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Health-Related Quality of Life & regulatory issues in Europe

ERIQA project

REFERENCE DOCUMENT

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Major biases encountered in the review of a dossier in the drug approval process

- No **justification of QoL choice** (relevance, instruments)
- No evidence of quality of life questionnaire **validation**
- No **objective** of QoL changes
- No justification of sample size
- No description of the follow up of patients during the study
- No clear handling of **missing data**
- Not all patients are analyzed
- 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. Authors are creating database of quality of life questionnaires. BMJ 1999; 318: 1142.

It is time to follow some guidelines

- HRQoL seems to be frequently added at the last moment without clear objective neither data quality procedures
- **Protocol, study report and clinical expert report do not document enough HRQoL assessment for a critical review**
- Reporting on quality of life should follow some **guidelines**.

Sanders C et al. Reporting on quality of life in randomised controlled trials: bibliographic study. BMJ 1998; 317: 1191-1194.

European regulatory authorities

- To convince them — that HRQoL is a relevant key outcome
- To make them confident — in the quality of the HRQoL results
- To help them — in reviewing and interpreting HRQoL results

Checklist on reporting on HRQoL in RCT

1- Study design clearly described ?

- Are basic methodological principles of RCT fulfilled and clearly reported

2- Scope and definition of the HRQoL component adequately described ?

- Relevance for assessing HRQoL for this trial
- **Justification for the choice of the HRQoL questionnaires**
- **Research objectives** of the HRQoL component clearly stated
- HRQoL a primary or secondary endpoint in the trial

3- Clear description of the study design elements as they related to the HRQoL component of the trial ?

- Sampling of patients and centres
- Eligibility criteria
- Timing and frequency of HRQoL assessment
- Mode and site of HRQoL administration
- Data monitoring and quality assurance

Where is HRQoL assessment ?

- Proton pump inhibitor / oesophagitis
- Phase III : 2 studies in USA, 1 study in Europe
- > 700 patients included

HRQoL claim : no clear definition of HRQoL in the study report, or in the protocol

- Overall physical well being (0 to 4)
- Time lost from usual activities of daily living

(less time lost in placebo group !)

No justification of choice of instruments

- Randomized, DB, placebo-controlled study of GH replacement in 40 patients with acquired GH deficiency
- **Assessment at baseline and 18 months :**
  - NHP (Nottingham Health Profile)
  - PGWB (Psychological General Well-being)
  - GHQ (General Health Questionnaire)
  - MMPI-2 (Minnesota Multiphasic Personality inventory)
- **Selection made on what ?**
  - Psychometrics properties ?
  - Prior use in a similar population ?
  - Cover several different concepts ?
- **What where the hypotheses of score changes ?**

Baum HBA et al. Effects of physiological growth hormone therapy on cognition and quality of life in patients with adult-onset GH deficiency. J Clin Endocrinol Metab 1998; 83: 3184-9.

Measuring HRQoL or symptom bothering ?

- **GSRS : Gastrointestinal Symptom Rating Scale**
- Disease-specific instrument to evaluate common symptoms of gastrointestinal disorders.
- 15 items, rated on a 7-point Likert scale from no discomfort to very severe discomfort into 5 scales :

1- abdominal pain
2- reflux syndrome (2 items)
3- diarrhoea syndrome
4- indigestion syndrome
5- constipation syndrome

- Have you been bothered by acid reflux during the past week ?
- Have you been bothered by heartburn during the past week ?

Reliability and validity of the gastrointestinal symptom rating scale in patients with gastroesophageal reflux disease. Qual Life Research 1998; 7: 75-83.

Checklist on reporting on HRQoL in RCT

4- Adequate description provided for the characteristics of the HRQoL measure(s) employed in the study ?

- Number of items and domains
- Instrument scaling and scoring
- Reliability
- **Validity**
- Responsiveness
- Respondent burden
- Cultural adaptation
- These properties have been shown in a population similar to the trial

HRQoL questionnaire validated ?

