
Evaluate patient understanding
Develop instructions
Identify scoring
Format instrument
Assess burden
Confirm conceptual framework
Finalize items & instrument

C. Assess Measurement Properties

Evaluate reliability, validity, and ability to detect change
Propose methods for interpretation



EMEA and PRO

EMEA document: short (*5* pages vs *40*), with a strange title (*Reflection paper on* vs *Guidance for*), a different focus (*HRQOL* vs *PRO*) and contents not fully in agreement with current science

Absence of an established Group to lead initiatives (with other counterparts)

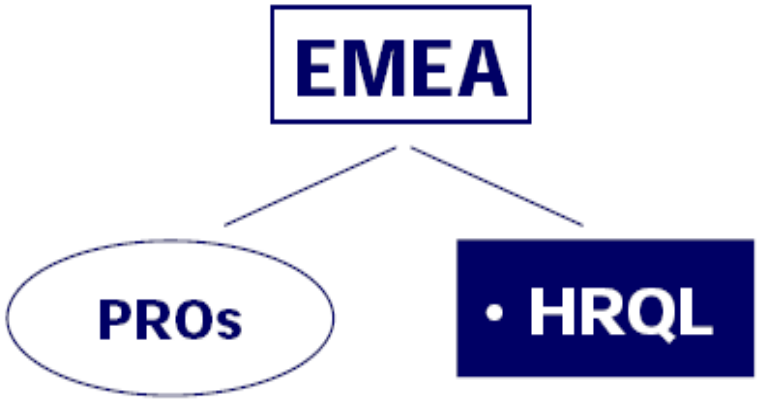
EMEA Document:background and scope

This is not a Guidance on methodological requirements for development, validation and use of Patient-Reported Outcome (PRO) measures in clinical trials. The scope of this reflection paper is to discuss the place that a health-related quality of life (HRQL), a specific type of PRO, may have in drug evaluation process and to give some broad recommendations on its use in the context of already existing guidance documents.

Any outcome evaluated directly by the patient himself and based on patient's perception of a disease and its treatment(s) is called patient-reported outcome (PRO).

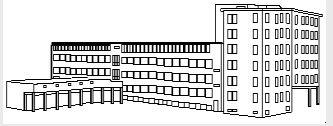
The term PRO is proposed as an umbrella term to cover both single dimension and multi-dimension measures of symptoms, health-related quality of life (HRQL), health status, adherence to treatment, satisfaction with treatment, etc.

Differences between FDA and EMEA



EMEA reflection paper
(Introduction)

HRQL should be clearly differentiated from the core symptoms of a disease (e.g. pain, migraine, pyrosis...) assessed by the patient himself which are well-accepted primary and secondary efficacy endpoints in registration trials.



The very questions about PRO

Old wine in new bottles with new labels?

Do we have valid and robust PRO measures and methods to be used in CTs?

Do PROs measures have an added value when used together with traditional clinical endpoints?

PROs in palliative setting

CONCEPT	PAIN	SATISFACTION
DEFINITION	WP Intensity	Satisf. with Care
INSTRUMENT	NRS (11)	NRS or VRS
ENDPOINT	-2 points	?

THE PROTOCOL

Health and Quality of Life Outcomes

BioMed Central

Research

Open Access

Pain in cancer. An outcome research project to evaluate the epidemiology, the quality and the effects of pain treatment in cancer patients

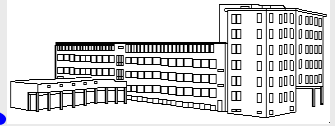
Giovanni Apolone*[1], Oscar Bertetto[2], Augusto Caraceni[3], Oscar Corli[4], Franco De Conno[3], Roberto Labianca[5], Marco Maltoni[6], Mariaflavia Nicora[7], Valter Torri[8], Furio Zucco[9] and the Cancer Pain Outcome Research Study Group

Published: 02 February 2006

Health and Quality of Life Outcomes 2006, 4:7 doi:10.1186/1477-7525-4-7

This article is available from: http://www.hqlo.com/content/4/1/7

Received: 28 July 2005
Accepted: 02 February 2006



Outcome and Endpoints in CPOR-SG

	OUTCOME	ENDPOINT
PAIN INTENSITY	5	15
PAIN RELIEF	1	2
SATISFACTION	2	4
SYMPTOMS	2	4
QUALITY OF LIFE	1	2
TOTAL	11	27

LONGITUDINAL RESULTS

Table 3. Details about the size, direction and statistical significance of endpoints used in the study on the whole longitudinal sample (N=1461)

Outcome	V_1 (sd)	V_5 (sd)	Delta (se)	95%CI Delta	p-value	Effect* size
Worst pain	6.8 (2.3)	4.9 (2.5)	-1.9 (0.07)	-2.0 – -1.7	<0.0001	0.84
Light pain	2.6 (2.0)	1.8 (1.8)	-0.8 (0.06)	-0.9 – -0.7	<0.0001	0.38
Mean pain	4.4 (2.0)	3.1 (2.0)	-1.3 (0.06)	-1.5 – -1.2	<0.0001	0.67
Actual pain	3.4 (2.7)	2.2 (2.1)	-1.2 (0.07)	-1.3 – -1.0	<0.0001	0.43
Overall pain mean	4.3 (1.9)	3.0 (1.8)	-1.3 (0.06)	-1.4 – -1.2	<0.0001	0.69
Pain relief	55 (27)	67 (23)	12 (0.8)	10 – 14	<0.0001	0.45
Satisfaction physician	3.4 (1.4)	4.2 (1.0)	0.8 (0.04)	0.7 – 0.9	<0.0001	0.59
Satisfaction patient	3.5 (1.4)	4.1 (1.1)	0.6 (0.04)	0.5 – 0.7	<0.0001	0.44
QoL	3.8 (1.4)	4.3 (1.4)	0.5 (0.04)	0.4 – 0.6	<0.0001	0.35