# European Guidance for the Improved Integration of Quality of Life in the Drug Regulation Process (ERIQA)

*How to increase the credibility of Quality of Life data in files submitted to regulatory authorities ?*

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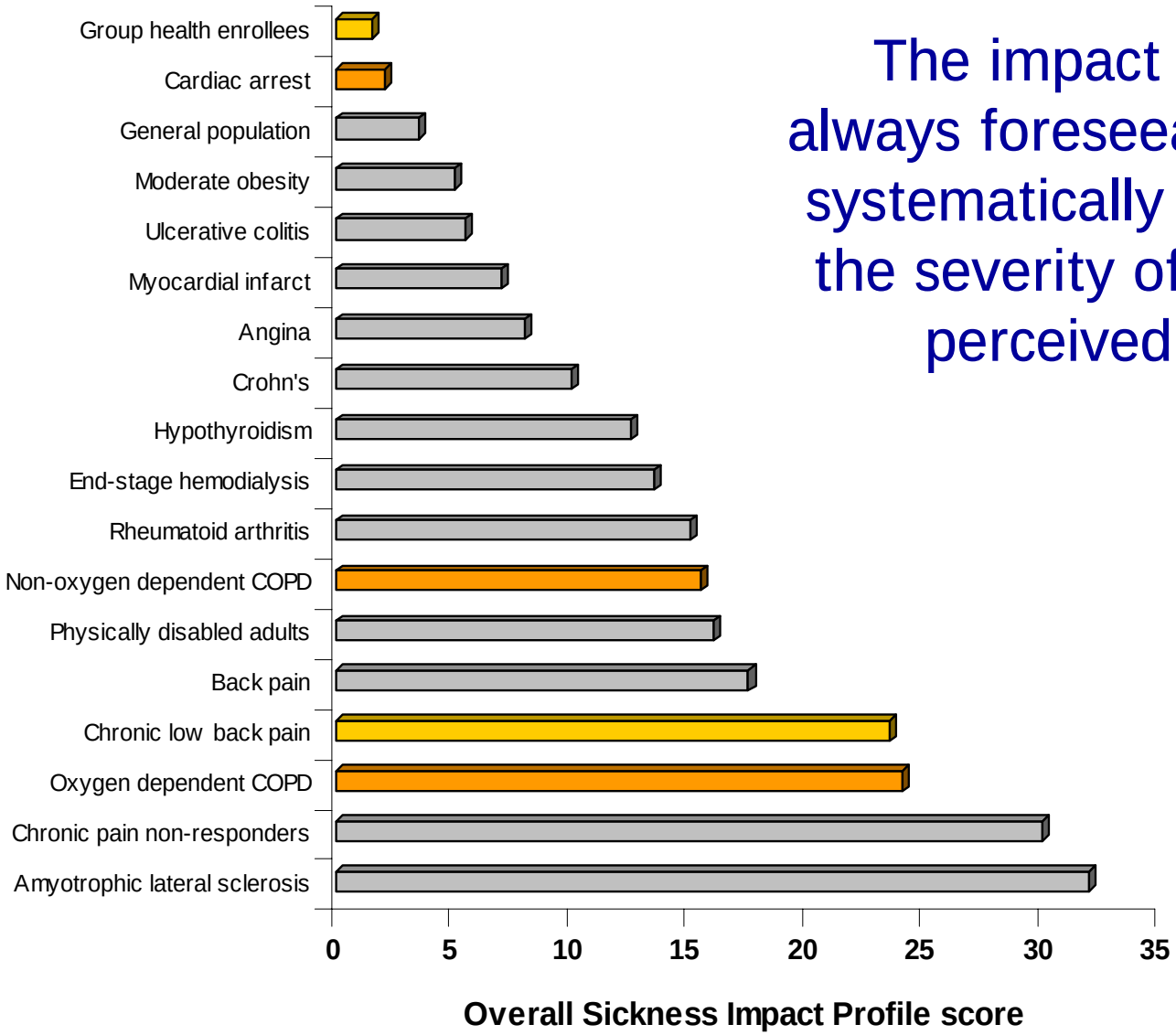
- **Which are the arguments in favour of HRQL ?**
- **Why there are so few HRQL mention in the labelling ?**
- **How to increase the credibility of the HRQL endpoint ?**

