# A REVIEW AND EVALUATION OF THE EMEA DOCUMENTS WITH REFERENCE TO QUALITY OF LIFE (QOL) ASSESSMENT

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## • SUMMARY •

In Spring 1998, the ERIQA project was launched with the objective of producing guidelines on the use of QoL data in the Drug Approval Process. A first step led to a thorough review of existing information.

**OBJECTIVE**: The purpose of the present study was to review and evaluate the EMEA guidelines, to identify diseases/drugs in which a formal QoL assessment is recommended, identify measures and methods recommended, and evaluate the reliability of recommendations across documents.

**METHODS**: Four types of documents were retrieved in the EMEA website (October 26th,1998): notes for guidance, concept papers, position papers, points to consider. A first review allowed the selection of 105 documents. The review of titles (by two independent reviewers) led to the identification of 45 documents likely to contain QoL recommendations.

**RESULTS**: Out of these 45 papers, only 12 showed explicit statements on QoL assessment. There are no documents directly focused on QoL measures, and few (11) explicit recommendations on specific diseases/drugs. QoL measures are often recommended as supportive criteria of efficacy, except in COPD where it is considered as a primary endpoint. There is only one example with recommendations regarding dimensions to be included (cardiac failure); only 2 questionnaires are cited (Minnesota Living with Heart Failure, St. George's Respiratory Questionnaires); there are no comments on the issue of generic/specific instruments, and no recommendations in expected diseases/drugs (i.e. hypertension).

**CONCLUSION**: Our review showed that QoL is not formally recognised as a criterion of evaluation by the EMEA, and recommendations are not consistent across documents. Further collaboration between regulatory bodies and QoL researchers are needed to improve the quality of recommendations.

## • INTRODUCTION - QOL: PRINCIPLES AND MEASUREMENT •

Quality of Life (QOL), subjective health status and health perceptions, Health-Related Quality of Life (HRQOL) are terms that are used interchangeably in the medical field, although conceptual and operational differences do exist (1-4).

*Health-Related Quality of Life* is an attempt to restrict the complex, abstract, and multidimensional concept of QOL to those aspects of life specifically relate to the persons' health that are potentially impacted by health care interventions (6-8). Most conceptualizations of HRQOL include the domains of physical, mental, social functioning and well-being, as well as general health perceptions (1-3). Although sometimes important signs and symptoms (i.e., perceptions of an abnormal physical, emotional or cognitive status), such as bodily pain, are included, patient-reported symptoms are considered not pertaining the conceptualization of HRQOL.

*Health status and health perceptions*, also referred as "perceived health status" are objective reports and subjective evaluations reported by a person on his/her health level. The need to distinguish between objective degrees of health status (reports) and subjective perceptions of health (evaluations) relies on the fact that individuals perceive themselves healthy or ill independently from the presence or evidence of biological, physiological signs and symptoms of diseases. In other words, two people with the same health status may have different perception of health (1).

In this scenario, four points may be identified and underscored:

1) Although the operationalization of concepts and the validation process have been well-codified, very few attempts at present exist to standardize the evaluation of the instruments characteristics through an explicit "instrument review process" based on explicit criteria (14).

2) Most of the criteria suggested actually regard the "intrinsic" characteristics of the instruments (reliability, validity, and responsiveness) and no recommendations are present on how to interpret HRQOL scores when yielded through formal clinical trial (clinically meaningful difference).

3) Although the issue of how transfer patients-based measures from the national to the international domain has received long-standing attention, the growing need to carry out clinical trials in several cultural and linguistic settings yielded a scenario in which shortcuts were used to translate ad adapt measures. Very few instruments were actually produced with cross-cultural approaches, and few established (English) measures were actually translated and adapted with formal procedures (23-25).

4) Although a few Scientific Societies have produced guidelines on the use of patient-oriented outcome measures in clinical research (26-28), debate on the true value of such measures in clinical research is still open (29, 30) and official (i.e., approved) recommendations from Regulatory Agencies on the use of such measures in the Drug Approval Process do not exist.

