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Health-Related Quality of Life (HR-QOL) and Regulatory Issues

An Assessment of the European Agency for the Evaluation of Medicinal Products (EMEA) Recommendations on the Use of HR-QOL Measures in Drug Approval

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Abstract

Interest in measuring qualitative aspects of life that are most closely related to health and healthcare has increased in recent years. Methods of describing patients' subjective health status now incorporate standardised measures, and several psychometric measures are available. Despite the thousands of empirical and conceptual papers in the medical and pharmacological literature on health-related quality of life (HR-QOL), the value of such measures in the regulatory process is still being debated.

We conducted an assessment to understand and document the position of the European Agency for the Evaluation of Medicinal Products (EMEA) on the use of HR-QOL measures in studies conducted for regulatory purposes. Official documents produced and circulated by the EMEA containing recommendations on trial design, conduct and analysis for sponsors and scientific experts were independently reviewed by authors to document the position of the Agency on the specific topic of HR-QOL. All documents found in the Agency website on 30 September 1999 were identified and then assessed to: (i) identify diseases or drugs for which formal HR-QOL assessment is recommended; (ii) identify measures and methods recommended; and (iii) evaluate the reliability of recommendations across documents.

Of the 189 documents retrieved, none focused directly on health-related quality of life. A few explicit recommendations were identified for 13 specific drugs or conditions. These recommendations were mostly general and vague, and used nonstandard terminology. In addition, terminology and recommendations were not consistent across documents and, in at least one case, were in contrast with the US Food and Drug Administration (FDA) guidelines.

EMEA guidelines incorporating quality-of-life outcomes are welcomed but it is obvious that more detailed guidance is required. Closer collaboration between the EMEA and the FDA is also recommended. Experts from different disciplines should be involved in the preparation of such documents to assure the necessary technical expertise and the representativeness of the various counterparts.

Quality of life, subjective health status and health perceptions, and health-related quality of life are terms that are used interchangeably in the medical field, despite certain conceptual and operational differences.[1-4]

Quality of life is a complex, abstract, multidimensional concept that defines an individual's satisfaction or happiness with life in domains he or she considers important. Often also referred to as 'life satisfaction' or 'subjective well-being', it is the broadest of all the concepts; health is only one of the several dimensions of life usually considered in the models and taxonomies proposed so far.[5]

Health-related quality of life reflects an attempt to restrict the complex concept of quality of life to those aspects of life specifically related to a persons health that potentially respond to healthcare.[6-8] Most definitions of health-related quality of life include the domains of physical, mental, social functioning and well-being, as well as general health perceptions.[1-3]

Health status and health perceptions, also referred to as 'perceived health status', are objective reports and subjective evaluations made by a person on his or her health. 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 as healthy or ill independently of biological or physiological signs and symptoms of disease. In other words, 2 people with the same health status may have different perceptions of health.[1]

Several approaches from the fields of clinimetrics, psychometrics and clinical decision theory have been used to measure these concepts; all have their pros and cons.[9] However, with the aim of evaluating health-related quality of life in clinical studies as an outcome (i.e. a change in a patient's health status that may be attributed to a specific intervention), most of the available measures are based on the psychometric method.[10]

Psychometric measures usually provide a comprehensive (all the relevant health concepts are included), multidimensional (each concept is represented by an individual score) assessment, ranging from disease-specific (health concepts tailored to a specific disease and treatment, relevant and sensitive only to the condition under evaluation) to generic (assessing health concepts that represent basic human values, relevant to every ones health) instruments.

These measures can be considered along a continuum ranging from patients' simple reports on health (e.g. most of the disease-oriented batteries on physical function limitations widely used in osteoarthritis and rheumatoid arthritis) to more comprehensive questionnaires aimed at measuring subjective feelings of psychological well-being and distress.[11] The modern multidimensional health status measures lie somewhere in the middle.[12,13]

Psychometric instruments, which are mostly questionnaires, are administered through standardised approaches; self-administration is recommended.[1-7] Questionnaires may be evaluated in terms of validity (the degree to which an instrument measures what it is intended to), reliability (the degree to which it is free of random error), responsiveness (its capability to detect meaningful differences be-

tween groups and over time) and robustness (how the instruments perform in terms of the above mentioned criteria in all the settings of application). A combination of qualitative (expert judgement) and quantitative (empirical data collection using standard methodology) empirical methods is used to evaluate questionnaires.[7]

These methods, applied in various combinations in the 'development and validation process' have been well codified.[14,15] Usually, instruments are developed and validated through prospective multistep procedures based on explicit conceptual models, in which biological and clinical variables are linked in an *a priori* hypothesised way with health-related quality of life (HR-QOL) outcomes, depending on the underlying health concepts they represent. Thus, a causal relationship pathway can be expected and then empirically tested.[16] Several examples of the empirical utilisation of HR-QOL instruments in clinical studies (observational or experimental) can be found in the literature,[17,18] with an impressive increase in their use from 1985 to 1994 (0.21 *vs* 0.76% of all papers in Medline contained HR-QOL–related keywords).[19] Examples cover all conditions and diseases, with cancer accounting for more than 20% of the total HR-QOL literature.[20] Hundreds of different instruments have been used.[21,22]