# Which are the arguments in favour of HRQL ?

- HRQL is based on several decades of research
- Agreement (more or less) on HRQL definition, multidimensionality and subjective assessment
- Availability of HRQL questionnaires correctly validated and translated for many diseases
- Many studies, especially using generic questionnaires made it possible to appreciate how diseases affected HRQL
- Nowadays, therapeutic benefits : rarely curative, or prolonging survival, but improving symptoms or functional status, thus preserving or restoring HRQL

# Which are the arguments in favour of HRQL ?




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

# Which are the arguments in favour of HRQL ?

## Weak correlation between HRQL and clinician-reported 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.

# Which are the arguments in favour of HRQL ?

## Weak correlation between HRQL & symptoms

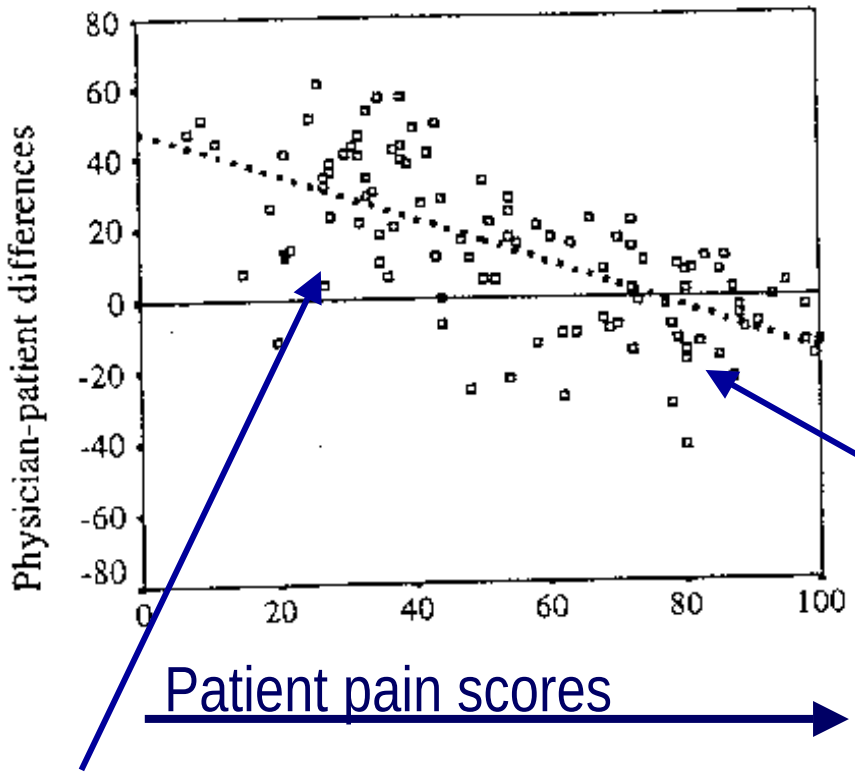
- e.g. **Irritable Bowel Syndrome (IBS)**
- The absence of abdominal pain (e.g. during a consultation with a physician) may not be linked with a good HRQL. The patient :
- May be anxious not to know when the next bout will occur
- May be limited in his inter-personal life and his leisure's
- Constrained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

