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INTEGRATION OF PATIENT PERSPECTIVES IN DRUG EVALUATION: HARMONIZATION, CONSENSUS, AND DIVERGENCE

Health-Related Quality of Life and Patient-Reported Outcomes

A European Perspective

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The views expressed are my own and do not represent an official position or policy of EMEA or AFSSAPS

Part of the presentation is based upon work of ERIQA group (European Regulatory Issues on Quality of Life Assessment) Coordinator : Dr C. Acquadro, Mapi Research Institute

EMEA RECOMMENDATIONS

CPMP / ICH Topic E9, Note for Guidance on Statistical Principles for Clinical Trials, 1998

2.2.2. Primary and secondary variables :

"... Measurements relating to **quality of life** and health economics are further potential primary variables ..."

CPMP : Committee for Proprietary Medicinal Products

EMEA RECOMMENDATIONS

Negative

- **Crohn's Disease (1999)**

  Other end-points such as…[..]…improvement in HRQL can be subsumed as response variables or outcomes measures of either the treatment of active disease or maintenance of remission. **Unless otherwise justified, they should not be mentioned in the indication**

Health-Related Quality of Life (HR-QOL) and regulatory Issues. An assessment of the European Agency for the evaluation of medicinal products (EMEA) recommendation on the use of HR-QOL measures in drug approval. *Apolone G, on the behalf of the ERIQA Group. Pharmacoeconomics 2001 ; 19 : 187-195.*

EMEA RECOMMENDATIONS

Study design issues

- **Chronic PAOD (1995)**

  In long-term therapeutic studies with an **appropriate sample size of patients**, the assessment of HRQL should also be performed by using general or disease specific questionnaires

- **Anticancer in Man (1995)**

  The choice of scales should be justified and the validity of the scale for the specific study population and its reliability should be documented. **Cultural aspects should be taken into account, especially in the case of multinational studies**

- **COPD (1999)**

  Care should be taken with respect to **statistical multiplicity if secondary endpoints become the basis for specific claims**

EMEA RECOMMENDATIONS

Study design issues

Cardiac Failure (1995)

It is particularly important to consider whether

- the scale is linear over the range of measurements
- is sensitive to the changes anticipated
- it is valid and useful to adjust results using the baseline scores
- there is any correlation between the score and the objective responses
- the observer and the patients should be blinded and
- training of both the observer and the patient is necessary

EMEA RECOMMENDATIONS

Points to consider (CPMP/EWP/562/98) on clinical investigation of medicinal products in the chronic treatment of patients with COPD, 1999

- In the major efficacy studies of symptomatic benefit the primary endpoint should reflect the clinical benefit the applicant wishes to claim in the future SPC (Summary of Product Characteristics)
- It should include the **FEV1** as a measure of lung function and include a measure of **symptomatic benefit**
- A significant benefit for **both endpoints**, should be demonstrated so that no multiplicity adjustment to significance levels is indicated
- **The primary symptomatic benefit endpoint** should be justified by referencing published data which supports its validity; one example is the **St George's Respiratory Questionnaire**
- There are number of **secondary endpoints** which may provide useful information. … e.g. symptom scales, … and **quality of life assessment**

CHECKLIST FOR DESIGNING, CONDUCTING AND REPORTING HRQL / PRO IN CLINICAL TRIALS

Patient Reported Outcomes and Regulatory Issues : the Example of Health-Related Quality of Life. A European Guidance Document for the improved integration of health-related quality of life assessment in the drug regulatory process. *O. Chassany et al for the European Regulatory Issues On Quality of Life Assessment (ERIQA) group. Drug Information Journal 2002, under press.*

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 content of 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