- Proton pump inhibitor / dyspepsia
- Phase III, RCT, DB, vs comparator & placebo
- n = 810, 2 weeks duration

HRQoL assessment (secondary)

Some unknown QoL index was used

➜ no description of validation data, no reference

➜ 10 additional items concerning gastro-intestinal symptoms were approved by Pr X !

Dossier for drug approval

Checklist on reporting on HRQoL in RCT

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- Instrument scaling and scoring
- Reliability
- Validity
- Responsiveness
- Respondent burden
- **Cultural adaptation**
- These properties have been shown in a population similar to the trial

International trials and linguistic validation of questionnaire

- Treatment in claudication
- Phase III, RCT, DB, vs placebo, n=422, 6 months
- Setting in France and Italy

Results : initial change distance : Δ 32% vs placebo

HRQoL assessment (secondary)

- PQVS French generic questionnaire

➜ Italian version : not a word about linguistic validation

European mutual recognition procedure

Checklist on reporting on HRQoL in RCT

5- Clear description of the statistical analysis plan of the HRQoL component of the trial ?

- Efficacy or equivalence trial
- Intent to treat analysis (ITT)
- Procedures for type I error
- Sample size and statistical power
- Descriptive and inferential statistics
- Imputation of missing data

6- **Reporting of Results :**

- **Is the following information provided on the results of the HRQoL investigation ?**
  - Participation rate (at study entry and during follow-up)
  - Characteristics of the final study population
  - **Data completeness** (i.e. missing questionnaires and missing items)
- **Are the results presented in accordance with the original statistical analysis plan ?**

Intent to treat analysis and missing data

- Treatment in claudication
- Phase III, RCT, DB, vs placebo, n = 422, 6 months
- Results : initial change distance : Δ 32% vs placebo

HRQoL assessment (secondary)

- PQVS French generic questionnaire
- First factor of principal component analysis : global satisfaction (p = 0.049, t-test)

➜ Analysis performed on 324 patients

➜ How many and how were handled missing data ?

Multiple test comparisons

- Treatment in claudication
- Phase III, RCT, DB, vs comparator, n=324, 3 months
- Results : NO difference in walking in ITT

HRQoL assessment (secondary) : PQVS

➜ univariate analysis : statistical difference for 5 items among 19 (Per protocol analysis, n = 268)

➜ A statistical difference is likely to appear by random in about 5 items (type I error = 25%) !