# Which are the arguments in favour of HRQL ?

## Weak correlation between patients & physicians



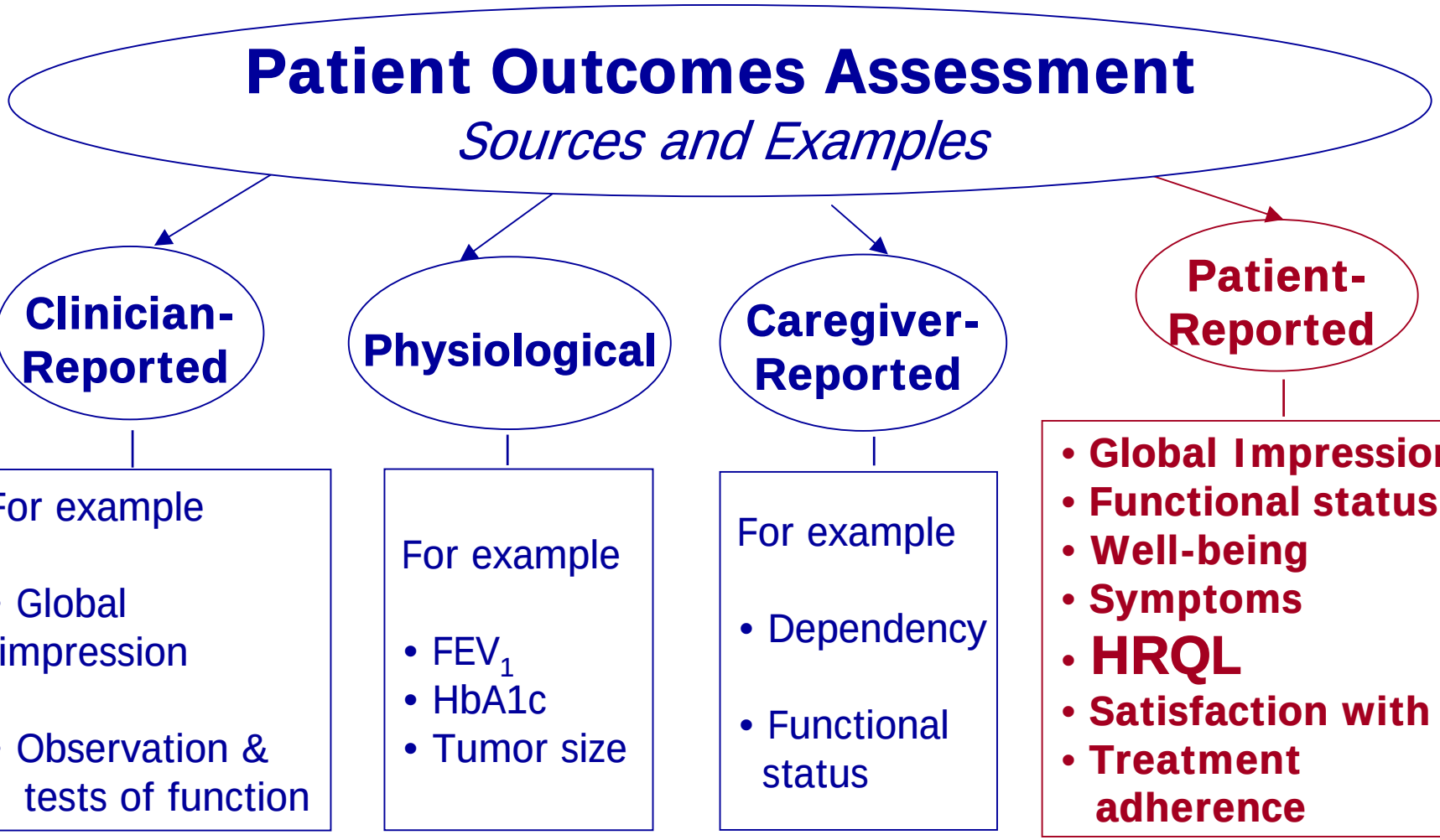

The physician is more disposed to bear the pain of his patient than the patient himself

**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.

# Which are the arguments in favour of HRQL ?




PRO Harmonization Group 2001. Incorporating the Patient's perspective into drug development and communication: report of the Patient-Reported Outcomes Harmonization Group Meeting. FDA, February 2001. www.pro-harmonization-group.com

# Why there are so few HRQL mention in labelling ?

## The limiting factors are (1)

- In a recent past and overall completed, the poor quality of the clinical trials having evaluated HRQL, which left a persistent feeling of mistrust
- The problem of the exact place of HRQL as an endpoint :
  - Is it an efficacy, tolerance, or utility endpoint ?
  - Can HRQL be a primary endpoint, and in which diseases ?
  - Or shall HRQL always be relegated as a secondary endpoint and thus be considered by some regulators as inevitably less rigorous ?

# Why there are so few HRQL mention in labelling ?

## The limiting factors are (2)

- The abuse of the development of HRQL questionnaires and the systematic measurement of HRQL in all diseases.
- 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.

# Why there are so few HRQL mention in labelling ?

## The limiting factors are (3)

- The lack of experience and training of the reviewers and regulators.
- The fears (legitimate) of the regulatory authorities to officially acknowledge the HRQL and to take into account a subjective criterion by nature :
  - Whose clinical interpretation remains difficult
  - Whose good practices of advertising remain to be specified in a market where competition is rough
  - Without counting the possibility for a drug which would have shown a substantial benefit on HRQL, to have claim in terms of rate of refunding, or price

# Why there are so few HRQL mention in labelling ?

## To improve Advertisements

What were hypotheses ?

