EUROPEAN GUIDANCE DOCUMENT FOR THE IMPROVEMENT OF INTEGRATION OF HEALTH-RELATED QUALITY OF LIFE (HRQL) ASSESSMENT IN THE DRUG REGULATORY PROCESS

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OBJECTIVE:

Many clinical trials include HRQL assessment, but very few drugs have obtained labeling or promotional approval. One of the reason could be to the poor quality of HRQL assessment and reporting. (See Table 1)

The **European Regulatory Issues on Quality of Life Assessment (ERIQA)** project has the following main objective:

To provide European regulatory authorities with guidance on how to assess the quality of HRQL studies in clinical trials, and on how to evaluate the validity of HRQL claims, for appropriate decision-making.

This objective was established considering the complexity of the European context of medicinal products regulation:
1. since 1995, the existence of a centralised registration process through the European Agency for the Evaluation of Medicinal Products (EMEA)
2. country-specific regulations regarding approval, reimbursement and promotion.

METHOD:

A guidance document entitled **« Establishing principles and practices for the integration of HRQL outcomes in the regulatory process »** as well as a checklist have been designed following a literature search and using the experience of the ERIQA group's members, i.e. HRQL researchers, pharmaceutical industry representatives, academic people, and reviewers for regulatory authorities. (See table 2)

RESULTS:

The guidance document reviews the major issues of HRQL assessment in clinical trials, and especially practical considerations. For each issue, recommendations are made, even where there is not yet a definite answer (e.g. interpretation of results). All the issues to be prespecified in the research protocol are mentioned.

The checklist summarizes all the issues. It is intended to help regulatory authorities reviewers in performing their clinical trial reviews. It can also be used by sponsors and investigators conducting a clinical trial with HRQL data and writing the study report.

CONCLUSION:

Final objective is to reach a large European agreement upon this guidance document, to improve the quality of HRQL studies and to convince European regulatory authorities of the usefulness and scientific value of HRQL assessment.

Table 1: **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.

Table 2: **Contributors to the ERIQA Project**

Neil Aaronson The Netherlands Cancer Institute	Catherine Acquadro Mapi Research Institute, France	Giovanni Apolone Mario Negri Institute, Italy
Harry Burns Greater Glascow Health Board, UK	Olivier Chassany Hôpital Lariboisière, France	Katrin Conway Mapi Research Institute, France
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Examples of questions raised during the quality assessment of HRQL evaluation in clinical trials:

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.

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

Intent to treat analysis and missing data

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

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)

European mutual recognition procedure

Checklist for Reporting HRQL in Clinical Trials

The checklist is primarily designed for HRQL considered as a primary end-point, but the same standards should apply when HRQL is a secondary endpoint.

I. Is the study design clearly described ?
It is assumed that basic methodological principles of RCTs are fulfilled and clearly reported and especially the blindness of the trial

II. Is the scope and definition of the HRQL component adequately described ?
- Is the **relevance** for assessing HRQL justified for this trial?
- Is there a **justification** for the choice of the HRQL questionnaire(s) ?
- Are the research **objectives** of the HRQL stated ?
- Is HRQL a primary or secondary endpoint in the trial?

III. Is there a description of and rationale for the study design elements related to HRQL ?
- Sampling of patients and centers
- Eligibility criteria
- Timing and frequency of HRQL assessment
- Mode and site of HRQL administration
- Data monitoring and quality assurance

IV. Is there a description and/or documentation provided for the characteristics of the HRQL measure(s) ?
The amount of psychometric data that should be provided depends on what is already known about the instrument
- Number of items and domains
- Instrument scaling and scoring
- Reliability (internal consistency; test-retest)
- Validity (content; construct, criterion)
- Responsiveness
- Respondent burden
- Cultural adaptation

V. Is there a description of and rationale for the statistical analysis plan of HRQL ?
- Efficacy or equivalence trial
- Sample size and statistical power
- Intent to treat analysis
- Descriptive statistics for evaluating changes

- Procedures for multiple statistical tests
- Imputation of missing data

VI. Reporting and Interpretation of results:

- Is the following information provided on the results of HRQL ?

- Participation rate, characteristics of the final study 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 within- and between groups
- 95% CI and/or OR of the difference
- Effect size and/or standardized response mean
- Comparison with other scores or external criteria