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Scientific Criteria in studies assessing Patient-Reported Outcomes (PROs)

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Patient-Reported Outcomes (PRO)

1- Added value

2- Instruments : Development and validation

3- Application to clinical research

4- What does that mean ?

Why should we measure the perception of patients ?

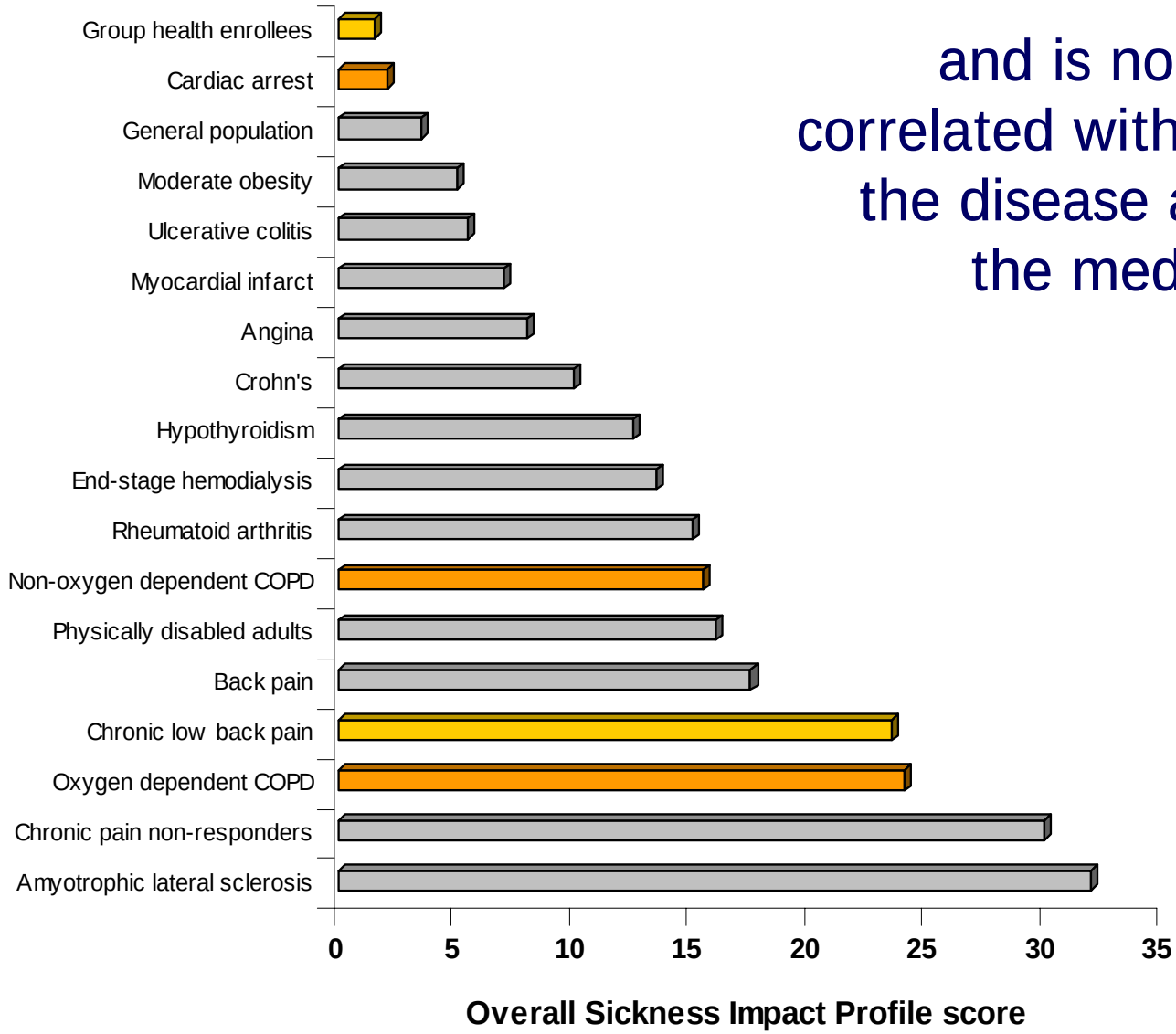
- Changes in the therapeutic targets in the growing context of chronic diseases and palliative treatment in a rising old population

- Nowadays, therapeutic benefits :
  - rarely curative, or prolonging survival,
  - but improving symptoms and functional status, and thus preserving or restoring HRQL

- Availability of PRO questionnaires correctly validated and translated for many diseases

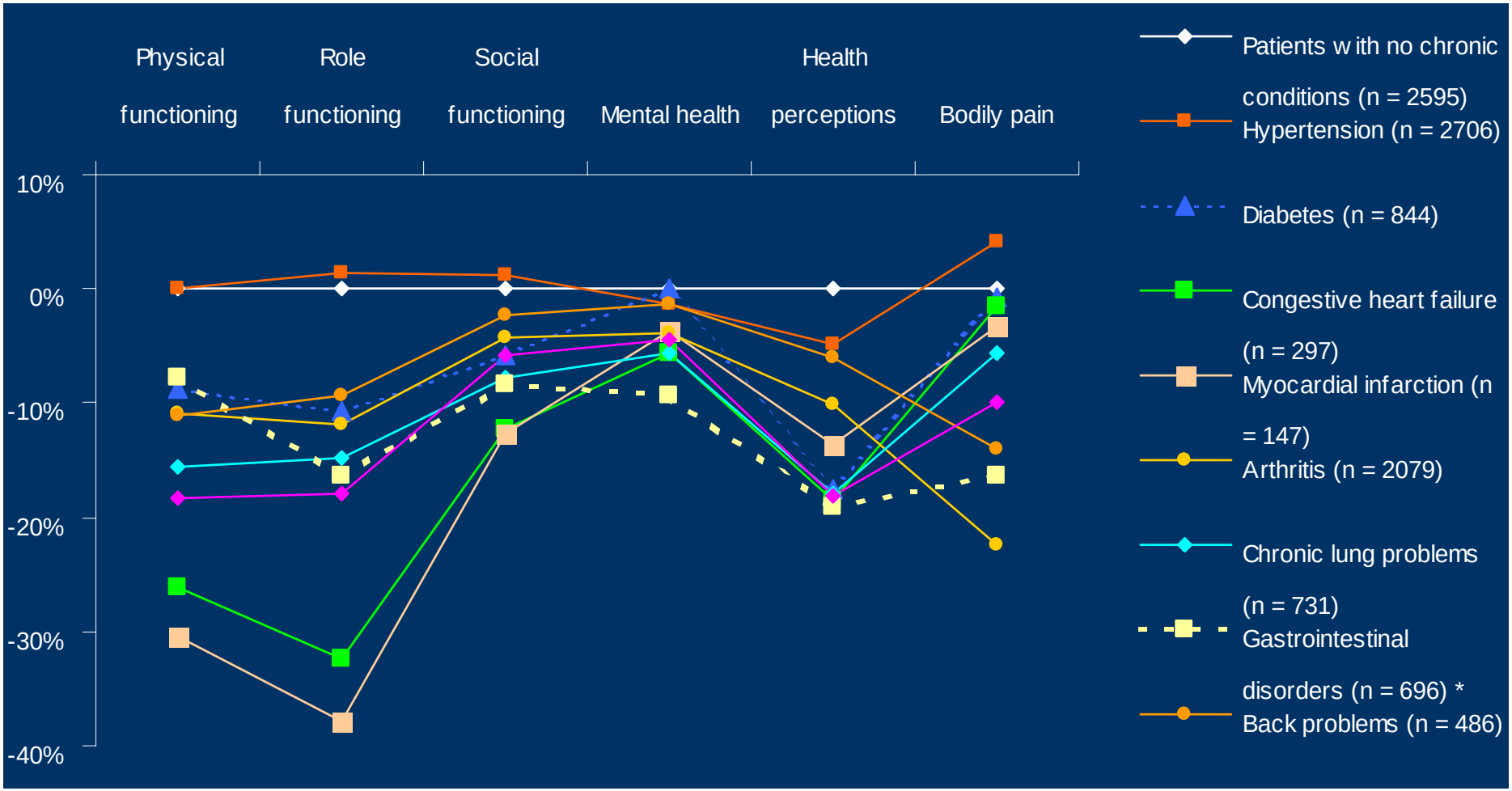
- cancer
- AIDS
- heart failure
- Parkinson's disease
- Alzheimer's disease
- asthma
- COPD
- osteoarthritis
- diabetes ...