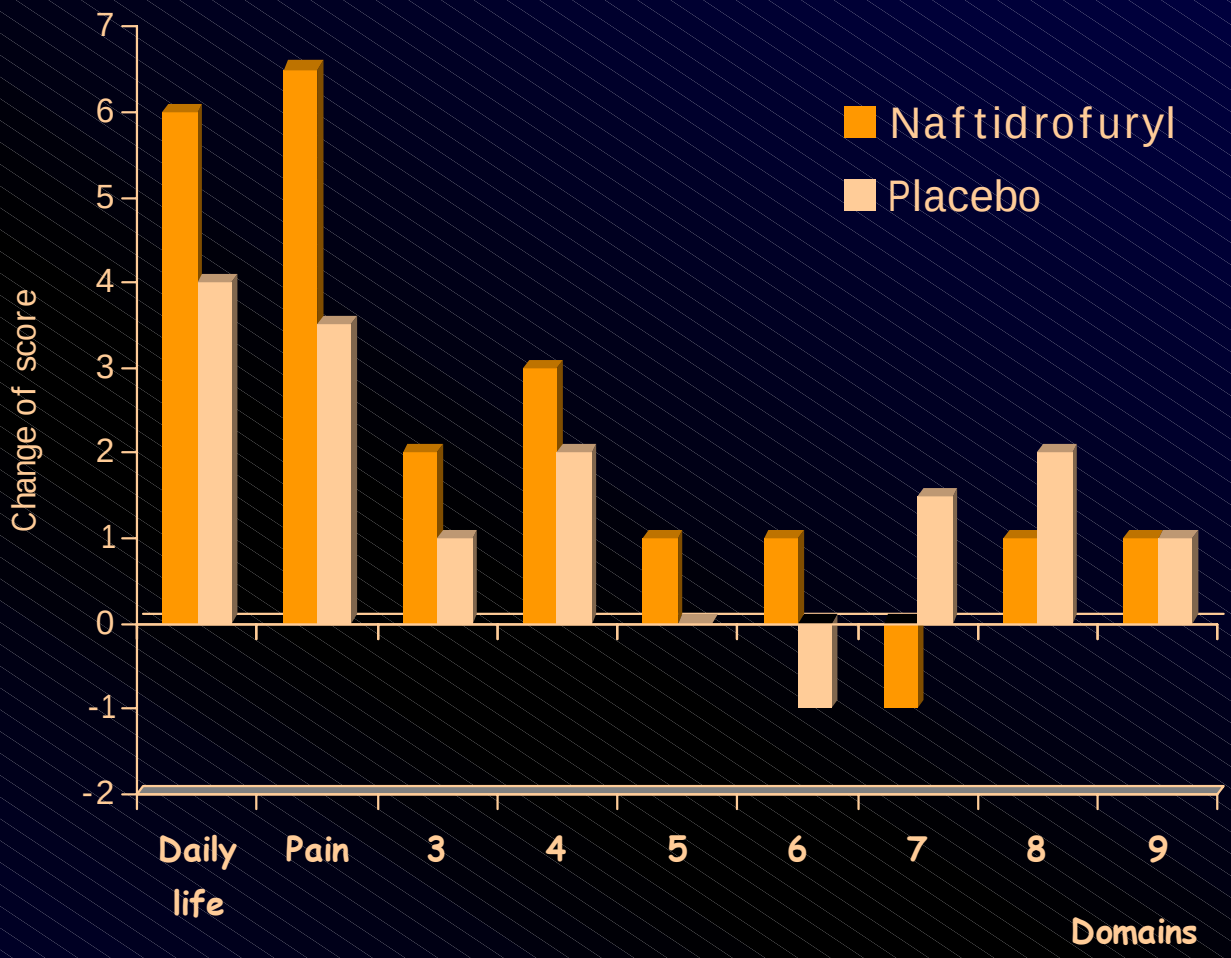
Checklist on reporting on HRQoL in RCT

7- Is there an attempt to interpret the statistical results in terms of clinical significance ?

- Description of the content of domains
- **Distribution of HRQoL scores within- and between groups**
- $_{95\%}$IC of the difference and/or odds ratio of the difference
- Effect size
- Comparisons of scores with norm scores (if available) and/or scores obtained in other studies in similar population to estimate a MID
- Comparison with external criteria to estimate a MID
- Number needed to treat

Distribution of HRQoL scores : no value

- Intermittent claudication
- RCT, DB, versus placebo
- Family practice
- 6 months
- HRQoL : primary end-point
- CLAU-S : 9 domains, 80 items
- ITT (234/250 included)
- Statistical significance set at 0.05/9
- Missing data : LVCF
- Not a value, just p-value and a graph



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

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- Number needed to treat

Clinical relevance of a difference

- Treatment in rheumatoid arthritis
- Phase III, RCT, DB, vs comparator, n=99, 6 months
- Results : Large improvement of ACR criteria (> 20% improvement : 71% (new drug) vs 27% (comparator)

HRQoL assessment (secondary)

- Health assessment questionnaire (HAQ)
- Differences on “disability”, “vitality” and “mental health” domains

➔ e.g.”disability” score (range : 0 to 3) at 6 months : 1.2 (comparator) vs 0.9 (new drug), how to interpret ?

Does it improve HRQoL or not ?

- Treatment in claudication
- Phase II, RCT, DB, dose-ranging vs placebo, n=340

Results : NO difference (absolute change distance)

HRQoL assessment (secondary) :

- SF36 : significant differences on "social function" and "mental health" scales
- NO difference on "pain", "physical function"

➔ Improvement of HRQoL ? (i.e. how many domains)

Checklist on reporting on HRQoL in RCT

7- Is there an attempt to interpret the statistical results in terms of clinical significance ?