How is defined a upholding of Well-Being ?

Physical Well-Being

In protocol : Quality of life = "Time lost from usual daily activities"


Better result in placebo group : less time lost (not disclosed in the publication)

1 single item ranging from 0 (very good) to 4 (very poor)

Comparison of Proton Pump Inhibitors in Gastro-oesophageal Reflux Disease

# Why there are so few HRQL mention in labelling ?

## The limiting factors are (4)

- The regulatory authorities do not wish to open into large the door, as they have the fear of seeing all the competitors of a drug for which a claim **“improvement of HRQL”** would have been granted.

- It is thus probable that currently the quotation **“do more and better”** apply when an HRQL improvement is claimed for a new drug.

  **In other words, the submitted file must be exemplary.**

# How to increase the credibility of the HRQL ?

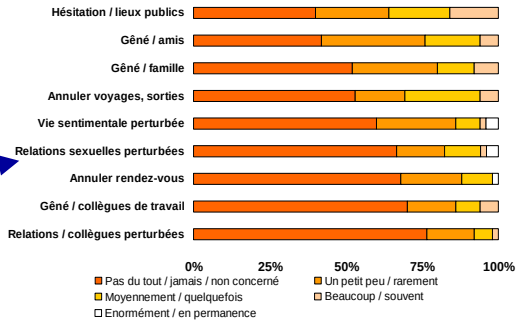
## To define the conditions for which the measurement of HRQL in clinical trial is useful

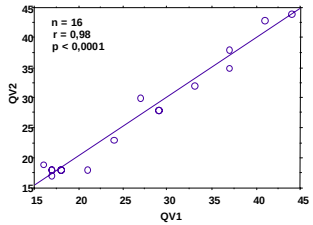
- Patient's self-report is the primary or sole indicator of disease activity, e.g. dermatological disorders (psoriasis, acne), erection dysfunction
- No objective marker or several possible markers of disease activity (migraine, osteoarthritis, asthma, menopause, heart failure)
- Disease expressed by 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.

# How to increase the credibility of the HRQL ?

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

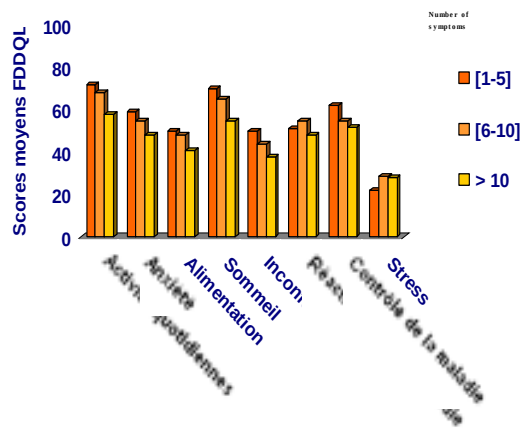
- Item generation
- Scaling
- Item reduction
- Reproductibility
- Content validity
- Construct validity
- Discriminant validity
- Criterion validity
- Responsiveness
- Cultural adaptation




| 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 to increase the credibility of the HRQL ?

## 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.**

# Statistical analysis plan - *Missing data*

- Treatment in rheumatoid disease
- Phase III, RCT, DB, vs comparator & placebo, n = 485, 52 weeks
- 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 ?

# How to increase the credibility of the HRQL ?

## Statistical analysis plan - *Multiplicity*

- 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.

# How to increase the credibility of the HRQL ?

## Interpreting the 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.

# Interpreting the results

## Effect size

| Effect Size | Small | Moderate | Large |
|---|---|---|---|
| Benchmark | > 0.20 | > 0.50 | > 0.80 |

