HRQL REGULATORY ISSUES: COMPARISON OF US AND EUROPEAN INITIATIVES

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INTRODUCTION and BACKGROUND

A number of groups have considered the use of health-related quality of life (HRQL) assessments for regulatory purposes. Their work has been prompted by a desire to achieve credibility for HRQL as an evaluation criterion in clinical trials.

The groups that have been involved in this work, are:

- The Pharmaceutical Research and Manufacturers of America (PhRMA) Health Outcomes Committee (HOC)
- The International Society for Pharmacoeconomics and Outcomes Research (ISPOR)
- The International Society for Quality of Life Research (ISOQOL)
- The European Regulatory Issues on Quality of Life Assessment (ERIQA) group

The first three of these have considered the US regulatory situation, whilst the ERIQA group has looked at current circumstances in Europe. Each of these initiatives has produced a document describing their discussion and views on regulatory issues related to HRQL.

OBJECTIVES

- To compare documents produced by the different initiatives
- To identify areas of agreement and dissent, highlight issues in need of further deliberation and define the scope for collaboration between the initiatives

SOURCE DOCUMENTS

PhRMA-HOC	*ISPOR*	*ISOQOL*	*ERIQA*
Summary / report following Washington Workshop 24-25/3/99. September 1999. Internal document	*Quality of life regulatory guidance issues. Development of a consensus document as a supporting document for FDA and other health regulatory authorities on HRQL guidances. 20 September 1999. Website document*	*Recommendations on HRQL research to support labeling and promotional claims in the United States. International Society for Quality of Life Research. September 1999. Internal document*	*Quality of life and regulatory issues. European guidance document for the improvement of the integration of health-related quality of life (HRQL) assessment in the drug regulatory process. February 2000. Internal document*

METHODOLOGY

In performing the comparison, seven topics were considered:

1. Concept (terminology, definition), 2. Rationale for HRQL evaluation, 3. Instruments, 4. Study design, 5. Data analysis, 6. Interpretation, 7. Conditions for HRQL claims

Within each topic, issues addressed by all or only some of the initiatives were identified. A separate document was prepared for each topic, including a summary of findings and a table detailing observations, opinions, suggestions and recommendations made for each of these issues. Text in each of the source documents was considered to constitute a recommendation if it was indicated as such, or if the wording includes phrases such as 'must', 'should', 'essential that'.

FINDINGS

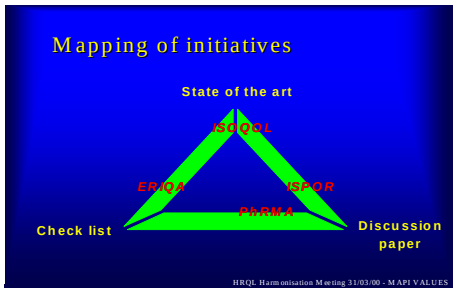
The documents compared showed some agreement on the broad topics considered, although not all topics were considered by all initiatives and there were marked differences in the structures of the documents (see Mapping).

CONCEPTS

- Definitions of HRQL were suggested in some but not all documents, with ISPOR the only group proposing a formal definition
- The most common opinion with regard to domains was that a minimum of two core domains, plus disease-specific domains should be included, with precise definition and accurate naming of the domains considered to be important
- HRQL was considered to be a separate concept from adverse event and side effect reporting.
- HRQL was considered to be a different outcome from patient satisfaction

✘ *A major outstanding issue is the establishment of links between a definition and a claim*

➢ Patient reported outcomes ?



➢ HRQL / well-being / physical functioning / vitality ... ?

RATIONALE FOR HRQL EVALUATION

- There was a general consensus that HRQL has been assessed increasingly due to the aging population, and prevalence of chronic diseases
- It was recommended that HRQL might be included as a primary or secondary end-point in a clinical trial

INSTRUMENTS

- All the initiatives were in agreement that regulatory bodies should not specify acceptable instruments and that the use of generic or specific instruments should not be mandatory
- All the initiatives were in agreement that the psychometrics of an instrument should have been proven if findings are to be credible; there was a general consensus that reliability, validity and responsiveness must be demonstrated, ideally in independent studies
- There were some differences in the recommendations for what should constitute minimum evidence of reliability, and only one initiative provided specific recommendations on what should constitute minimum evidence of validity
- One initiative recommended that for cross-cultural use, equivalent questionnaire structure must be demonstrated by a formal cultural adaptation process
- The initiatives differed in their opinion regarding proving the psychometric properties of an instrument using data from a clinical trial also used to assess the impact of treatment on HRQL; it was generally recommended that this is acceptable under certain conditions but should not bias item selection

✘ *Operationalization of criteria for assessing reliability and validity needs to be agreed*

➢ precise words / simple criteria ?