The impact on HRQL is not always foreseeable



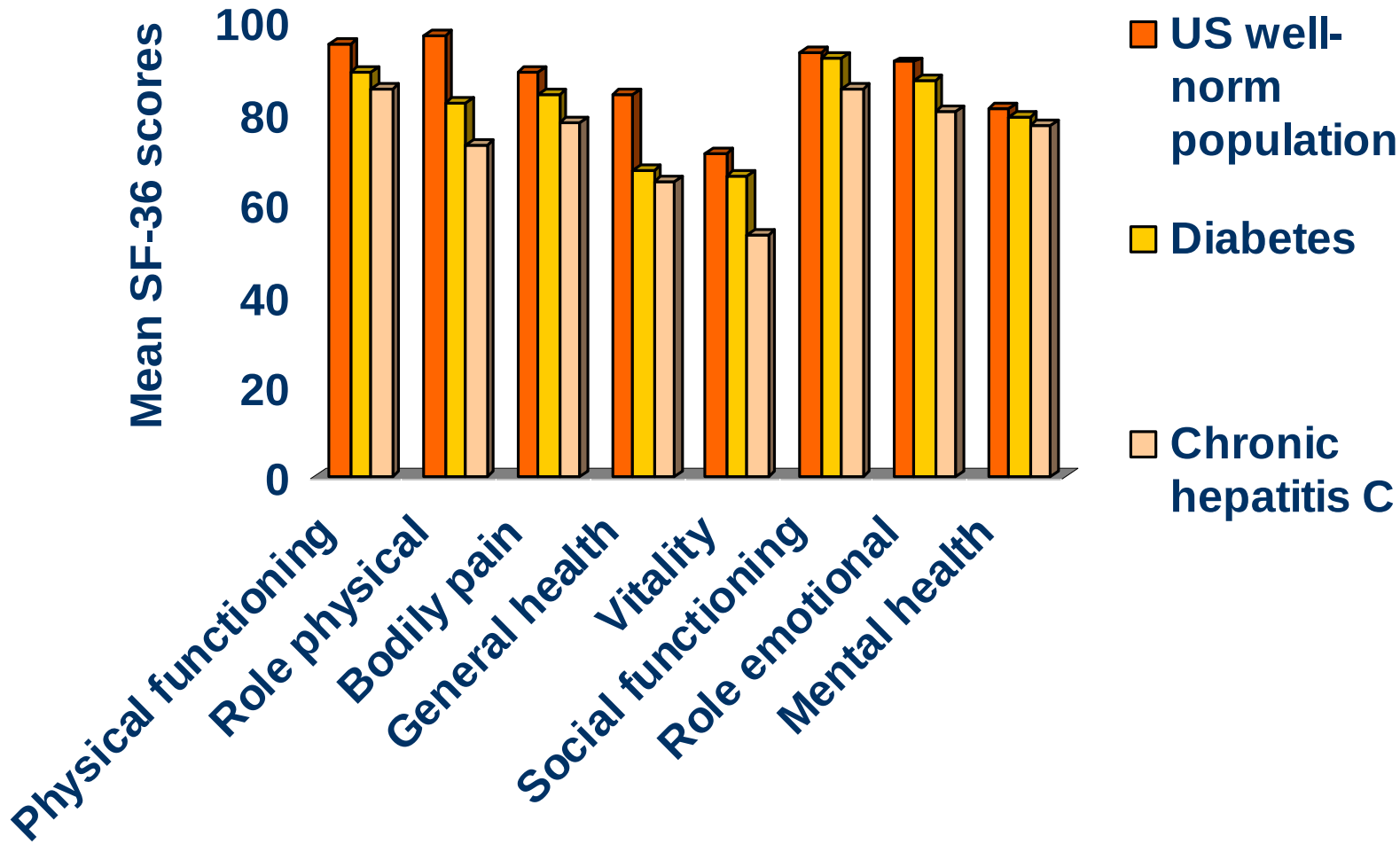
and is not systematically correlated with the severity of the disease as perceived by the medical community

The impact on HRQL is not always foreseeable



Stewart AL et al. Functional status and well-being of patients with chronic conditions. Results from the Medical Outcomes Study. JAMA 1989; 262: 907-913.

The impact on HRQL is not always foreseeable



Bayliss MS et al. A questionnaire to assess the generic and disease-specific health outcomes of patients with chronic hepatitis C. Qual Life Res 1998; 7: 39-55.

Weak correlation between Patient-Reported Outcomes and physiological endpoints

(n = 96)	*r*	*BPQ*	*CRQ*
6-min walk test		0.17	0.07
Pre SaO2		0.14	0.17

Symptoms BPQ : Breathing Problems Questionnaire
HRQL CRQ : Chronic Respiratory Disease Questionnaire

→ Variability in exercise capacity contributed to only 3% of the variability in BPQ score

Quality of life in elderly patients with COPD: measurement and predictive factors. Yohannes AM et al. Resp Med 1998.

Correlation between glycemic control and perception of Quality of Life

DQOLY (Diabetes Quality of Life for Youths)	**Hb1Ac**
Impact (23 items)	**r = - 0.21**
Worry (23 items)	**r = - 0.28**
Satisfaction (11 items)	**r = - 0.04**

Grey M, et al. Personal and family factors associated with quality of life in adolescents with diabetes. Diabetes Care. 1998 ;21: 909-914.

Weak correlation between HRQL & symptoms

- e.g. **Irritable Bowel Syndrome (IBS)**
- The absence of abdominal pain (e.g. during a consultation with a physician) may not be linked with a good HRQL. The patient :
- May be anxious not to know when the next bout will occur
- May be limited in his inter-personal life and his leisure's
- Constrained to take drugs and to pay attention to food

- The same is true in asthma, migraine, osteoarthritis, acne, heart failure, HIV (e.g. impact of lipodystrophia induced by antiretroviral therapy, even in patients who have not yet the side effect) ...

Chassany et al. Validation of a specific quality of life questionnaire in functional digestive disorders (FDDQL). Gut 1999.

Moderate correlation between patients & physicians

IBS is a chronic disease

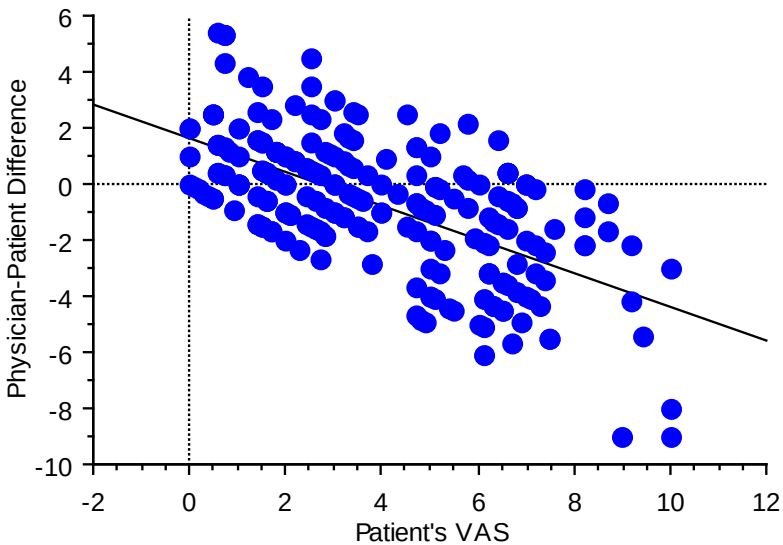
which impacts daily life by its repeated symptomatic flares over years