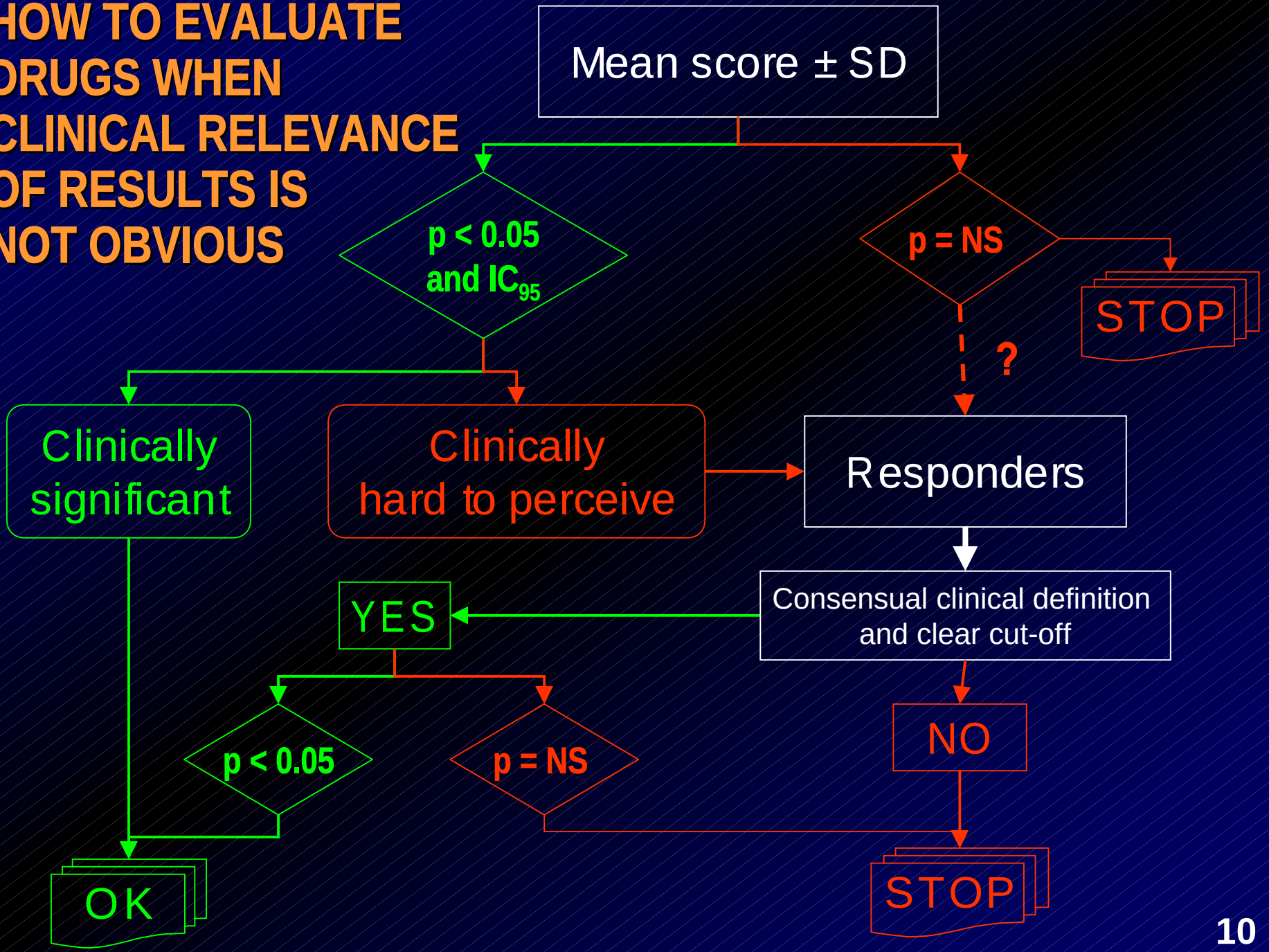
Interpreting the results

- Effect size, MCID
- Comparison with other scores
- Comparison with external criteria
- Number needed to treat…