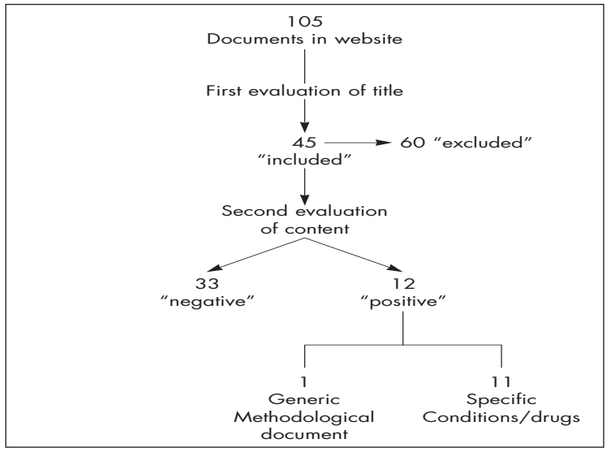
## • THE EVALUATION OF THE EMEA DOCUMENTS •

In 1997 two distinct and independent activities were launched in Europe with the goal to bring together HRQOL researchers, pharmaceutical industries and representatives of regulatory agencies in order to discuss the role and value of such measures in the specific framework of registration and reimbursement of pharmaceutical drugs. Both activities are described in details elsewhere (31). Briefly, the first was launched in Italy by the Mario Negri Institute of Milano in collaboration with GlaxoWellcome Italy on October 1997. The second was sponsored by the MAPI Research Institute and started with a first meeting in Vienna, November 4-5, 1997. At the end of 1998 a merge of the 2 initiatives were formalized, and a new group was created: **E**uropean **R**egulatory **I**ssues on **Q**oL **A**ssessment (**ERIQA**) Group.

### ERIQA Group

The mission of the novel group was "*establishing principles and practices for the integration of HRQOL outcomes in the regulatory process*", that is to make possible an appropriate use of measures in studies that have the objective to document the clinical value of the drug under evaluation, in the context of the regulatory environment. Operationally, the first objective identified as relevant was "*reviewing the existing outcomes guidelines and to produce a synthesis of existing information to underscore the points to be improved or developed*". As in the first preliminary search no EMEA official documents on the specific issue of (HR)QOL measures were found, an additional more thorough search was carried out to understand and document the implicit position of the Agency on the use of such measures in registrative studies. The objectives of such evaluation were: a) to identify disease or drugs in which a formal (HR)QOL assessment is recommended; b) to identify measures and methods recommended; c) to evaluate the reliability of recommendations across documents.

■ **Figure 1** - Synopsis of data collection and evaluation




*Material and Methods*

All documents present in the EMEA Website (October 26°,1998) were identified, downloaded and printed. Four types of documents were retrieved (Notes for guidance, concept papers, position papers, points to consider), yielding a total of 105 documents available for the review. The evaluation was carried with a 2-step process. First, all the titles of the 105 documents were independently reviewed by 2 reviewers to identify the documents that, according to the title, were more likely to contain (HR)QOL recommendations in the text; disagreement between reviewers were solved through a deeper evaluation of the document. Second, the content of the documents selected were then read and evaluated by one of the 2 reviewers. Each reviewer evaluated half of the documents.