Cross-sectional survey

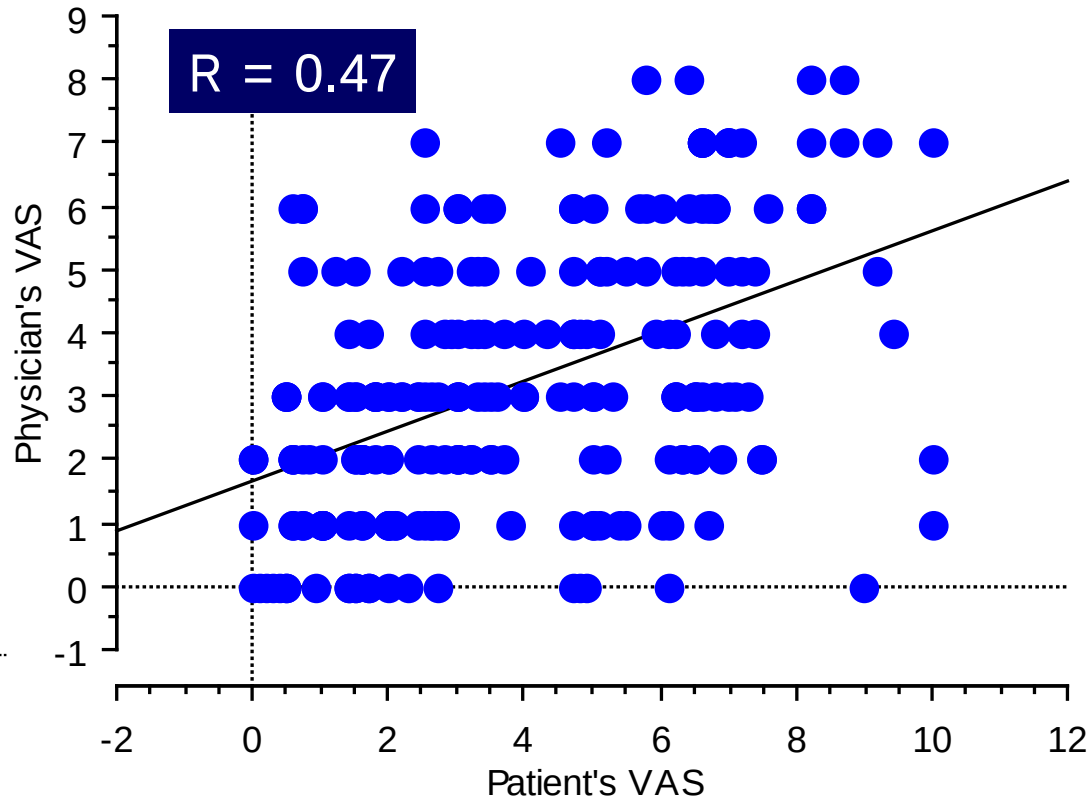
239 IBS patients

57.5 ± 16 years

64% women

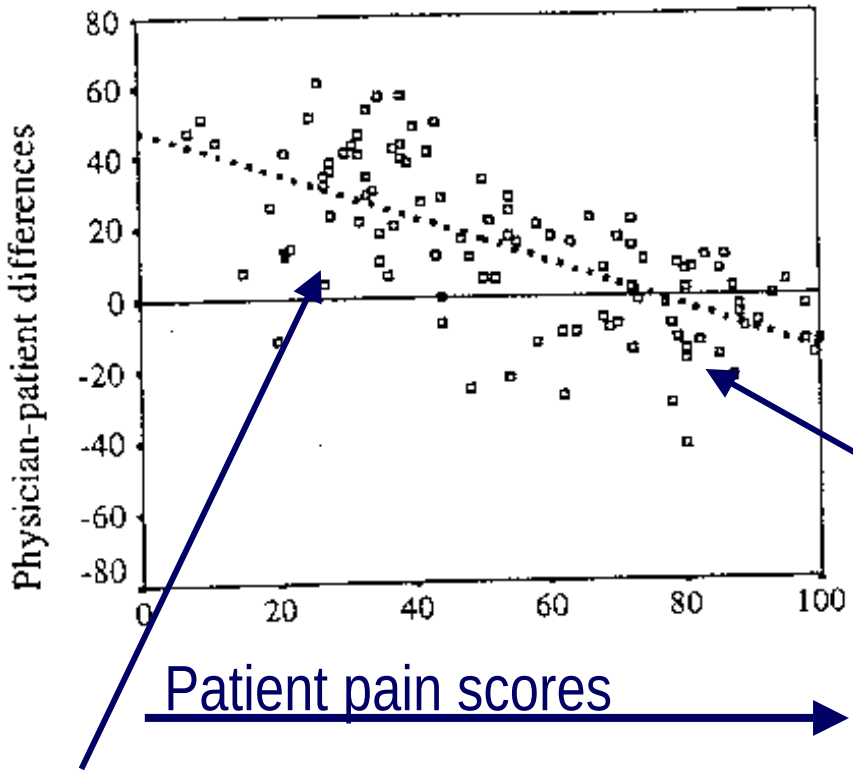


VAS Pain severity



Survey conducted by Thalès and sponsored by ALFIS (Association des Laboratoires et des Firmes de Santé)

Weak correlation between patients & physicians



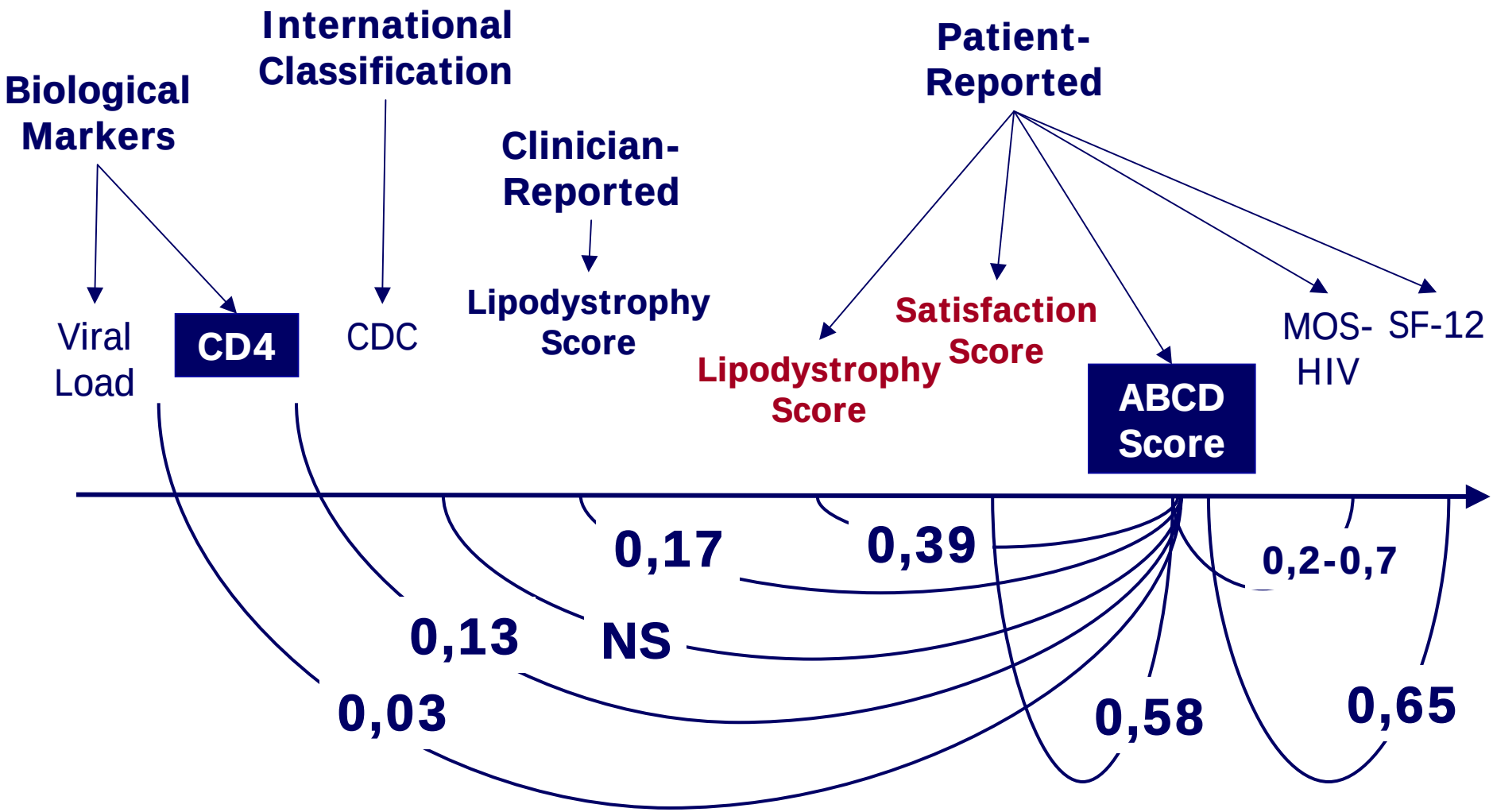
The physician is more disposed to bear the pain of his patient than the patient himself

Tendency of physician to underestimate the pain

Tendency of physician to overestimate the pain

Lack of congruence in the ratings of patients' health status by patients and their physicians. Suarez-Almazor ME et al. Med Dec Making 2001.

The impact of Lipodystrophy (HIV) on the Quality of Life in not adequately captured by other criteria



Duracinsky M, Chassany O. Linguistic and psychometric validation in french of a specific quality of life questionnaire in Lipodystrophy (ABCD)

Define the conditions for which the measurement of HRQL/PRO in clinical trial is useful

- Patient's self-report is the primary or sole indicator of disease activity, e.g. dermatological disorders (psoriasis, acne), erection dysfunction
- No objective marker or several possible markers of disease activity (migraine, osteoarthritis, asthma, menopause, heart failure)
- Disease expressed by many symptoms (IBS)
- To ensure that treatments prolonging survival (AIDS), do not adversely affect patients' lives due to morbidity, functional or psychological impairments or side effects
- The treatment does not seem to improve survival (cancer, rheumatoid arthritis, Parkinson's disease), but it could improve HRQL, by reducing pain, anxiety, level of stress or by improving the functional status.

What is not quality of life ?