➢ for cross-cultural research ?

✘ *The full requirements for inclusion of an HRQL instrument in phase III clinical trials need to be established*

➢ role of phase II ?

STUDY DESIGN

- Three of the initiatives addressed HRQL hypotheses, with a consensus that these should be clearly specified and testable
- All initiatives referred to inclusion of HRQL in the clinical trial protocol, with a general agreement that all relevant sections should be included (from hypotheses to statistical analysis) and that clinical research standards should be followed
- Blinding was addressed by two groups and was recommended but recognized as impossible in some circumstances
- All documents acknowledged the need to calculate and/or justify sample size, and it was suggested that this should be estimated even when HRQL is a secondary end-point
- There was agreement that the number and timing of assessments should be related to the expected disease course and should be justified
- Two initiatives suggested that eligibility criteria could include a requirement for HRQL impairment
- Two initiatives recommended that study design should minimize missing data; follow-up of withdrawn patients being one factor in achieving this

✘ *Implications of sample size estimation when HRQL is a secondary end-point should be considered*

➢ inconsistency of samples with the primary end-point ?

➢ increased sample / omit HRQL ?

✘ *Screening patients using HRQL criteria should be discussed further*

➢ clinical versus HRQL impairment ?

➢ recommendations and acceptability ?

DATA ANALYSIS

- The general recommendations of three of the initiatives were that HRQL analysis should follow standard clinical trial statistical analysis procedures and standards, including the choice of end-point (assessments, domains, etc.) and justification for decisions
- All the documents dealt with the handling of missing data but with no real consensus on recommended procedures to handle missing data
- All but one group discussed multiple testing and recommended that procedures to control type I error should be described and justified

✘ *Agreement is needed on the analysis of HRQL data if considered as a secondary end-point*

➢ same level of requirement as primary end-point ?

INTERPRETATION AND REPORTING

- There was agreement that interpretation should include not just statistical significance, but must consider clinical significance, but that effect size and minimum important difference should not be thought of as "gold-standards"
- Interpretation of HRQL findings in the light of clinical findings was addressed in the documents and the consensus reached that perfect agreement between the two should not be expected, although the findings should not conflict (one initiative suggested that if they do, clinical findings would currently carry more weight than HRQL)
- It was agreed that reporting of HRQL results should be precise, fair, balanced and transparent and one group recommended that the existing CONSORT guidelines for reporting clinical trials should be followed

✘ *Some form of recommendation is needed on how clinical significance can be assessed*

➢ what evidence ?

CONDITIONS FOR CLAIMS

- There was agreement that an HRQL claim requires data from well designed, randomized, appropriately implemented clinical research
- No clear recommendation whether one trial with HRQL as the primary end-point and showing unequivocal results, or two trials with HRQL as a secondary end-point, would be acceptable
- The initiatives agreed that evidence that the instrument used was well developed and validated and appropriate for the trial should be required
- There was consensus that data analysis should meet clinical research standards to allow a claim
- Two initiatives considered the requirements to make a claim of an HRQL difference and recommended that:
  - ➢ at least half of the scales must be positive, including all scales prespecified as important
  - ➢ at least two of the three major domains plus any "global" score must be positive
  - ➢ positive defined as statistically and clinically significant
- Two initiatives considered the requirements to make a claim of HRQL equivalence and recommended that:
  - ➢ responsiveness of the instrument must have been demonstrated
  - ➢ " not meaningful" differences must be prespecified
  - ➢ at least two of the three major domains plus any "global" score must be equivalent
  - ➢ the trial must have adequate power to reject minimal clinically significant difference

✘ *Consensus should be reached on the conditions required for different types of claim*

➢ what is an HRQL claim ?

➢ what is a domain related claim ?

➢ should the intended claim be prespecified ?

➢ should the intended claim be integrated into the protocol ?

CONCLUSIONS and FUTURE STEPS

The documents produced by the four initiatives are complementary and between them have provided a general paper (ISOQOL), a CONSORT guideline type of check list detailing which precise and practical points to consider in implementing HRQL in a clinical trial (ERIQA) and a number of points which are still under discussion (PhRMA and ISPOR). Comparison of the documents has hopefully started a process that will allow integration of the perspectives of HRQL instrument developers, users and, eventually, decision-makers.

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The remaining challenge is to produce consolidated recommendations on the development of HRQL sections in clinical trial protocols, ways in which HRQL results can be interpreted and reported and the formulation of HRQL claims. Such recommendations must provide clear and precise guidance but should probably remain descriptive rather than prescriptive if they are to gain acceptance. Most importantly, if such recommendations are to be worthwhile, they must successfully convince the regulators of the credibility of HRQL as an evaluation criterion in clinical trials.