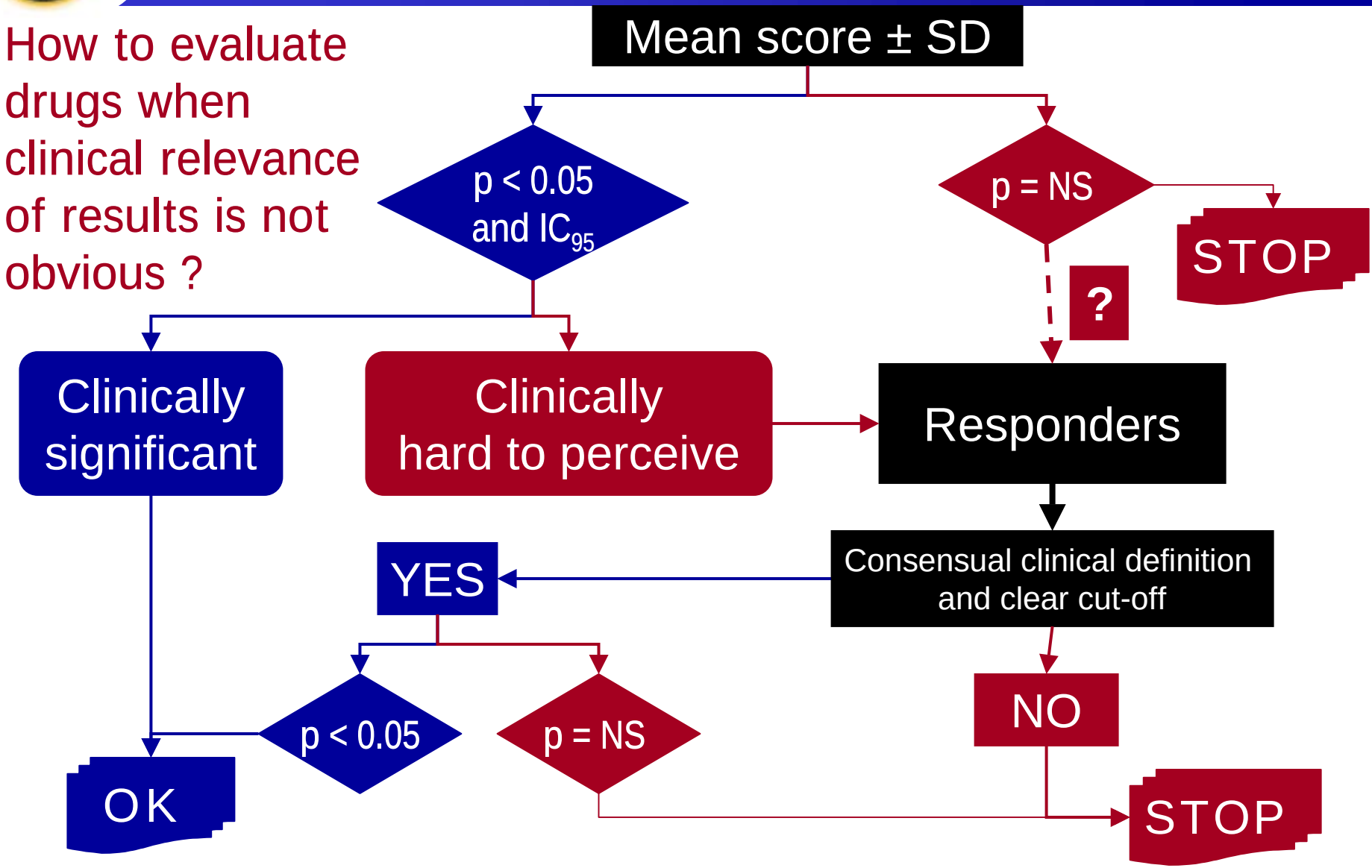
Dividing a difference between 2 groups or the change over time in one group by the SD at baseline (or the SD of the difference : Standardized Response Mean)

| Criteria | Effect Size |
|---|---|
| Walking distance | 2.13 |
| Specific HRQL questionnaire (CLAUS) | 0.48 |

- Treatment in claudication (Peripheral Arterial Occlusive Disease)
- Phase III, randomized, double-blind, vs placebo

# How to increase the credibility of the HRQL ?

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



# Interpreting the results

## Minimal Important Difference (MID) - vs 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 | - 6 | + 6 | Moderate | 1.0 |
| A good deal | - 5 | + 5 | | |
| Moderately | - 4 | + 4 | | |
| Somewhat | - 3 | + 3 | Small | 0.5 |
| A little | - 2 | + 2 | | |
| 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 ?”