The abuse of the term HRQL in some clinical trials, whereas the questionnaire measured anything else

- A listing of symptoms or of **side effects** cannot claim to measure HRQL
- The following concepts cannot alone explore all HRQL:
- **physical or intellectual performance scale**
- **handicap or functional incapacity scale**
- **anxiety or depression scale**
- **tiredness or pain scale**
- **symptom bother scale.**

Patient-Reported Outcomes (PRO)

1- Added value

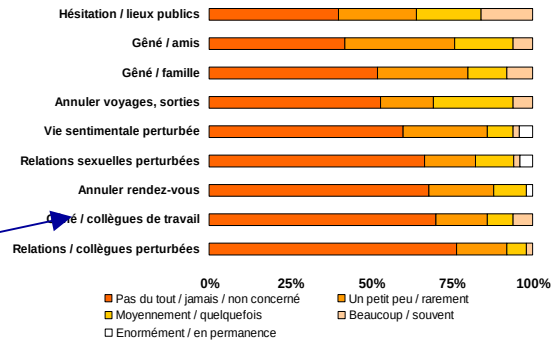
2- Instruments : Development and validation

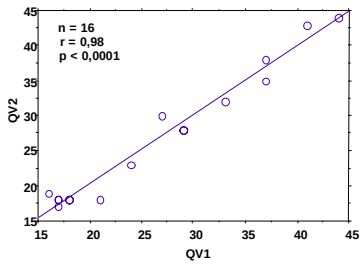
3- Application to clinical research

4- What does that mean ?

To follow the rigorous procedures of development of HRQL or PRO questionnaires

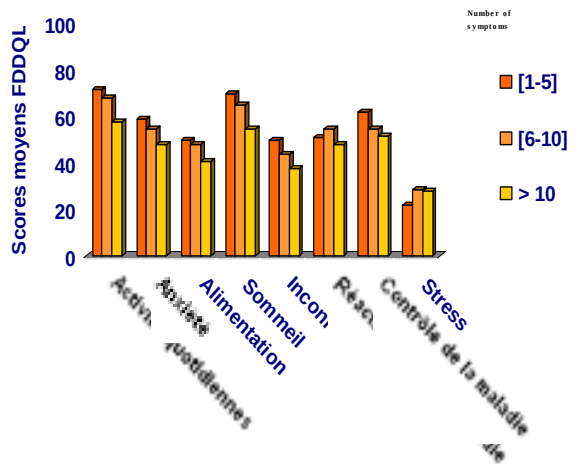
- Item generation
- Scaling
- Item reduction
- Reproductibility
- Content validity
- Construct validity
- Discriminant validity
- Convergent validity
- Responsiveness
- Cultural adaptation





Items	Factor	I	II	III	IV
1.	**Emotional distress**				
	Discouraged or distressed	0.74			
	Frustrated	0.69			
	Anxious or upset	0.74			
	Worry/fear about health	0.77			
	Irritable	0.64			
	Worry serious disease	0.75			
2.	**Sleep disturbance**				
	No good night sleep		0.83		
	Tired-lack of sleep		0.75		
	Wake up at night		0.84		
	Not waking fresh/rested		0.61		
	Trouble getting to sleep		0.73		
3.	**Food/drink problems**				
	Discomfort due to eating/drinking			0.71	
	Eat smaller meals			0.65	
	Unable eat food one likes			0.78	
	Food seems unappealing			0.63	
	Intolerance to food			0.73	
	Avoid certain food/drink			0.74	
4.	**Physical/social functioning**				
	Avoid bending over				0.42
	Kept from doing things with family/friends				0.68
	Difficulty socializing				0.61
	Unable carry out daily activities				0.72
	Unable to carry out physical activities				0.78

	Physical functioning	Role physical	Bodily pain	General health	Vitality	Social functioning	Role emotional	Mental health
Daily activities	0.51	0.63	0.63	0.48	0.52	0.60	0.43	0.48
Anxiety	0.34	0.54	0.46	0.44	0.45	0.43	0.35	0.45
Diet	0.32	0.37	0.43	0.37	0.35	0.50	0.28	0.28
Sleep	0.40	0.41	0.48	0.30	0.39	0.36	0.33	0.36
Discomfort	0.35	0.34	0.49	0.42	0.46	0.44	0.31	0.39
Coping	0.51	0.51	0.54	0.69	0.51	0.54	0.43	0.50
Control	0.24	0.27	0.33	0.40	0.40	0.35	0.25	0.36
Stress	0.06	0.08	0.20	0.15	0.18	0.21	0.20	0.35



Scientific Advisory Committee of the Medical Outcomes Trust. Assessing health status and quality-of-life instruments: attributes and review criteria. Qual Life Res 2002

How measuring fatigue ?

Are we sure that the questionnaire really measures fatigue ?

Multiple causes

- Lack of rest or exercise
- Improper or inadequate diet
- Psychological stress (depression, anxiety)
- Use of recreational substances
- Anemia
- Abnormalities of the thyroid gland and hypogonadism
- Infections
- Side effects of medications
- Sleep disturbances
- Fever

Fatigue description

- Lack of energy
- Sleepiness
- Tiredness
- Exhaustion
- Inability to get enough rest
- Weakness

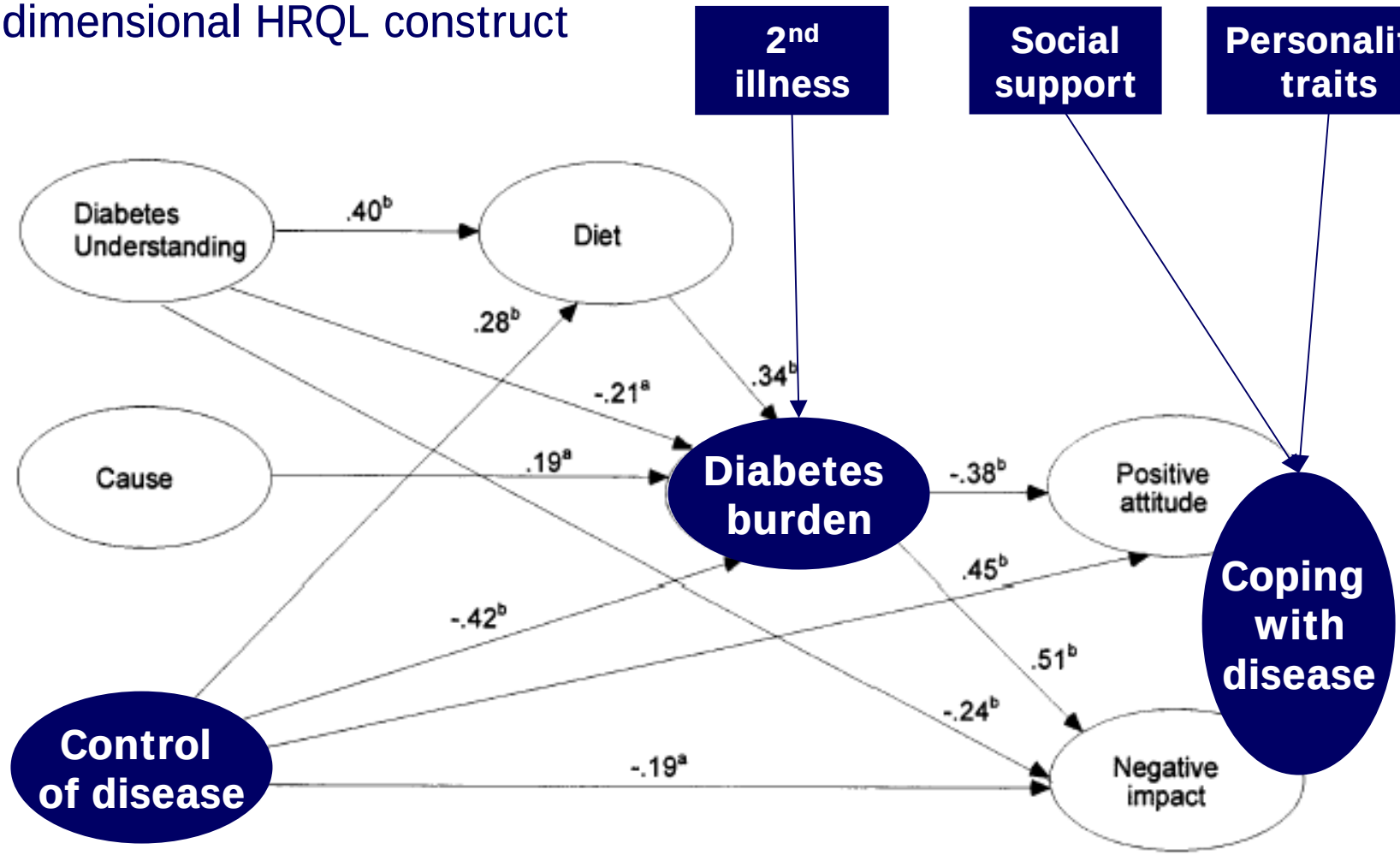
Specific fatigue questionnaire

HRQL questionnaire : must have items related to fatigue

Assessment and treatment of HIV-related fatigue. Adinofi A. J Assoc Nurses AIDS Care 2001.

Determinants of the Quality of Life

Various factors involved in the multidimensional HRQL construct



Rose M, et al. Determinants of the quality of life of patients with diabetes under intensified insulin therapy. Diabetes Care. 1998; 21: 1876-85.