- Description of the content of domains
- Distribution of HRQoL scores within- and between groups
- $_{95\%}$IC of the difference and/or odds ratio of the difference
- **Effect size**
- Comparisons of scores with norm scores (if available) and/or scores obtained in other studies in similar population to estimate a MID
- Comparison with external criteria to estimate a MID
- Number needed to treat

➔ **Try at least something !**

Effect size

- Randomized, DB, placebo-controlled, parallel groups trial (n = 367)
- Chronic heart failure

HRQoL assessment (primary) : SIP

1- **POMS** : profile of mood states
2- Inability of patients to carry out regular activities
3- Number of hobbies and whether treatment interfered on them
4- **HSI** : health status index
5- Mahler index of dyspnea-fatigue

	Cilazapril vs placebo			Captopril vs placebo		
	Mean ± SD	95% CI	**ES**	Mean ± SD	95% CI	**ES**
Total SIP	0.08 ± 6.6	-1.71, 1.44	-0.01	0.56 ± 6.5	-1.41, 2.53	0.09
Physical. dimension	0.73 ± 6.1	-0.86, 2.34	**0.12**	0.87 ± 6.1	-0.96, 2.7	**0.14**

Bulpitt et al Quality of life in chronic heart failure: cilazapril and captopril versus placebo. Heart 1998; 79: 593-8.

DHEA : a fountain of youth (1)

- Randomized, DB, placebo-controlled, cross-over (24 women)
- Each treatment period : 4 months
- Washout period : one month
- Assessment after one and 4 month of each period and one month after the 2nd period

1- SCL-90 : revised version of the 90-item Symptom Checklist
2- Multidimensional Mood Questionnaire
3- Von Zerssen Symptom list
4- Short form of the Giessen Complaint list
5- German version of the Hospital Anxiety and Depression
6- Sexual functioning

Alrt W et al. Dehydroepiandrosterone replacement in women with adrenal insufficiency. N Engl J Med 1999; 341: 1013-20.

DHEA : a fountain of youth (2)

- **SCL-90 : revised version of the 90-item Symptom Checklist**
  - Psychological well-being
  - Psychometric properties verified prior to the trial in similar population ?
- **Multidimensional Mood Questionnaire**
  - How reliable is the questionnaire ?
- **Von Zerssen Symptom list**
  - Content not provided
- **Short form of the Giessen Complaint list**
  - More a symptom listing
- **Sexual functioning**

No evidence of validation provided

Alrt W et al. Dehydroepiandrosterone replacement in women with adrenal insufficiency. N Engl J Med 1999; 341: 1013-20.

DHEA : a fountain of youth (3)

- No primary end-point defined
- No sample size justified (i.e. no hypotheses)
- Choice of multiple instruments not justified (i.e. SCL-90, MMQ, Zerssen and HAD reflect the same concept)
- Multiple statistical test comparisons :
  - **At least 23 tests repeated 3 times (α > 32%)**
  - No adjustment for multiple comparisons
  - No selection of the most important measures
- Double-blind respected ? most women receiving DHEA experienced skin-related androgenic effects

Alrt W et al. Dehydroepiandrosterone replacement in women with adrenal insufficiency. N Engl J Med 1999; 341: 1013-20.

DHEA : a fountain of youth (4)

- **No data about completeness of assessments of the 2 periods:** About **204 items** completed at least **6 times**.
- Significant differences between groups at 4 months in favour of DHEA for several questionnaires :
  - SCL-90 (e.g. global score : **Δ of 0.11**, 0-4 range)
  - Clinical pertinence ? **(Effect size = 0.28)**
- **Conclusion: DHEA improves well-being**
- **Editorial:** "it is now justifiable, to prescribe DHEA as long-term treatment in patients with adrenal insufficiency, **provided that they are monitored for breast or prostatic cancer**".

Alrt W et al. Dehydroepiandrosterone replacement in women with adrenal insufficiency. N Engl J Med 1999; 341: 1013-20.

Conclusion

- Regulatory authorities will accept more easily HRQoL statistical significant results if :
  - they have confidence in the quality of the trial itself
  - and protocol, study report and clinical expert report document enough HRQoL assessment for a critical review
- Thus, the clinical relevance of results will appear less important.
- Whether the endpoint is considered primary or secondary, the scientific principles of clinical trial design must apply to Health-Related Quality of Life.