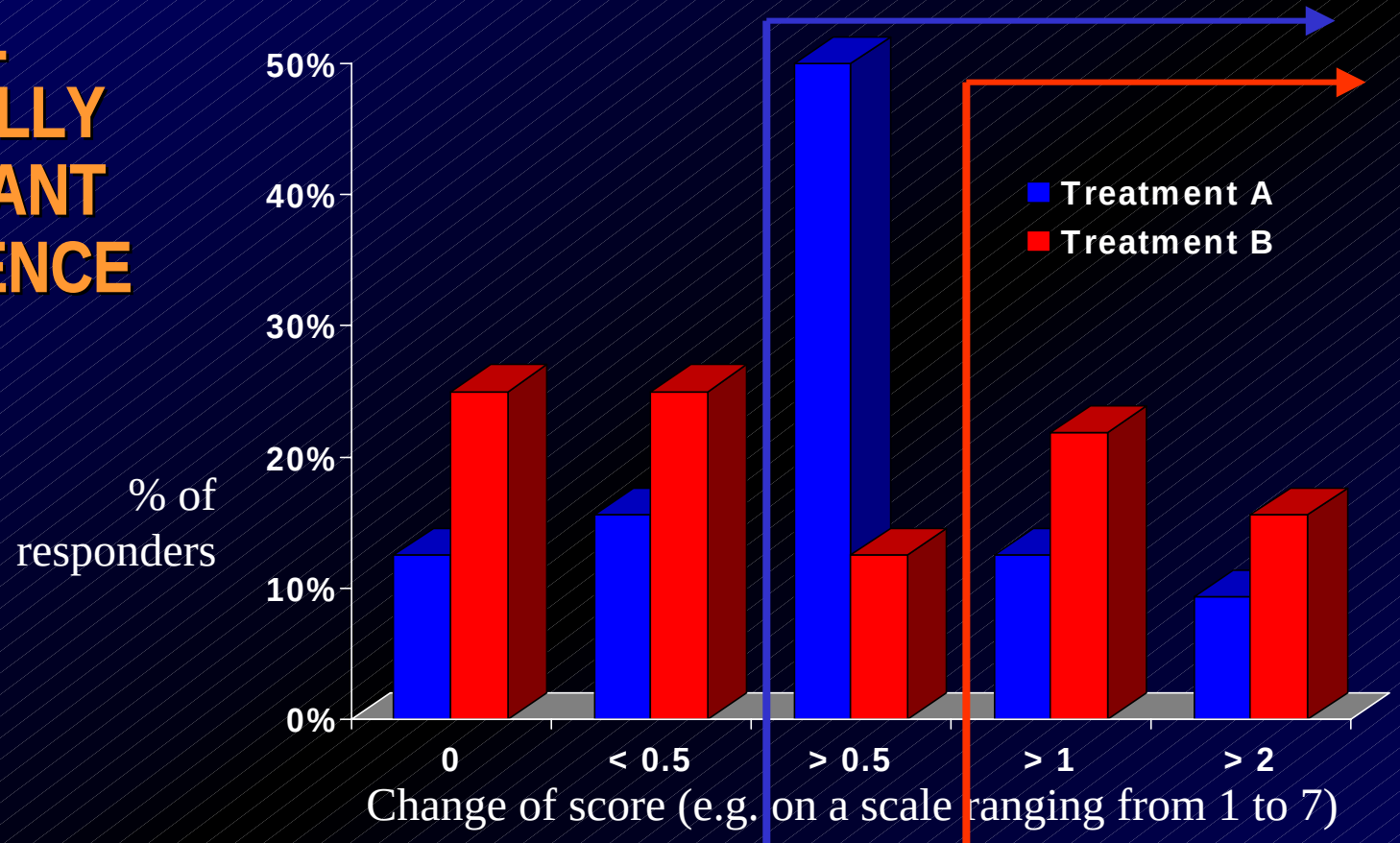
DISCREPANCIES MAKE APPRAISAL HARDER

- **In the way to interpret HRQL data**
- Between standard criteria and HRQL / PRO
- Among HRQL / PRO outcomes
- In direction and magnitude within HRQL domains

HOW TO EVALUATE DRUGS WHEN CLINICAL RELEVANCE OF RESULTS IS NOT OBVIOUS



% OF RESPONDERS (R) DEPENDS OF THE CUT-OFF OF MINIMAL CLINICALLY IMPORTANT DIFFERENCE (MCID)



Cut-off : change unit	R_A	R_B	*Conclusion*
> 0.5	72%	50%	A > B : + 44%
> 1	22%	38%	B > A : + 73%

MCID : DEPENDS ON WORDING

Impact of the global on patient perceivable change in an asthmatic specific QOL questionnaire. *Barber BL et al. Qual Life Res 1996; 5: 117-22.*

Changes in AQLQ symptom-domain anchored to global	Asthma control global		Asthma change global	
Global category	Average	n	Average	n
Worse	- 0.04	3	- 1.05	3
Minimally w orse	0.13	49	0.18	11
No change	0.35	102	0.33	45
Minimally improved	0.78	135	0.42	86
Improved	1.48	18	0.85	121

- 343 patients with mild to moderate asthma
- Global asthma control question : **“ How well is your asthma controlled ? ”**
- Global asthma change question : **“ Overall has there been any change in your asthma since the beginning of the study ? ”**
- Response from 0 to 6 (poorly controlled / much worse)

MCID MAY DEPENDS ALSO ON ...

- 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 clinically relevant

- **Effect size** should be **> 0.5**

Effect Size	*Small*	*Moderate*	*Large*
Benchmark	> 0.20	> 0.50	> 0.80

- **MCID** should be **> 0.5** on a range score from 1 to 7
- **Number needed to treat** should be **< 10**

NUMBER NEEDED TO TREAT

Economic analysis of respiratory rehabilitation.

Goldstein RS et al. Chest 1997; 112: 370-9.