Items about DIET can express different concepts
Input of patients in item generation is critical

Diabetes --> Cause --> **Food** --> consequence --> **DIET**

I am able to do the things I need to do for diabetes

I am able to keep my diet regimen under control

Control of disease / self-management

My diabetes and its treatment keeps me going out with friends / to restaurant / as much as I want

Interference with social and personal relationships

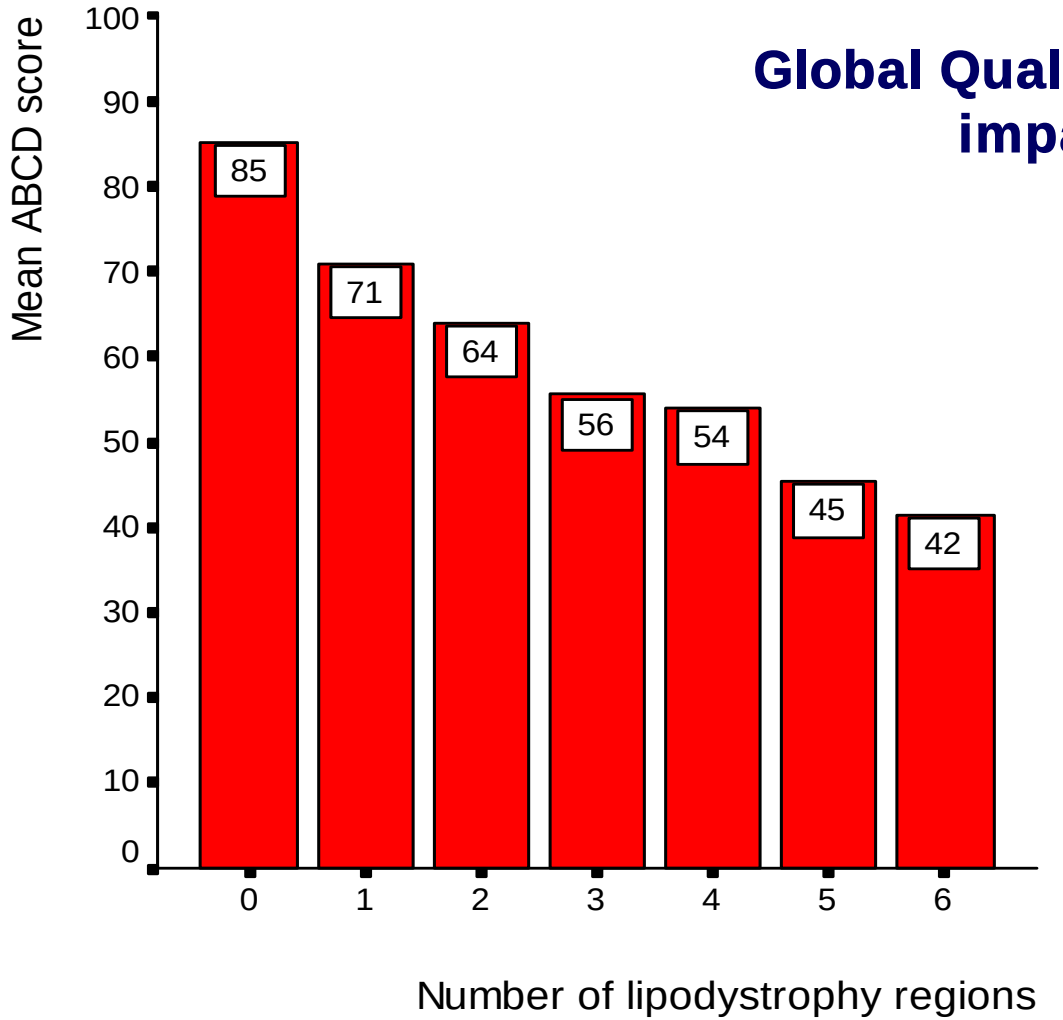
I find it hard to do all the things I have to do for my diabetes

Diabetes doesn't not affect my life at all

Coping with disease

Watkins KW, et al. Effect of adults' self-regulation of diabetes on quality-of-life outcomes. Diabetes Care 2000; 23: 1511-5.

Discriminant validity of a Lipodystrophy specific quality of life questionnaire



Global Quality of Life score (ABCD) impairs with the number of sites of lipodystrophy (n = 155)

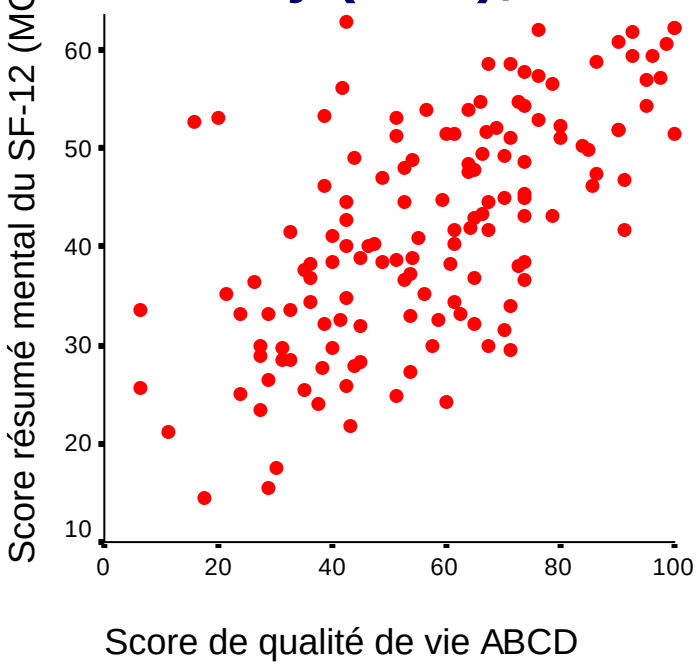
score min-max : 0-100
[0 = worse quality of life,
100 = good quality of life]
ANOVA, $p < 0.001$

Duracinsky M, Chassany O. Linguistic and psychometric validation in french of a specific quality of life questionnaire in Lipodystrophy (ABCD)

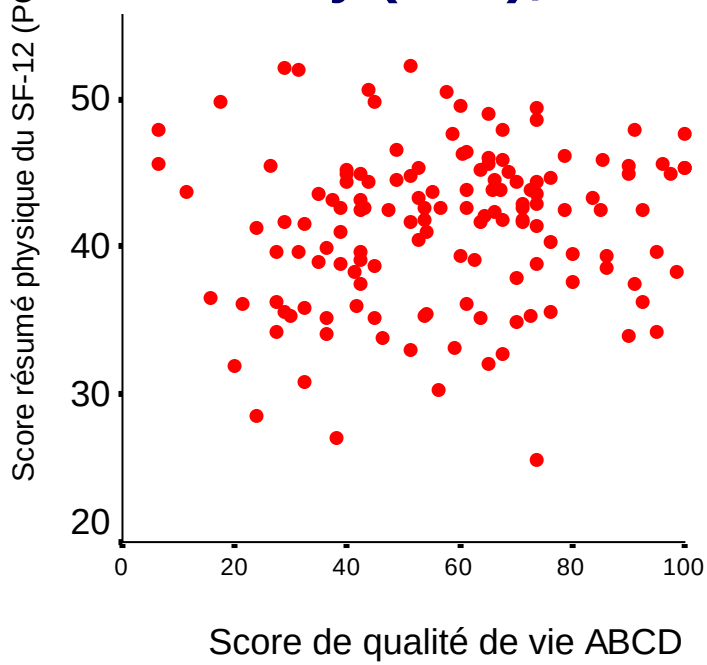
Convergent validity of a Lipodystrophy specific quality of life questionnaire

Logical correlation between Global ABCD score and generic quality of life (SF-12) (n = 155)

vs Mental Component Summary (MCS), r = 0.65



vs Physical Component Summary (PCS), r = 0.101



Duracinsky M, Chassany O. Linguistic and psychometric validation in french of a specific quality of life questionnaire in Lipodystrophy (ABCD)

Cultural adaptation

Forward-backward translation

Disease: Asthma - Original version developed in Canada

Item: *Here is a list of activities in which some people with asthma are limited, among them: « shoveling snow »*

- **US** **Shoveling the snow**
- **Japan** **Beat futons**
- **Norwegian** **Going fishing**

Define the conditions for which the measurement of HRQL/PRO in clinical trial is useful

I was **upset** that I can't control my body

To distress or perturb mentally or emotionally, to disturb, to sadden, to trouble, to offend, to disappoint

---

How often did your asthma make you feel **frustrated** during the past week?

To prevent from accomplishing a purpose or fulfilling a desire. To cause feelings of discouragement

Literal translation in French : **frustré**

Backward translation : offended, dispossessed, injured, shocked

Patient-Reported Outcomes (PRO)

1- Added value

2- Instruments : Development and validation

3- Application to clinical research

4- What does that mean ?

Why there are so few HRQL mention in labelling ?