*Results*

Out of the 105 documents that were identified in the EMEA website, 45 were selected through the double independent titles evaluation. In this step, 90% agreement was observed between reviewers. The evaluation of the content of each of the 45 documents identified 12 examples in which explicit statements about (HR)QOL assessment were present (See Figure 1 for a synopsis of data available and Table 1 with the complete list of "positive" documents). Out of the 12 "positive" documents, 11 are on specific conditions/drugs, such as Anti-cancer, Cardiac Failure, Stable Angina Pectoris, and 1 is an ICH document on generic principles (Note for Guidance on statistical principles for clinical trials). The ICH document is a generic paper intended to give directions in the design, conduct, analysis to sponsors and scientific experts in charge with preparing applications summaries or assessing evidence about the value of the drugs. The focus is on general methodological and statistical principles and not on the use of specific statistical procedures and methods. In the section 2.2.2 (Considerations for overall clinical development. Trial context. Scope of trial. Primary and secondary variables) when defining the characteristics of primary (target) variable, and the criteria to be satisfied, it is quoted that "... measurements relating to quality of life and health economics are further potential primary variables"). As to the 11 specific documents, most of the times (10/11) the assessment of (HR)QOL was recommended with a variable degree of cautions and warnings, while in the case of Alzheimer's Dementia (AD) it was stated that "... 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...". Seven out of the 11 specific documents are actually Note for Guidance, namely official recommendations that come into operation during (N.= 4) or before (N.= 4)1998. Among the 33 "negative" documents, there were conditions/drugs in which explicit recommendations about the use of (HR)QOL measures were actually expected, as the consensus existing about the value of such measures in clinical research and the huge amount of papers published containing examples of their use in pharmacological RCTs. It is the case of anti-hypertensive and anti-HIV/AIDS drugs. The evaluation of the 11 specific documents also permitted the identification of 2 examples in which a questionnaire was explicitly recommended. It happened in the case of Chronic Cardiac Failure (CCF) and in Chronic Obstructive Pulmonary Disease (COPD). The questionnaires quoted were, respectively, the Minnesota Living with Hearth Failure Questionnaire and the Saint George's Respiratory Questionnaire, two psychometric, disease-oriented instruments. In all the cases where (HR)QOL was recommended as potential (primary or supportive) variable to describe the efficacy of medicinals, recommendations were usually very vague, such as "QOL should be performed by using general or disease specific questionnaires" or "QOL measurement can provide valuable information about the effect of therapy on the general health status". Warnings and cautions also were most of the time very generic, such as "A quality of life assessment may be considered, provided the questionnaire is validated in the context of the proposed target groups" or " the choice of the scales should be justified, and the validity of the scale for the specific study population and its reliability should be documented". In at least one case (The note for Guidance for CHF), however, details were furnished with respect to dimensions to be included and assessed, and validity and reliability criteria to be satisfied. In the document on COPD, despite a well-known specific (HR)QOL questionnaire (the Saint George's Respiratory Questionnaire) is actually recommended as primary endpoint, when discussing the opportunity to chose secondary endpoints, QOL assessment (sicl) is quoted as example of potential additional variables to be used. The implicit underlying concept is that this specific questionnaire is not a (HR)QOL measure, but something else, may be a "mere" measure of (disease specific) symptomatic benefit.

In the case of Anti-Cancer medicinals "... symptom control supported by QOL data..." are considered an additional efficacy endpoint in studies that assess the symptomatic effect of the compound under evaluation, "... provided that "... established quality of life questionnaires (including for example level of hospitalization) are used...". In this case the implicit assumption is that (HR)QOL measures are all the data that come from questionnaire delivered to patients, including health and non-health outcomes, such as health resources utilization.

### • NOTES FOR GUIDANCE - EMEA (CPMP) •

**INCLUDING RECOMMENDATIONS ABOUT THE USE OF QOL MEASUREMENT**

1. General statistical principles (ICH)
2. Weight control
3. Alzheimer disease
4. Anti-cancer
5. Chronic peripheral arterial occlusion
6. Cardiac failure*
7. Parkinson disease
8. Stable angina
9. Rheumatoid arthritis
10. Osteoarthritis
11. Amyotrophic lateral sclerosis
12. COPD (point to consider)*

** Specific reference for the tool*

http://www2.eudra.org/humandocs/PDFs/EWP/023595en.pdf

The European Agency for the Evaluation of Medicinal Products
*Human Medicines Evaluation Unit*

CPMP/EWP/235/95 final

**CPMP**

**NOTE FOR GUIDANCE ON THE CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS IN THE TREATMENT OF CARDIAC FAILURE**

**3.2.2 SUPPORTIVE ENDPOINTS OF EFFICACY**

3.2.2.1 Quality of Life

Prominent components of quality of life measures which require addressing are physical function, social and emotional function, intellectual function, symptoms and their consequences, occupational activities, job satisfaction, leisure activities, sexual adjustment, perceived health status, life satisfaction and interpersonal relationships. Various quality of life questionnaires have been used in the past and new ones devised. Until these have been fully validated, evidence of efficacy derived from quality of life questionnaires must be viewed as supportive only.