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

NUMBER NEEDED TO TREAT

Examples of literature

Study		Drug	Treatment duration	Criterion	NNT
Woscops	NEJM 1995	Pravastatin	5 yrs	Mortality (primary prevention)	**111**
4S	Lancet 1994	Simvastatin	5.4 yrs	Morality (secondary prevention)	**30**
LIPID	NEJM 1998	Pravastatin	6.1 yrs	Morality (secondary prevention)	**32**
Left Ventricular dysfunction	J Am Coll Cardio 1994	Enalapril	41 wks	Mortality	**22**
MIRACL	JAMA 2001	Atorvastatin	16 wks	Composite score	**38**
CAPRIE	Lancet 1996	Clopidogrel	1 yr	Composite score	**196**
MUCOSA	Ann Intern Med 1995	Misoprostol	6 months	Severe gastrointestinal complications (NSAID)	**263**

DISCREPANCIES MAKE APPRAISAL HARDER

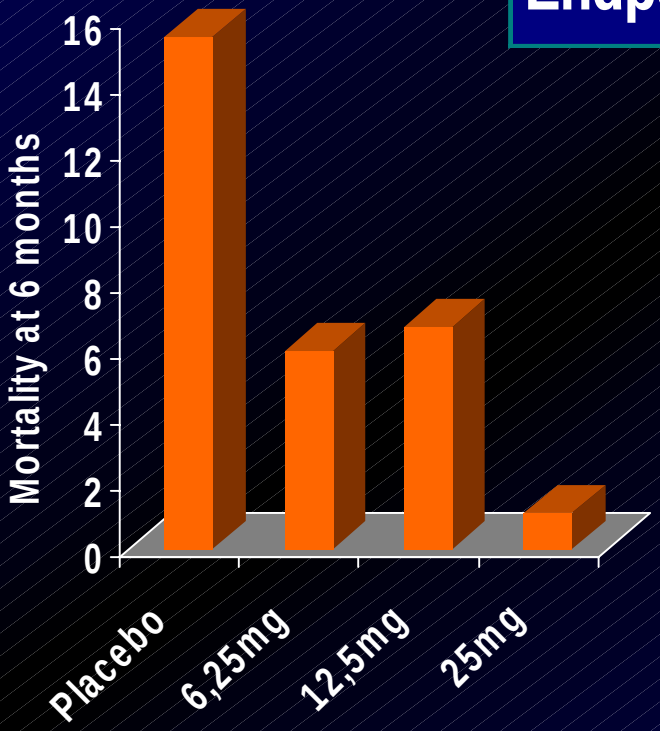
- In the way to interpret HRQL data
- **Between standard criteria and HRQL / PRO**
- Among HRQL / PRO outcomes
- In direction and magnitude within HRQL domains

DISCREPANCY WITH MORTALITY

Carvedilol produces dose-related improvements in LVF and survival in subjects with CHF. (MOCHA study). *Bristow MR et al. Circulation 1996.*

MLwHF (0-105)	Placebo	6.25 mg	12.5 mg	25 mg
Baseline	47.7	45.8	43.9	43.6
Endpoint	40.4	38	36.5	38.2

MLwHF : 21 items, 0 (best) - 105 (worst)



Double-blind, placebo-controlled trial (n=345), 6 months, 3 doses.

DISCREPANCY WITH PULMONARY FUNCTION

Randomised, double-blind, placebo controlled study of fluticasone propionate in patients with moderate to severe COPD: the ISOLDE trial. *Burge PS et al. BMJ 2000; 320: 1297-303.*

- Fluticasone dipropionate 500 µg bid leads to a lower decline in heath-status (SGRQ)
- **but does not affect the decline in FEV_1**