Drug Approval Process

Major biases encountered in reviewing dossiers

- No **justification of HRQL choice**
- No evidence of questionnaire **validation**
- No **objective** of HRQL changes
- No justification of sample size
- No description of the follow up of patients
- No clear handling of **missing data**
- Not all patients are **analysed**
- No correct presentation of results
- No adjustment for **multiple comparisons**
- **No interpretation of results**

Chassany O, et al. Reporting on quality of life in randomised controlled trials. BMJ 1999.

Checklist for designing, conducting and reporting HRQL - PRO in clinical trials

HRQL / PRO objectives
- Added value of HRQL / PRO
- Choice of the questionnaires
- Hypotheses of HRQL / PRO changes

Study design
- Basic principles of RCT fulfilled ?
- Timing and frequency of assessment
- Mode and site of administration...

HRQL / PRO measure
- Description of the measure (items, domains…)
- Evidence of validity
- Evidence of cultural adaptation

Statistical analysis plan
- Primary or secondary endpoint
- Superiority or equivalence trial
- Sample size
- ITT, type I error, missing data

Reporting of results
- Participation rate, data completeness
- Distribution of HRQL / PRO scores

Interpreting the results
- Effect size
- Minimal Important Difference
- Number needed to treat…

Patient Reported Outcomes (PRO) and Regulatory Issues : A European Guidance Document for the improved integration of health-related quality of life assessment in the drug regulatory process. Chassany O et ERIQA Working Group. Drug Information Journal 2002.

Study Design : specific issues related to PRO measure

- **Eligibility criteria :** if HRQL primary endpoint, set a minimal impairment of HRQL (as for other criteria, e.g. pain, asthma onset...)
- **Timing and frequency** of HRQL assessment :
  - At baseline, at the end of the study or at withdrawal
- **Mode and site** of HRQL administration :
  - Self-administered whenever possible
  - Assure the confidentiality
  - Before the medical consultation
- **Data monitoring** and quality assurance
- **Procedures** for prevention and handling of missing data

Statistical analysis plan : Estimating the adequate sample size

- HSQ (Health Status Questionnaire)
- before / after scores on 1300 patients
- All p values < 0.0001
- Conclusion: all HRQL domains were significantly different across treatment groups

- Problem: 1300 provide 80% power to detect a change of **1 unit** on a **0-100** point scale

JCO 2001 (anonymous).

Statistical analysis plan : PRO Missing data

- Treatment in rheumatoid disease
- Randomized, double-blind vs comparator & placebo, n = 485, 52 wk
- Results : **some modest improvement** in clinical endpoint (ACR)

HRQL assessment (secondary endpoint : HAQ & SF-36) appears better with the new drug, but	
• Only 280 patients analysed	• How many missing data ?
• Multiple comparisons	• Type I error ?
• Many adverse events	• Withdrawal 22% vs 8% placebo

➲ is the impact of Adverse Events recorded by instruments ?

➲ are the patients with AE analyzed for HRQL ?

Statistical analysis plan : PRO Missing data

New drug in urinary disorders

European Mutual Recognition Procedure 2003

- Several randomized, placebo-controlled, double-blind trials
- Primary endpoint : Episode frequency
- Secondary endpoints : Specific HRQL, Patient's Global Impression
- Sample size > 1500 (pooled trials), Duration : 12 weeks

Pooled data	Change differences active vs. placebo	% of missing data (withdrawals due to AE)	Imputation of MD (ITT)
Episode frequency / wk	**- 2 episodes / wk**	< 5% (placebo) 12-18% (active)	LOCF
Specific HRQL	**- 2.8 [0-100]**	< 5% (placebo) 17-24% (active)	LOCF
Responders (1)	**10-14%**		

(1) At least 30% of the greatest possible improvement in score from baseline to endpoint

Is the LOCF, the adequate method to impute MD in patients who probably worsened their perception of HRQL, due to AE ?

Statistical analysis plan : PRO multiplicity

Salmeterol / COPD

- Open label
- Salmeterol 50 µg
- or SR Theophylline bid
- Randomized (n = 178)
- Completers (n = 145)
- HRQL (secondary) : SF-36
- Mean changes between baseline and the 4 assessments over time, for each dimension : Student t test

SF-36	*Assessment*
8 (+1) dimensions	3 months
"	6 months
"	9 months
"	12 months
Number of tests	36

(n = ???) in favor of Salmeterol	*Assessment*	*p*
Physical Functioning (PF)	3 months	0.02
Change in Health Perception (HT)	9 months	0.03
Social Functioning (SF)	12 months	0.04

Efficacy, tolerability and effects on HRQL of inhaled Salmeterol in COPD. Di Lorenzo G et al. Clin Ther 1998.

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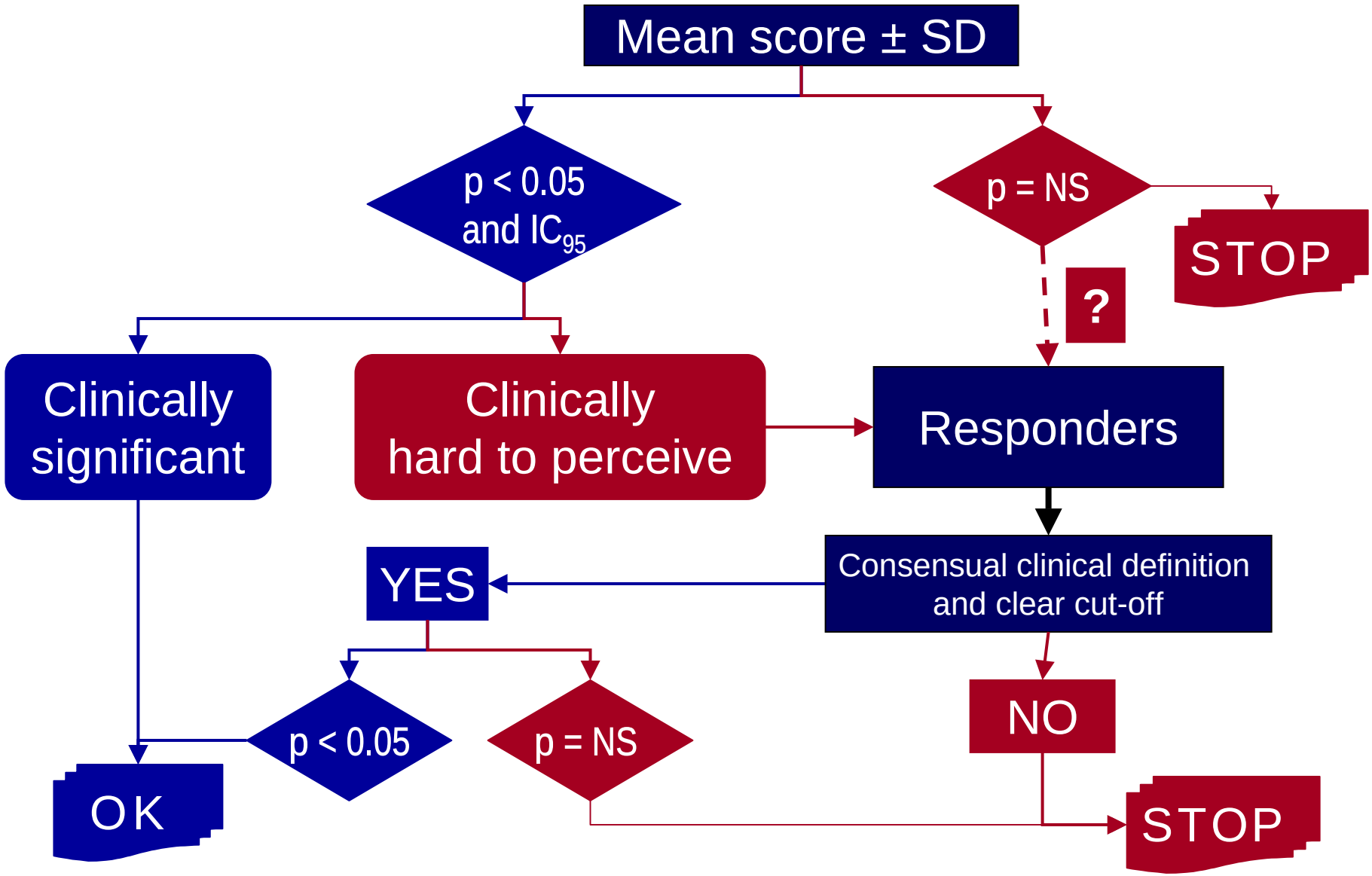
Interpreting PRO results ?

	Zk vs Pl	*p*
Daytime symptoms (0 to 3 (severe))	- 0.14	< 0.001
Nighttime awakening (per wk)	- 0.63	< 0.001
β 2 agonist use (puffs/day)	- 0.64	< 0.001
FEV1	0.05	0.331
Morning PEF (BL : 362)	+ 13,1 L/min	< 0.001
Evening PEF (BL : 398	+ 11,5 L/min	< 0.001
Global AQLQ score (BL : 4.28)	+ 0.26	0.004

Zafirlukast improves asthma symptoms and HRQL in patients with moderate reversible airflow obstruction. Nathan RA et al. J Allergy Clin Immunol 1998.