# Interpreting the results

## Minimal Important Difference (MID) - vs global rating

- Wording of the Global Rating
- 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 or > 4 on a range score from 0 to 100** (St George's Respiratory Questionnaire)

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

# Interpreting the results

## Number needed to treat (NNT)

- derived from the difference of responders (patients who improved their HRQL score > MID) between groups

| *Chronic Respiratory Questionnaire* | *mean Δ* | NNT to have 1 patient receive at least a small benefit | NNT to have 1 patient receive at least a moderate or large benefit |
|---|---|---|---|
| Dyspnea | 0.61 | 4.1 | 5.8 |
| Fatigue | - 0.63 | 4.4 | 6.9 |
| Emotional function | - 0.64 | 3.3 | 6.3 |
| Mastery | 0.05 | 2.5 | 2.8 |

Prospective randomized controlled trial of rehabilitation

84 subjects completed

Intervention : 2 months of impatient rehabilitation followed by 4 months of outpatient supervision

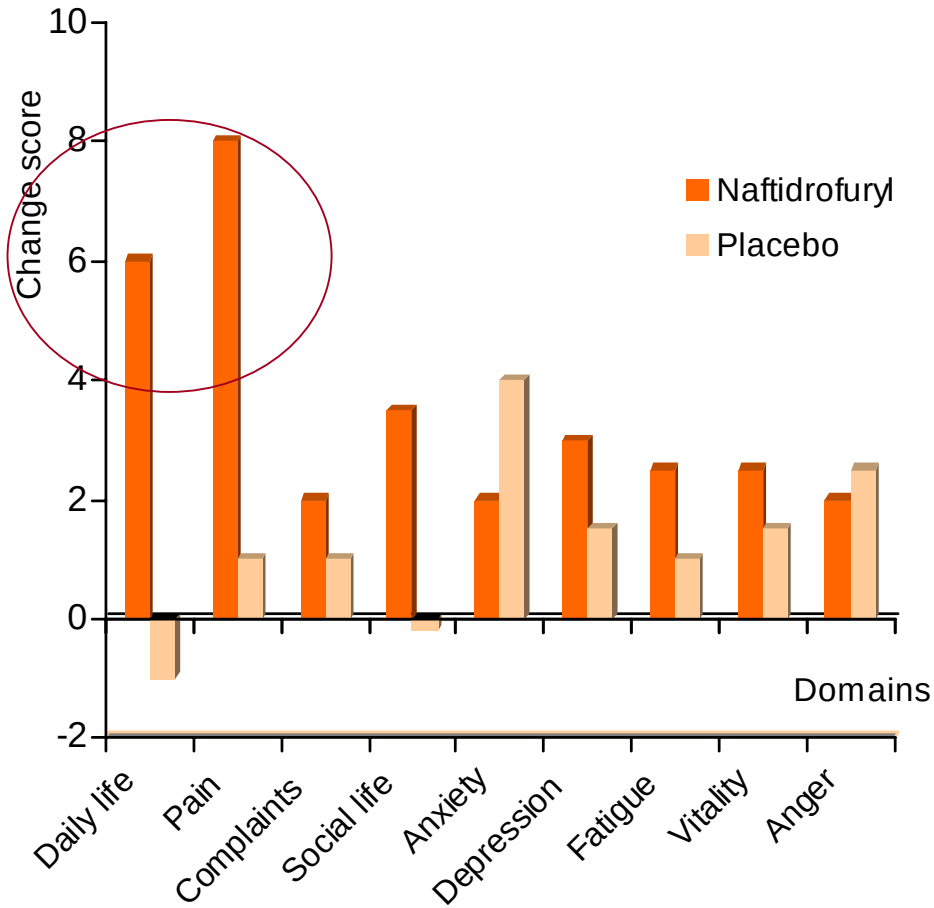
Economic analysis of respiratory rehabilitation. Goldstein RS et al. Chest 1997; 112: 370-9.