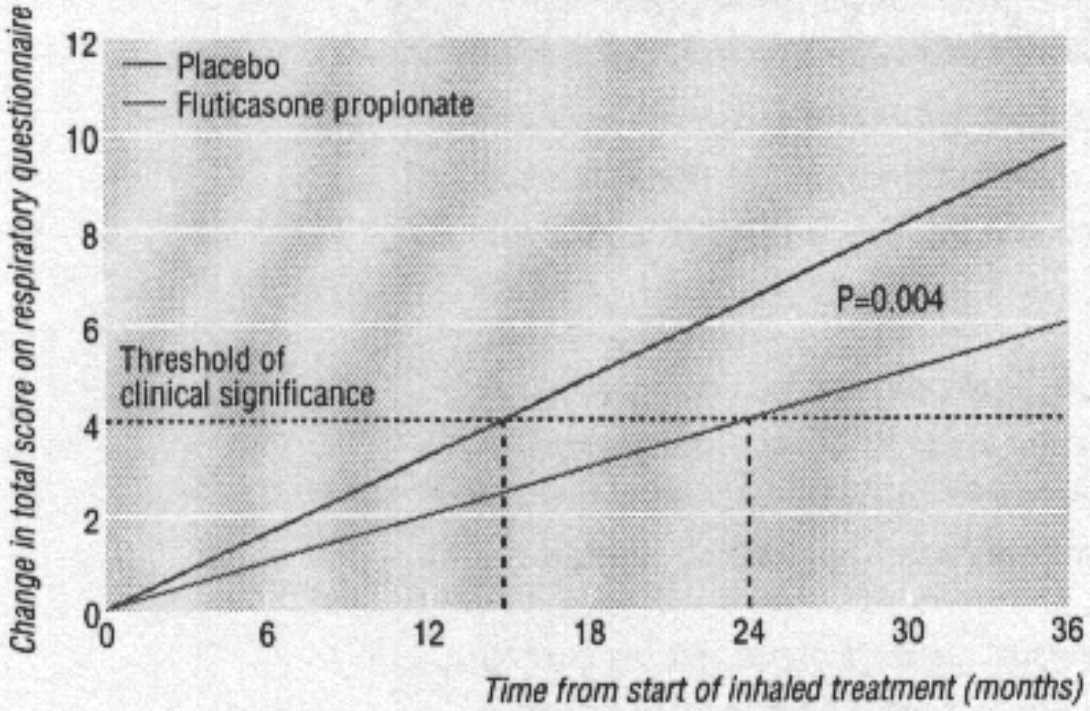


Fig 4 Weighted regressions from random coefficients (mixed) model (see text) to account for the effect of differences in the number of observations between patients, with adjustment for baseline covariates (baseline questionnaire score, age at entry, sex, centre, and smoking during the study)

LOW CORRELATION WITH WALK-TEST, SaO_2

Quality of life in elderly patients with COPD: measurement and predictive factors.

Yohannes AM et al. Resp Med 1998; 92: 1231-6.

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

BPQ : Breathing Problems Questionnaire

CRQ : Chronic Respiratory Disease Questionnaire

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

CONSISTENCY WITH OTHER CRITERIA IN ASTHMA

Fluticasone propionate versus zafirlukast: effect in patients previously receiving inhaled corticosteroid therapy. *Kim KT et al. Ann All Asthma Immunol 2000; 85: 398-406.*

Fluticasone > zafirlukast	p
FEV1	0.001
Morning PEF	0.004
Evening PEF	0.002
% of symptom-free days	0.007
% of rescue-free days	0.001
Albuterol use	0.001
Combined symptom scores	0.001
Awakening-free nights	0.001
Asthma exacerbation	0.035
AQLQ	0.001

Randomized, double-blind, parallel group
437 patients randomized (FEV1 % predicted : 74%)

DISCREPANCY WITH WALKING DISTANCE

European mutual recognition procedure

- Treatment in claudication (Peripheral Arterial Occlusive Disease)
- Phase II, RCT, DB, dose-ranging vs placebo, n = 340
- Primary endpoint : absolute change distance : **NO DIFFERENCE**
- HRQL assessment (secondary) : SF-36

Significant difference	*No difference*
• Social Functioning • Mental Health	• Bodily Pain • Physical Functioning

→ Can HRQL replace clinical end-point ?

→ How many domains to be improved for a global HRQL claim ?

DISCREPANCY WITH WALKING DISTANCE

Dossier for Approval - French Drug Agency (AFSSAPS)

- Treatment in claudication (Peripheral Arterial Occlusive Disease)
- Phase III, RCT, DB, vs placebo

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

DISCREPANCY WITH CLINICAL OUTCOMES & AE

Dossier for Approval - French Drug Agency (AFSSAPS)

- Treatment in rheumatoid arthritis
- 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 AE recorded by instruments ?

→ are the patients with AE analyzed for HRQL ?

DISCREPANCIES MAKE APPRAISAL HARDER

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- Between standard criteria and HRQL / PRO
- **Among HRQL / PRO outcomes**
- In direction and magnitude within HRQL domains

DISCREPANCY PYROSIS VS HRQL (PGWB) AND SYMPTOM SCALE (GSRS) IN GERD

Comparison of several controlled randomized trials

	Festen 99	Havelund 99	Lind 99	Carlsson 98	Revicki 98	Galmiche 97
Treatment	Ome Ran	Ome Placebo	Ome Placebo	Ome Placebo	Ome Ran	Ome Cis
Nb of patients	448	408	424	506	294	423
Pyrosis resolution between groups	**24%**		**27%**	**25%**		**24%**
Effect size						
PGWB		**0.26**	NS	NS	**0.22**	NS
GSRS total score	**0.30**	NS	NS	NS	**0.16**	NS
GSRS reflux score		**0.72**			**0.55**	**0.43**

Ome : omeprazole, Ran : ranitidine, Cis : cisapride

DISCREPANCY BETWEEN PRO OUTCOMES IN ERECTILE DYSFUNCTION

Dossier for Approval - French Drug Agency (AFSSAPS)

Study	Cross-over vs placebo	Parallel vs placebo	Cross-over vs placebo
Satisfaction (Fugl Meyer)	only sexual scale improved : Δ of 0.7 (range 1-6)		
Treatment satisfaction	Δ of 4 (range 1-42)		
HRQL (SF-36)	No difference with placebo		

GENERIC VS SPECIFIC HRQL QUESTIONNAIRE

The influence of an inhaled steroid on quality of life in patients with asthma or COPD.