4.5 Quality of Life

A broadly based assessment of the quality of life scales is recommended in heart failure studies because almost all the components of the life quality may be influenced by an intervention for heart failure. 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 patient should be blinded and (f) training of both the observer and the patient is necessary. Rating scales to assess quality of life should also be considered and should have been validated beforehand in the context of the proposed trial and its aims. The effects of therapy on daily activity and self-care, sleep, recreational and pleasure activities, in performing social roles, intellectual and cognitive functions, life satisfaction and expectations from the therapy require particular assessment. The Minnesota Living With Heart Failure Questionnaire is one of the many systems used in cardiac failure. Translations of questionnaires used should also have been well validated beforehand. Nevertheless, at present these data must be viewed as supportive only.

http://www2.eudra.org/humandocs/PDFs/EWP/056298en.pdf

The European Agency for the Evaluation of Medicinal Products
*Human Medicines Evaluation Unit*

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CPMP/EWP/562/98

**COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP)**

**POINTS TO CONSIDER ON CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS IN THE TREATMENT OF PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)**

**VI RECOMMENDED PRIMARY AND SECONDARY ENDPOINTS**

1. In the major efficacy studies of symptomatic benefit the primary endpoint should reflect the clinical benefit the applicant wishes to claim in the future SPC. It should include the forced expiratory volume in 1 second (FEV1) as a measure of lung function and include a measure of symptomatic benefit. A significant benefit for both endpoints, FEV1 and the clinical endpoint, should be demonstrated. The primary clinical endpoint should be justified by referencing published data which support its validity; one example is the St. George's Respiratory Questionnaire. Several secondary endpoints can be chosen 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 pulmonary function tests, oxygen saturation, CO2 retention, exercise tolerance such as the 6 minute walk, symptom scales, exacerbation rates and quality of life assessment. Which are chosen will depend upon the claims being made in the SPC. Care should be taken with respect to statistical multiplicity if secondary endpoints become the basis for specific claims.

## • DISCUSSION •

Despite the debate still ongoing on the true objective to measure (health status vs. happiness and satisfaction with life), on the focus (general vs. disease-tailored values), and on the terminology (QOL vs. HRQOL) (32,33) interest in measuring relevant qualitative aspects of life that are most closely related to health and to health care has increased in recent years. Not infrequently (HR)QOL measures are included as a therapeutic efficacy endpoint in several industry studies both to assist the industry in the regulatory process and for marketing purposes, though the Regulatory Agencies such as FDA and EMEA currently do not require these kind of data for regulatory purposes. In fact, there are indications that the present situation may change. The facts that suggest a potential change are the following:

• several version of (draft) guidelines intended to serve as starting point in discussion on the use of pharmacoeconomic data to support claims have been prepared by a subdivision of the FDA (Division of Drug marketing, Advertising ad Communications), containing statements and recommendations on HRQOl issues;

• a few Scientific Societies (American Society of Clinical Oncology, American Thoracic Society, International League Against Epilepsy) have set-up and appointed working groups to debate the issue of the role of such evaluations in clinical research and authoritative reports have been published in leading medical journals.

• the use of measures based on patients' perception in clinical trials is a way to introduce the patients' point of view into clinical research and enhance their involvement and role in the medical-decision making.

According to this scenario, one of the first objective of the ERIQA Project was to produce a synthesis of existing information to underscore the points to be improved or developed. The only one example in which details were furnished with respect to dimensions to be included and assessed, and validity and reliability criteria to be satisfied was the Note for Guidance for CHF, an indication in which FDA also has drafted guidelines.

As documented elsewhere by the ERIQA investigators (I. Wiklund, Personal Communication) relevant differences were observed between the 2 documents with respect to relevant points, suggesting difficulties in conducting studies suitable for both Europe and the US. Importantly, the EMEA requirements will result in exactly the problems that the FDA want to avoid. EMEA guidelines incorporating QoL outcomes are welcomed but it is at the same time obvious that further and more detailed guidance is required. Importantly, it is desirable that a greater degree of harmonization between the EMEA and the FDA should occur. Experts from the discipline of Outcome Research should be involved in the preparation of such documents, trying to assure both coverage of technical skills (statistics, epidemiology, psichometry, etc.) and representativeness of relevant counterparts (scientific societies, public agencies, pharmaceutical industries).

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