# How to increase the credibility of the HRQL ?

## Interpreting the results

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

- 234 Patients with 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?**

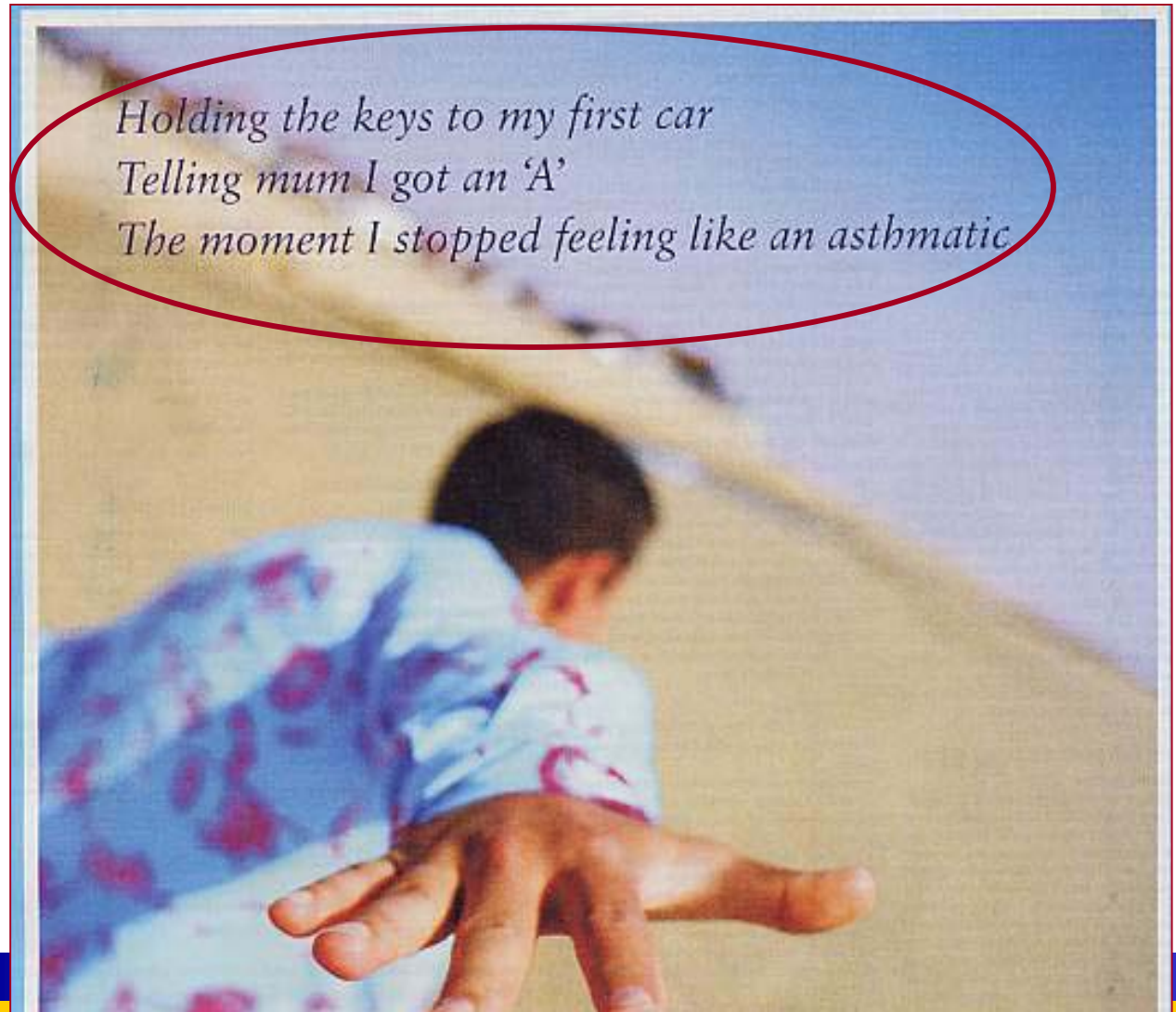



The effects of naftidrofuryl on quality of life. Liard F et al. Dis Manage Health Outcomes 1997.

# What can one wish for the future ?

- Training of reviewers and regulators to HRQL & PRO
- Appropriation and adaptation by regulatory agencies of the published recommendations
- Questionnaires constantly in adequacy with the beneficial and harmful effects of the new treatments
- Choice among the various questionnaires available for each disease, of those which have the best psychometric properties (responsiveness)
- That HRQL and PRO be part of the daily medical-decision making

# HRQL endpoint, as useful as spirometry



# Conclusion

## 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 with respect to other criteria
2- Psychometric properties of the HRQL instruments
3- International validation of the HRQL 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