Van Schayck CP et al. Chest 1995; 107: 1199-205.

- Improvement of lung function (FEV_1, $p < 0.0001$) with added beclomethasone dipropionate (BDP)
- Temporary decrease of symptoms
- HRQL assessment : **No improvement of NHP and ISP**
  - NHP (Nottingham Health Profile) : 38 statements, 6 domains : physical mobility, pain, social isolation , emotional reactions, energy, sleep. Binary Answer
    - **Changes would have been better detected with a specific questionnaire**
  - ISP (Inventory of Subjective Health) : 21 items related to subjective complaints : tiredness, chest and heart problems, gastric problems, indigestion, headache…
    - **Is that measuring HRQL ?**

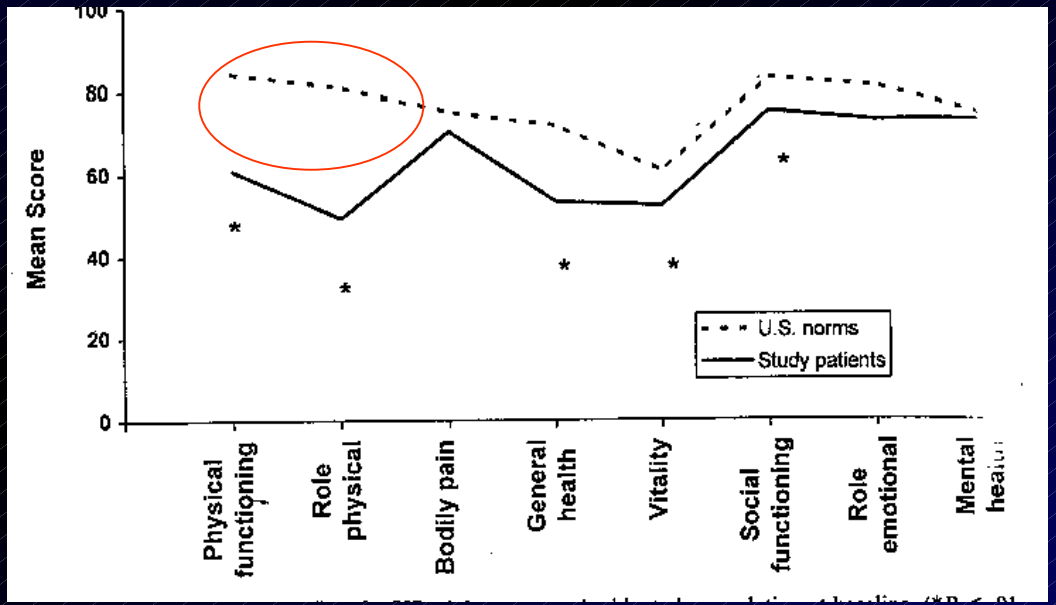
DISCREPANCIES MAKE APPRAISAL HARDER

- In the way to interpret HRQL data
- Between standard criteria and HRQL / PRO
- Among HRQL / PRO outcomes
- **In direction and magnitude within HRQL domains**

WHICH DOMAINS ARE IMPAIRED ?

Fluticasone propionate improves quality of life in patients with asthma requiring oral corticosteroids. *Okamoto CJ et al. Ann All Asthma Immunol 1996; 76: 455-61.*

FP 1000mg vs placebo	p	r (FEV)
PF	< 0.001	0.44
RP	0.0001	0.29
GHP	0.02	
VT		0.27
SF		0.23



- Only **Physical Functioning** and **Role-Physical** scales show large differences between drug and placebo groups
- Only **Physical Functioning** shows a high correlation with FEV

DISCREPANCY AMONG HRQL QUESTIONNAIRES

RESPONSIVENESS : AQLQ > LWAQ

Comparison of performance of 4 instruments in evaluating the effects of salmeterol on HRQL. Van Mölken MP et al. Eur Resp J 1995; 8: 888-98.

AQLQ (32)	0.820
Activities (11)	*0.860*
Symptoms (12)	*0.723*
Environment (4)	*0.550*
Emotions (5)	*0.302*
	Effect size
LWAQ	0.694
Health knowledge	*0.625*
Health appraisal	*0.333*
	Effect size
SIP	0.320

- 6-wk
- Salmeterol 50 µg or Salbutamol 400 µg bid
- 120 patients randomized
- FEV_1 % predicted : 59%

RESPONSIVENESS : LWAQ > AQLQ

Quality of life during formoterol treatment: comparison between asthma-specific and generic questionnaires. Van Der Molen T et al. Eur Respir J 1998; 12: 30-34.