How to evaluate drugs when clinical relevance of results is not obvious ?



Minimal Important Difference (MID)

MID obtained from comparison with a Global Rating

Answer to the GLOBAL RATING change*	Worse	Better	Interpretation of change	Mean change in HRQL scale (range 1-7)
A very great deal	- 7	+ 7	Large	1.5
A great deal A good deal Moderately	- 6 - 5 - 4	+ 6 + 5 + 4	Moderate	1.0
Somewhat A little	- 3 - 2	+ 3 + 2	Small	0.5
Almost the same	- 1	+ 1		
About the same				

* “Overall, has there been any change in your shortness of breath during your daily activities since the last time you saw us ?”

Guyatt GH, Juniper EF. Several publications

Minimal Important Difference (MID)

MID obtained from comparison with a Global Rating may be different according to :

- Wording of the Global Rating
- Improvement vs. worsening
- Characteristics of patients (age, gender...)
- Characteristics of disease (severity ...)
- Setting of the trial, type of intervention
- Cross-cultural differences
- Baseline level of scores ...

Currently, there is no consensus, whether to be relevant, MID should be **> 0.5 on a range score from 1 to 7**

Impact of the global on patient perceivable change in an asthmatic specific QOL questionnaire. Barber BL et al. Qual Life Res 1996.

Minimal Important Difference (MID)

	MID [range of the scale]	Corresponding MID on a range scale 0-100
PGWB [1]	**3** [0-110] [2] **8** [0-110] [3]	**2.7** **7.3**
SGRQ	**4** [0-100]	**4**
AQLQ [4]	**0.5** [1-7]	**7**
CRQ [4]	**0.5** [0-6]	**7**
I-QOL [4]	**6** [0-100] (GR : little better) **13** [0-100] (GR : much better)	**6** **13**
SF-36	**10** [0-100]	**10**
Dyspnoea index [5]	**1** [-3, +3]	**14**
VAS pain [4]	**2** [0-10]	**18**

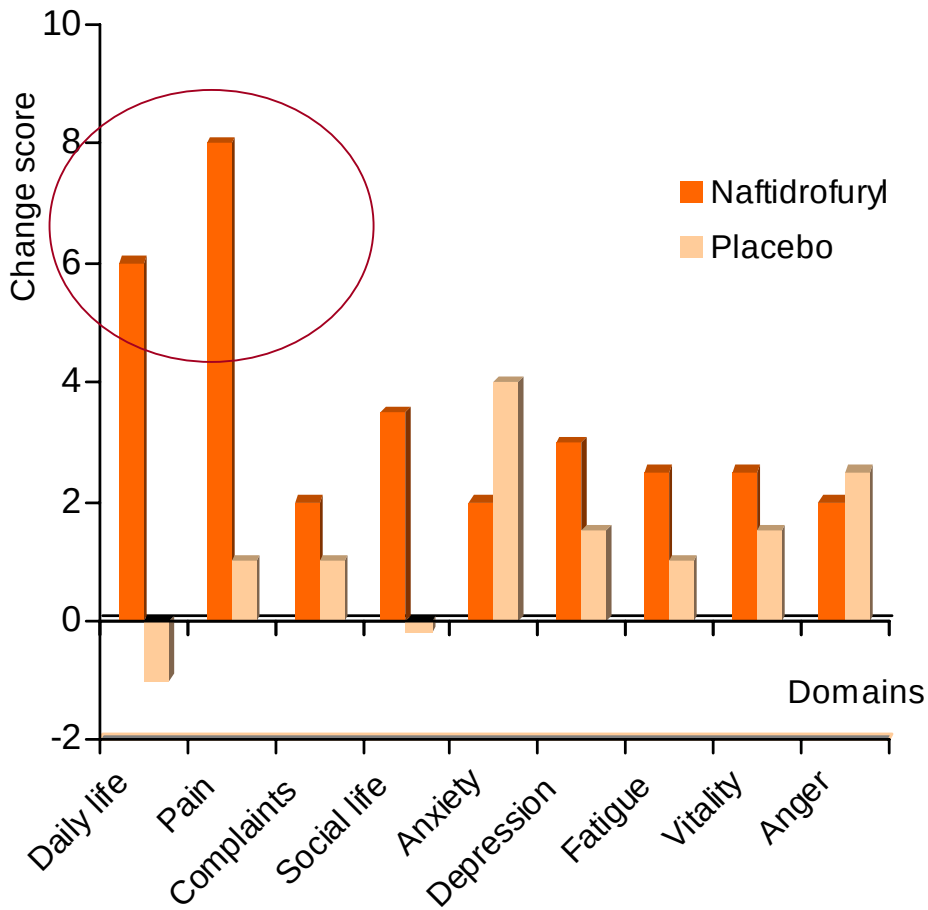
(1) Informal meeting with Harold Dupuy (Paris, June 2003), (2) group level, (3) individual level

(4) values obtained by correlation with a global rating (GR)

(5) Baseline and transitional dyspnoea index (BDI/TDI)

How many and which PRO domains should improve for a claim ?

- 234 Patients with Peripheral Arteriopathy Occlusive Disease (PAOD)
- **HRQL primary endpoint** using the specific questionnaire : CLAU-S (9 domains, 80 items)
- **Results** : 2 domains significantly improved with drug (daily life, p=0.004; pain, p=0.001)
- **Should the planners have hypothesized that only these 2 domains would improve?**



The effects of naftidrofuryl on quality of life. Liard F et al. Dis Manage Health Outcomes 1997.

Interpretation of PRO results

Antacid in GERD

- Randomized, placebo-controlled, double-blind trial
- Primary endpoint : heartburn (diary)
- Secondary endpoint : SF-36 questionnaire
- Sample size > 230
- Duration : 28 days

SF-36 domains	Score differences at 4 wks antacid vs placebo	p	Effect size
PF	< 3	NS	**0.15**
RP	< 7	NS	**< 0.15**
BP	< 3	NS	**0.20**
HP	< 3	NS	**< 0.15**
VT	< 3	**< 0.04**	**< 0.25**
SF	< 3	**< 0.05**	**< 0.10**
RE	< 3	NS	**0.20**
MH	< 4	**< 0.03**	**< 0.20**

- Justification of measuring HRQL at 4-wk (and not after 6 months of taking 3 to 6 pills/day) ?
- Why no difference with placebo on Bodily Pain domain (BP) ?
- Number Needed to Treat on the primary endpoint is **20** patients for one to reduce its heartburn by over 50%

French Drug Agency 2003

How many and which PRO domains should improve for a claim ?

Broad HRQL claim ?

Unlikely, unless

- most of scales of HRQL questionnaires improved
- consistency with standard criteria

Specific-domain claim ?

- If pre-specified
- If consistency with standard criteria
- If evidence of clinical relevance

Where ? Indications or Pharmacodynamic properties chapter ?

ADVAIR experience in asthma

- Juniper-Guyatt's "Asthma Quality of Life Questionnaire"
- AQLQ was administered at day 1 and week 12 (or endpoint, for patients terminating early)
- **Minimal Important Difference = 0.5 for overall score and for individual domains**

Results - Change from Baseline to Endpoint

	Placebo	Advair	Salm	FP
AQLQ global	-0,33	0,99	-0,03	0,56
activity	-0,13	0,99	-0,06	0,74
symptoms	-0,51	1,04	-0,08	0,55
Emotion	-0,45	1,07	0	0,42
Environ.	-0,14	0,87	0,14	0,45

- Results appeared consistent, were not driven by any single domain and were replicated in another trial

ADVAIR : combination Salmeterol + Fluticasone Propionate

Patient-Reported Outcomes - Harmonization Team 2000-2002

- European Regulatory Issues on Quality-of-Life Assessment (ERIQA)
- International Society of Pharmacoeconomic and Outcomes Research (ISPOR)
- International Society of Quality of Life (ISOQOL)
- Pharmaceutical Research and Manufacturers of America (PhRMA) Health Outcomes Committee (HOC)

4 meetings with FDA (Laurie Burke)

Patient-Reported Outcomes - Harmonization Team 2000-2002

Areas of Agreement
February 2001

- Patient Reported Outcomes (PRO) evaluation is a valid concept
  - The subjective impact of treatment provides value over observer-based assessments or simple symptom scales
  - The measure captures information that is missed with traditional measures
- PRO can be operationalized
- PRO claims should conform with the evidence and be pre-specified
- PRO should be reported with fair balance in labeling and promotional claims

Patient-Reported Outcomes - Harmonization Team 2000-2002

March 2002 Forum Agenda

- **Instrument development**: what are the standards
- **Instrument selection**: demonstrating hypothesis, relationships to measurement
- **Statistical issues**: focus on handling missing data
- **Divergence**: explaining and living with deviations

Patient-reported Outcome

- The patient's report of a health condition and it's treatment

Health-related quality-of-life

- Represents the patient's evaluation of the impact of a health condition and its treatment on the most important aspects of life

What is a PRO Instrument ?
Instrument development

- A PRO instrument is comprised of one or more self-reported items that reflect some underlying concept
- Items must provide good coverage of the concept
  - Comprehensiveness of coverage is a qualitative determination, but instrument should:
    - Include items that are relevant and important to the patient
    - Exclude items that are not relevant to the patient
    - Not be overly weighted toward less important concepts

Patient-Reported Outcomes - Harmonization Team 2000-2002

How do we know when we have enough evidence to support a claim?

