Role of Health-Related Quality of Life (HRQL) outcomes in the European Drug Regulatory Process: A review of the EMEA documents

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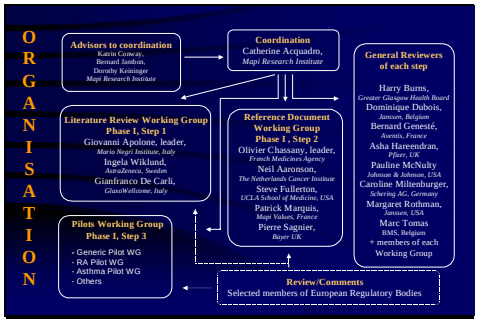
BACKGROUND

The ERIQA Group was created in 1998 with the following mission statement: *"establishing principles and practices for the integration of Health-related Quality of Life (HRQL) outcomes in the drug regulatory process".*



Objectives of the ERIQA Project are:

- to convince European Regulators that HRQL is a relevant key outcome, i.e. a credible criterion of evaluation of medicines;

- to have them confident in the quality of HRQL outcomes;

- to provide European regulatory authorities with guidance on:
  - how to assess the quality of HRQL studies in clinical trials,
  - how to evaluate the validity of HRQL claims

In August 1999, a first review of the documents produced by the European Agency for the Evaluation of Medicinal Products (EMEA) was performed by Giovanni Apolone et al and published elsewhere *(Apolone G, De Carli G, Brunetti M, Garattini S. Heath-Related Quality of Life and (HR-QOL) and Regulatory Issues. Pharmacoeconomics 2001; 19(2):187-195)*. As part of its activities of year 2000, the ERIQA Group performed an update of this review in August 2000.

OBJECTIVES

- To identify disease or drugs in which a formal HRQL assessment is recommended.
- To identify measures and methods recommended.
- To evaluate the reliability of recommendations across documents.

METHODS

All documents present on the the EMEA website (www.eudra.org/emea.html) – August 2001, 31st) were investigated, using two key words: "Quality of life" and "QoL". All the documents retrieved were reviewed by Dr Acquadro.

RESULTS

133 documents were retrieved excluding duplicates (129: Quality of Life, 25: QoL).
- 19 documents derived from the Efficacy Working Parties (EWP) including:
  - 9 notes for guidance
  - 3 concept papers,
  - 5 points to consider,
  - 2 position statements
- Only one document was a note for guidance for ICH.
- 104 European Public Assessment Report (EPAR) were retrieved, representing 26 products.
- 9 miscellaneous documents were found including minute reports, workshop, letters (5), assessment/opinion (2) from the CPMP and 2 documents were produced by the CVMP.

Identification of Conditions/Diseases
CPMP/EWP NG: 9
Weight Control, Cancer, Chronic Peripheral Arterial Occlusive Disease, Cardiac Failure, Stable Angina Pectoris, Anti-arrythmics, Parkinson, Alzheimer, Multiple Sclerosis
CPMP/EWP PC: 5
Amyotrophic Lateral Sclerosis, Osteoarthritis, COPD, Rheumatoid Arthritits, Crohn's Disease

CPMP/EWP CP: 3
Asthma, Cardiac Failure, Acute Ischemic Stroke

Identified of Measures
Cited as examples of measures that might be used
- Chronic Cardiac Failure: Minnesota Living with Heart Failure Questionnaire
- Chronic Obstructive Pulmonary Disease: Saint George's Respiratory Questionnaire
- Crohn's Disease: IBDQ

CPMP/ICH/363/96: Statistical Principles for Clinical Trials
2.2.2. Primary and secondary variables: *Measurements relating to quality of life and health economics are further potential primary variables.*

CPMP/EWP/235/95, Rev 1: Cardiac Failure
3.4. Quality of Life: *A broadly based assessment of the quality of life scales is recommended in Heart Failure studies because almost all components of the life quality may be influenced by an intervention for heart failure. Various QOL questionnaires have been used in the past and new ones devised. Unless these have been fully validated, evidence of efficacy derived from QoL questionnaires must be viewed as supportive only.*
It is particularly important to consider whether (a) the scale is linear over the range of measurements, (b) is sensitive to the changes anticipated, (c) it is valid and useful to adjust results using the baseline scores, (d) there is any correlation between the score and the objective responses, (e) the observer and the patients should be blinded and (f) training of both the observer and the patient is necessary.
Rating scales to assess QoL should also be considered and should have been validated beforehand in the context of the proposed trial and its aims. The Minnesota Living with Heart Failure Questionnaire is one of the many systems used in cardiac failure. Translations of questionnaireshly vlidated *beforehand.*
CPMP/EWP/205/95 Rev 1: Anticancer MP in Man
4.12. To study the effects of a new agent. Appropriate end-points of assessment include: *…symptom control/quality of life*
4.5.4. Symptom control and quality of life: *The choice of scales should be justified and the validity of the scale for the specific study population and its reliability should be documented. Cultural aspects should be taken into account, especially in the case of multinational studies.*
5.3.2.Quality of Life Studies: *QOL studies may be used to support symptom control data provided that established quality of life questionnaires (including for example level of hospitalisation) are used, which are relevant to the study population treated.*