Table 3. – Effect sizes of changes in quality of life during treatment with formoterol in comparison to treatment with placebo

	Effect size	95% CI
AQLQ	0.128	-0.267–0.532
Activity	0.106	-0.343–0.559
Symptoms	0.316	-0.083–0.724
Emotional	0.132	-0.266–0.534
Environment	0.051	-0.347–0.451
LWAQ	0.394	-0.003–0.796
Physical problem	0.407	-0.015–0.809
Emotional problem	0.196	-0.192–0.589
SF36 total	0.008	-0.380–0.397
PGWB total	0.268	-0.120–0.664

CI: confidence interval; AQLQ: Asthma Quality of Life Questionnaire; LWAQ: Living with Asthma Questionnaire; SF36: Short Form 36; PGWB: Pscyhological and General Well-Being scale.

- 6 months, 110 patients
- FEV1 % predicted : 65%

DISCREPANCY IN DIMENSIONS OVER TIME (AND MULTIPLICITY OF STATISTICAL TESTS)

Efficacy, tolerability, and effects on HRQL of inhaled Salmeterol in COPD.

Di Lorenzo G et al. Clin Ther 1998; 20: 1130-48.

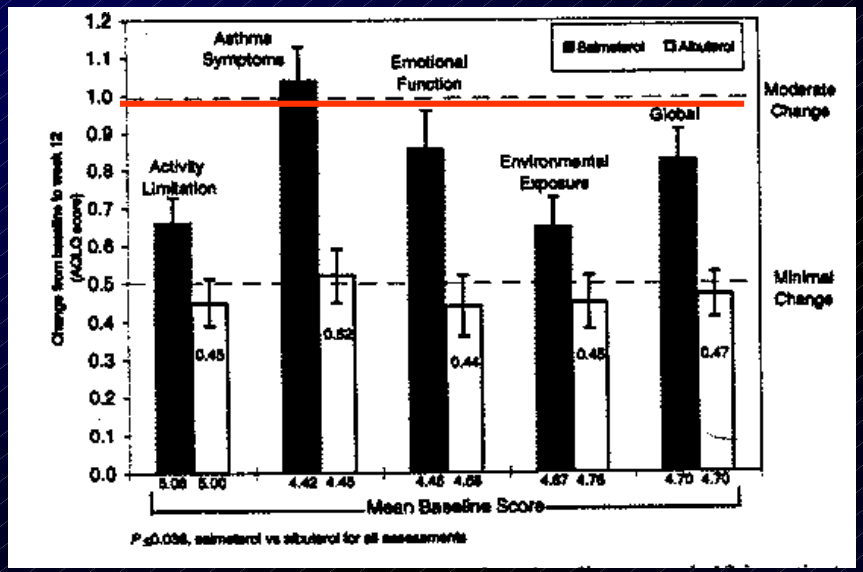
- Open label
- Salmeterol 50 µg
- or SR Theophylline bid
- Randomized (n = 178)
- Completers (n = 145)
- HRQL (secondary) : SF-36
- Mean changes between baseline and the 4 assessments over time, for each single dimension : Student t test

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

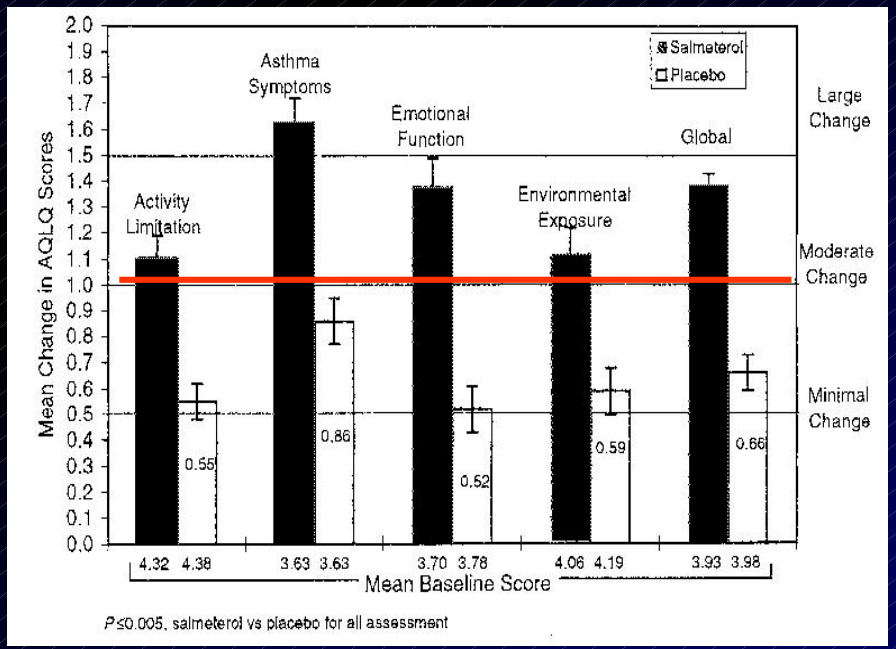
CONSISTENCY OF IMPROVEMENT OF THE SAME HRQL QUESTIONNAIRE THROUGH STUDIES

Efficacy, safety, and effects on quality of life of salmeterol versus albuterol in patients with mild to moderate persistent asthma. Wenzel SE et al. Ann Allergy Asthma Immunol 1998; 80: 463-70.



