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European guidance document for the improvement of the integration of Health-Related Quality of Life (HRQL) assessment in the drug regulatory process

Olivier Chassany, MD

Agence Française du Médicament

Senior Lecturer in Therapeutics, University Lariboisière Hospital, France

for the European Regulatory Issues on QoL Assessment (ERIQA) Group

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.

ERIQA working group : Objectives

(European Regulatory Issues on Quality of Life Assessment)

Many clinical trials include an HRQL assessment, but very few drugs have obtained labeling or promotional approval. This is due in part to the poor quality of HRQL assessment and reporting.

Mission statement: « Establishing principles and practices for the integration of health-related quality of life outcomes in the regulatory process »

Objective: To provide European regulatory authorities (RA) with guidance on:

- how to assess the quality of HRQL studies in clinical trials,
- how to evaluate the validity of HRQL claims

for appropriate decision-making...

Checklist on reporting on HRQL 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 HRQL for this trial
- Justification for the choice of the HRQL questionnaires
- Research objectives of the HRQL stated
- HRQL a primary or secondary endpoint ?

3- Clear description of the study design elements related to HRQL component ?

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

4- Adequate description provided for the HRQL measure(s) ?

Number of items and domains

- Instrument scaling and scoring
- Reliability, Validity, Responsiveness
- Respondent burden, Cultural adaptation

5- Clear description of the statistical analysis plan of the HRQL component ?

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

6- Reporting and interpretation of Results :

- Is the information provided on HRQL results ?
  - Participation rate, description of the population
  - Data completeness
- Are the results presented in accordance with the original statistical analysis plan ?
- Is there an attempt to interpret the statistical results in terms of clinical significance ?
  - Description of the content of domains
  - Distribution of HRQL scores
  - 95% CI and Odds ratio of the difference
  - Effect size
  - Comparisons of scores with other scores
  - Comparison with external criteria
  - Number needed to treat

➢ **Try at least something !**

Conclusion

- Regulatory authorities will accept more easily HRQL statistical significant results if :
  - they have confidence in the quality of the trial itself
  - and protocol, study report and clinical expert report document enough HRQL 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.