CPMP/EWP/561/98: Multiple Sclerosis
4.4. Quality of Life: *Few data are available on validation of specific instruments for QoL in patients suffering multiple sclerosis. If a claim with respect to QoL in MS is considered, reliable and valid scales should be used.*
CPMP/EWP/563/95: Parkinson's Disease
4. Methods to assess efficacy: *the use of indirect efficacy variables as primary efficacy variable in pivotal studies, such as..[..] quality of life.. is not recommended unless the association between these variables and improvement in core symptoms or motor fluctuations or handicap has been proven*

CPMP/EWP/553/95: Alzheimer's Disease
2.2.5. Quality of Life: *Although QOL is an important dimension of the consequences of diseases, the lack of validation of its assessment in AD does not allow specific recommendations to be made as yet. When adequate instruments to assess this dimension in patients and their care givers become available, QOL assessment may be justified in AD trials*

CPMP/EWP/233/95 final: Chronic PAOD
3.1.2. & 3.2.4. Other clinical parameters: *In long-term therapeutic studies with an appropriate sample size of patients, the assessment of QoL should also be performed by using general or disease specific questionnaires. However, at present not fully validated scales are available for this purpose*

CPMP/EWP/234/95: Stable Angina Pectoris
2.3. Quality of life: *QoL measurement can provide valuable information about the effect of therapy on the general health status.* 3.3. Quality of life: *A QoL assessment may be considered, provided the questionnaire is validated in the context of the proposed target group.*

CPMP/EWP/281/96: Weight control
2.2. Secondary (supportive) Efficacy Endpoints: *Choice of secondary variables should be justified by the applicant and could include variables such as quality of life parameters…*

CPMP/EWP/784/97: Osteoarthritis
II. Recommended efficacy endpoints: *Secondary endpoints include ….Quality of Life….*

CPMP/EWP/556/95: Rheumatoid Arthritis
5. Supportive evidence for efficacy. e) quality of life: *Of the above list only d) and e) are established as useful additional secondary endpoints.*

CPMP/EWP/565/98 draft: ALS
VIII.5. Assessment of Quality of Life: *Measurement of QoL is a valuable and independent measure of therapeutic efficacy, which may be applied as a secondary end-point in ALS trials. Use as a primary endpoint is not recommended. Quality of Life scales specific to ALS have not been developed, and the use of a well-known general Quality of Life scale as an additional secondary end-point should be validated.*
CPMP/EWP/2284/99 draft 5: Crohn's Disease
2.2. Management of Crohn's disease and potential claims: *Other end-points such as…[..]…improvement in QoL can be subsumed as response variables or outcomes measures of either the treatment of active disease or maintenance of remission. Unless otherwise justified, they should not be mentioned in the indication.*
CPMP/EWP/562/98: COPD
VI. Recommended Primary and secondary endpoints:
The Primary symptomatic benefit endpoint should be justified by referencing published data which support its validity; one example is the St George's Respiratory Questionnaire.
There are a number of secondary endpoints which may provide useful information. These measure different aspects of the disease but they should be justified by referencing published data which support their validity; examples include…..symptom scales, exacerbation rates and QoL assessment. Care should be taken with respect to statistical multiplicity if secondary endpoints become the basis for specific claims

CONCLUSION

The recommendations from the EMEA are vague in most cases, too generic, inconsistent between each other and reveal in some cases a lack of knowledge of the field. These recommendations are not up-dated and do not exist in relevant diseases (HIV/AIDS, HBP). Nevertheless, recommendations do exist showing a real interest in HRQL and recognition of HRQL as a valuable endpoint (mainly secondary). Positive" - the "door" is open. Recommendations: do exist…= real interest in HRQL, HRQL recognized as a valuable endpoint (mainly secondary), reveal in some cases a certain level of knowledge of the field the word