- Baseline AQLQ global score : 4.70
- 12-wk

Nocturnal asthma. Effects of Salmeterol versus placebo on quality of life and clinical outcomes. Lockey RF et al. Chest 1999; 115: 666-73.

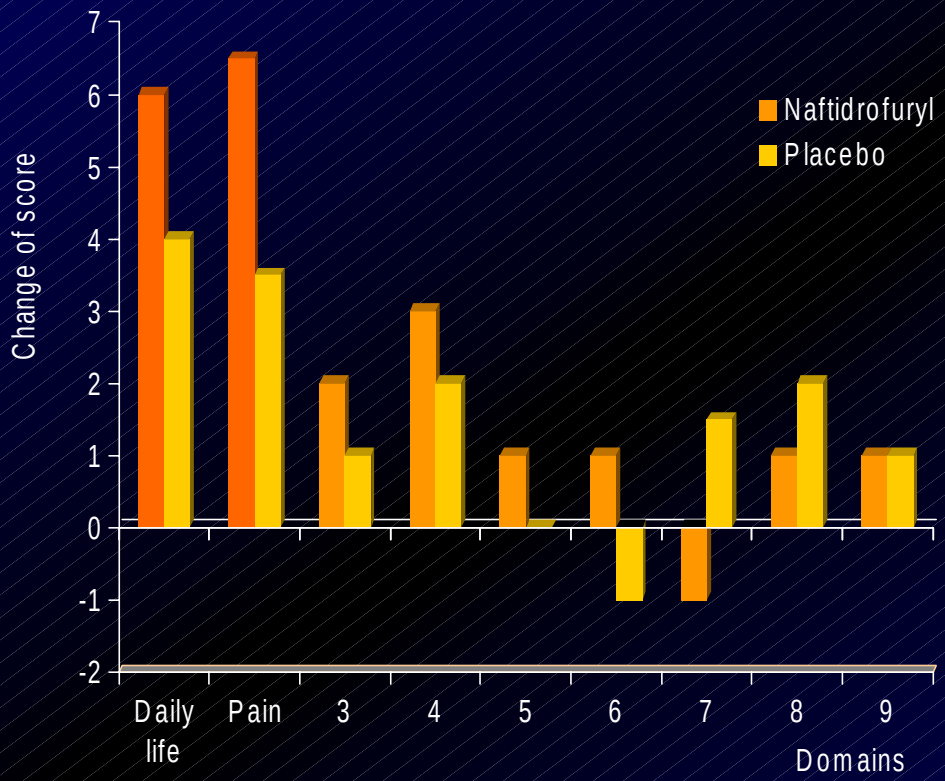


- Baseline AQLQ global score : 3.93-8
- 12-wk

Global score AQLQ : 1 to 7 best

HOW MANY DOMAINS AND WHICH DOMAINS SHOULD IMPROVE FOR A CLAIM IN PAOD ?

The effects of naftidrofuryl on quality of life. *Liard F et al. Dis Manage Health Outcomes 1997; 2 (Suppl. 1): 71-78.*



Broad HRQL claim ?

Unlikely

Specific-domain claim ?

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

WHY PHARMACEUTICAL FIRMS ARE SO INTERESTED IN HRQL / PRO ?

Reimbursement / Price

France : “Transparency committee”

- Medico-economic evaluation of drugs
- Rank the new drug / indication according to
  - Efficacy
  - Therapeutic strategy (availability of other treatments)
  - Severity of disease, public health concern
  - Cost-efficacy, cost-utility
  - Quality of life, Patient-Reported Outcomes ?

  → **Score : “Amélioration du Service Médical Rendu”**
- **Propose a reimbursement rate**

Advertising

- Physicians
- Patients - Consumers

Grappling With the Quality of Life: Patients, FDA and Drug Companies Struggle to Link Therapies With Well-Being. C Lewis. U.S. Food and Drug Administration. FDA Consumer magazine. March-April 2001.

WHY REGULATORS ARE RELUCTANT (SOME TIME) ?

- To give the official global claim “Improvement of Quality of Life”, especially for drugs with overall weak efficacy

- To give a reimbursement / price on HRQL data which interpretation is no clear

- To authorize such advertising with the risk of abuse...