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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

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.

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!)

Dossier for drug approval
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?**

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?

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
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
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: $\Delta 32\%$ 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: $\Delta$ 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?

European mutual recognition procedure
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%)!
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

Checklist on reporting on HRQoL in RCT

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**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

<table>
<thead>
<tr>
<th>Cilazapril vs placebo</th>
<th>Captopril vs placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean ± SD</strong></td>
<td><strong>Mean ± SD</strong></td>
</tr>
<tr>
<td><strong>95% CI</strong></td>
<td><strong>95% CI</strong></td>
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<tr>
<td><strong>ES</strong></td>
<td><strong>ES</strong></td>
</tr>
<tr>
<td>Total SIP</td>
<td></td>
</tr>
<tr>
<td>0.08 ± 6.6</td>
<td>0.56 ± 6.5</td>
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<tr>
<td>-1.71, 1.44</td>
<td>-1.41, 2.53</td>
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<tr>
<td>0.01</td>
<td>0.09</td>
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<tr>
<td>Physical dimension</td>
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<tr>
<td>0.73 ± 6.1</td>
<td>0.87 ± 6.1</td>
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<tr>
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<td>-0.96, 2.7</td>
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<tr>
<td><strong>0.12</strong></td>
<td><strong>0.14</strong></td>
</tr>
</tbody>
</table>

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
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

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

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 ($\alpha > 32\%$)
  - No adjustment for multiple comparisons
  - No selection of the most important measures
- Double-blind respected? Most women receiving DHEA experienced skin-related androgenic effects

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: ∆ 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”.

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.