PRO instruments intended for use in labeling based on trial data should show

- Evidence of reliability and validity in the target population studied independent of the trial on which claim is based
- Additional validity support should be obtained from trials on which claims are based
- Sponsor should provide full evidence of development and assessment upon request

Instrument Development Conclusions

Instrument development is an iterative process

No single *right* way to develop an instrument
although best practices available for steps in the process

Cannot tell by looking at items in an instrument whether it is an appropriate and unbiased measure of concept

- Must look at process of development
- Reasonable to request description of development process

Patient-Reported Outcomes - Harmonization Team 2000-2002

Rationale for Measuring PROs in Clinical Trials
<u>Needs to be explicit</u>

- Demonstrate the clinical relevance to target disease, population, treatment and study setting
  - Understand patient outcomes in clinical trial settings
  - **Understand relationship to clinical measures**
  - **Add patient relevant information not captured by clinical measures**
- Respond to interest by physicians, patients and payers to better understand impact of treatment on patient outcomes

Patient-Reported Outcomes - Harmonization Team 2000-2002

PRO Rationale & Measurement
Operationalize the measurement strategy:

- **Select measure(s) that cover identified domains**
  - Single domain versus multidimensional assessments
  - Generic versus disease-specific instruments
  - Psychometric versus preference-based instruments
- **Evaluate measurement characteristics**
  - e.g. validity, reliability, responsiveness
- **Consider feasibility in clinical trial setting**
  - Attention to respondent and investigator burden
  - Attention to mode of administration
    - e.g. self completed, in-person, telephone or computer interview
  - Be consistent in methods of administration

Patient-Reported Outcomes - Harmonization Team 2000-2002

Statistical Issues: Focus on Handling Missing Data

- Principles for handling missing PRO data and clinical efficacy are the same
- Good study design and administration will maximize PRO data quality
- Understanding reasons for and pattern of missing data is essential for selecting and applying appropriate methods

Patient-Reported Outcomes - Harmonization Team 2000-2002

Divergent Outcomes

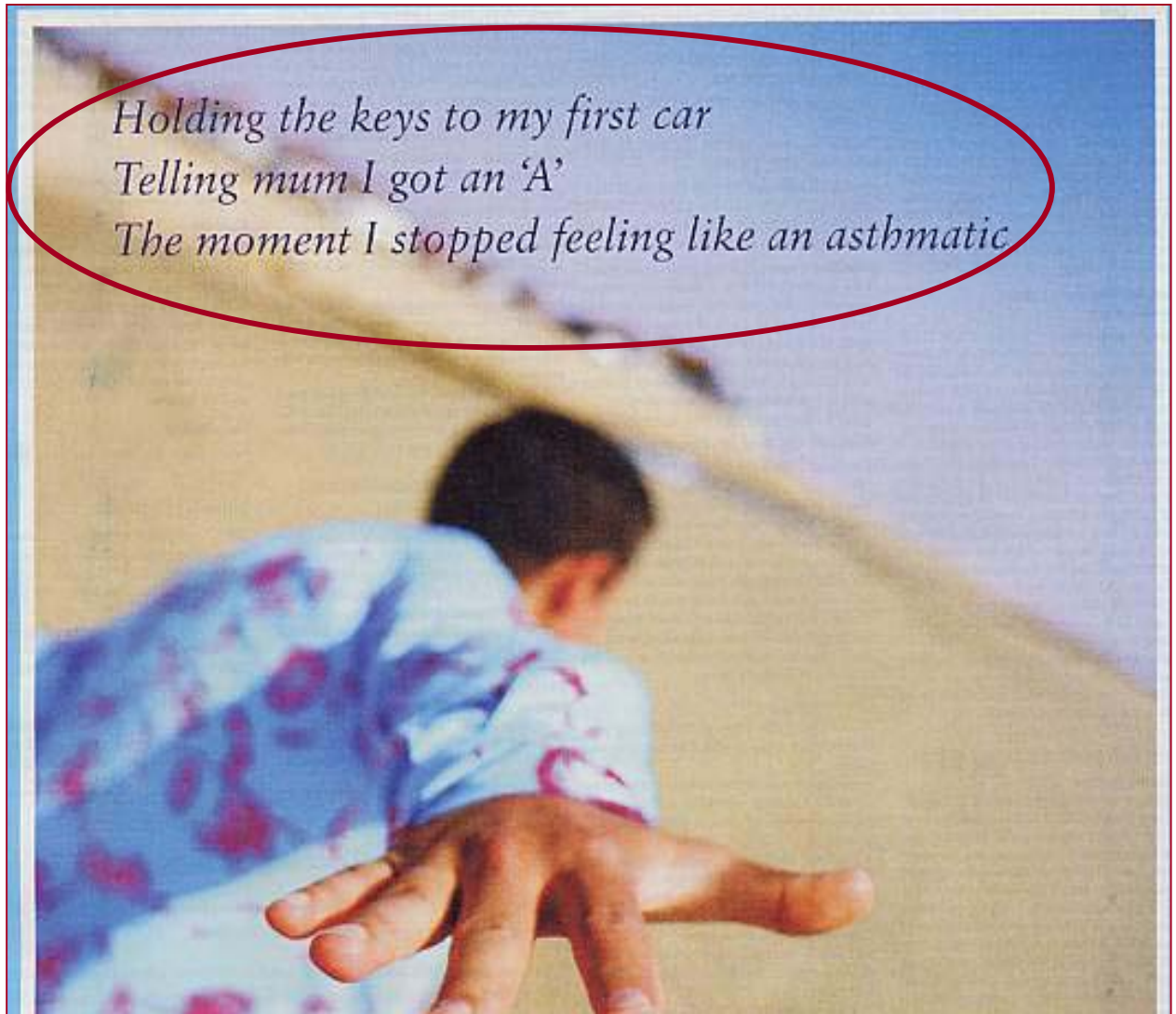
Reasons for Divergence

- Physiologic and PRO measures may assess different constructs
- Not all positive effects occur simultaneously (some effects lag)
- Some subscales measure items that are more trait than state (some patient attributes do not change)
- Only one subscale may be affected (true change in only one subscale)

Divergent Outcomes RECOMMENDATIONS

- Specify the primary and secondary endpoints
- Select PRO subscales **a priori** in the analysis plan
- View all findings together to understand the overall therapeutic benefit of the treatment (“weight of evidence”)

Patient ’s perception as useful as spirometry

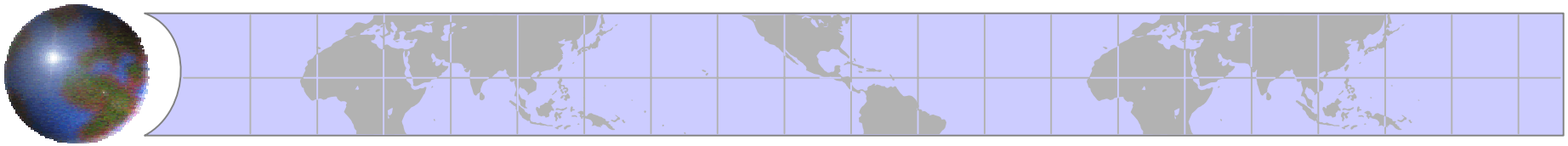


5 key issues for Drug Approval Process

- ***HRQL (and PRO) to be considered as a credible criterion if there is enough evidence (in the file) about the :***

1- Added-value of HRQL/PRO with respect to other criteria
2- Psychometric properties of the HRQL/PRO instruments
3- International validation of the HRQL/PRO instruments
4- Adequacy of the statistical analysis plan
5- Clinical significance of observed changes

Meeting with representatives of AFSSAPS, EMEA and ERIQA Working Group, Paris, 1999



What can one wish for the future ?

- Training of reviewers and regulators to HRQL & PRO
- Questionnaires constantly in adequacy with the beneficial and harmful effects of the new treatments and with the characteristics of the population (children, adolescents, adults, ageing people)
- That HRQL and PRO be part of the daily medical-decision making
- Appropriation and adaptation by regulatory agencies of the published recommendations

What can one wish for the future ?

- Training of reviewers and regulators to HRQL & PRO

WORKMAT : Educational Program for Reviewers

- Appropriation and adaptation by regulatory agencies of the published recommendations

Guidelines FDA (Laurie Burke)

Position Paper (EWP)

MAYO Clinic next meeting