However, the following important points need to be considered:

- although the operational application of concepts and their validation process have been well codified, very few attempts have been made to standardise the evaluation of the instruments' characteristics through an 'instrument review process' based on explicit criteria;[14]
- most of the criteria suggested actually regard the 'intrinsic' characteristics of the instruments, namely their reliability, validity and responsiveness, and no recommendations are made about how to interpret health-related quality of life from clinical trials;
- although a few scientific societies (American Society of Clinical Oncology, American Thoracic Society, International League Against Epilepsy) have set up working groups to debate the role of such evaluations in clinical research and authoritative reports have been published in leading medical journals,[23-25] the debate on their true value in clinical research is still open[26,27] and there are no official (i.e. approved) recommendations from regulatory agencies on their use in the drug approval process.

In 1997, 2 independent projects were launched in Europe with the aim of bringing together HR-QOL researchers, the pharmaceutical industry and representatives of regulatory agencies in order to discuss the role and value of these measures in the specific context of drug registration and reimbursement. Both projects are described in detail elsewhere.[28] At the end of 1998, the 2 initiatives were formally merged and a new group was created, the European Regulatory Issues on Quality of life Assessment (ERIQA).

The mission of ERIQA was 'to establish principles and practices for the integration of HR-QOL outcomes in the regulatory process' thereby ensuring the appropriate use of measures in studies designed to document the clinical value of a drug under evaluation, in the regulatory environment. Operationally, the first major objective was 'to review the existing outcomes guidelines and to produce a synthesis of existing information to highlight the points to be improved or developed.'

In a preliminary search, conducted by ERIQA members, of the several documents produced by national and regulatory agencies, no guidelines on the specific issue of the use of HR-QOL measures were found. Therefore, we conducted a more thorough search among the official documents produced and made available for the public by the European Agency for the Evaluation of Medical Products (EMEA) to document the position of this agency on the use of such measures in studies conducted for regulatory purposes. The objectives of such evaluation were to: (i) identify diseases or drugs for which a formal HR-QOL assessment is recommended; (ii) identify measures and methods of evaluation recommended; and (iii) evaluate the reliability

of recommendations across documents. The findings from this evaluation are presented in this article.

1. European Agency for the Evaluation of Medicinal Products (EMEA)

Until 1995 in Europe, the regulatory approval process with respect to pharmaceutical products was implemented at a national level, with an increasing cooperation between national registration authorities at European Union level.

In 1995, a new European system came into effect, and an EMEA was established in London.[29] The mission of this novel agency is to contribute to the protection and promotion of public and animal health by providing the member states with the best possible scientific advice on the value of medical products, by:

- establishing multinational scientific expertise through the mobilisation of existing national resources;
- organising rapid, transparent and efficient procedures for centralised and decentralised marketing authorisation;
- and advising companies on the conduct of preclinical and clinical research, reinforcing the supervision of existing medical products.

In addition, the harmonisation of scientific requirements to optimise pharmaceutical products worldwide is also an important task of EMEA.

The major objective of EMEA is to make possible a transparent, rapid and efficient centralised procedure for medical products that is, so far, compulsory for biotechnological products[29] and available for other innovative medical products. Issues related to cost, pricing, reimbursement and drug advertising, and communication would still pertain to each member state.

EMEA comprises a management board, 2 scientific committees [the Committee for Proprietary Medical Products (CPMP) for the evaluation of the human product and Committee for Veterinary Medical Products (CVMP) for the veterinary products] and a permanent secretariat. The CPMP consists of 2 members appointed by each of the 15 member states and its main task is to facilitate the adoption of common decisions by member states on the basis of scientific criteria of quality, safety and efficacy. The CPMP is assisted by specific working parties that provide additional expertise and advises on specific issues. Among them, the Efficacy Working Party, established in 1995, is in charge of creating methodological guidelines and elaborate position and concept papers, and discusses and comments on the documents produced by the International Conference on Harmonisation (ICH) in order to enhance the quality and assure the harmonisation of the conduct of clinical trials within the framework of the drug approval process.

2. Methods

2.1 Data Source

All documents present in the EMEA website[29] on 30 September 1999 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 189 documents for review. Some dealt with technical preclinical aspects of the drug review process, such as the 'note for guidance on modified-release oral and transdermal dosage forms: section II (quality)', whereas others were apparently relevant to the topic under evaluation, such as the 'note for guidance on clinical investigation of medicinal products in the treatment of hypertension'.

2.2 Data Analysis

Given the heterogenous nature of the documents retrieved, the evaluation was carried out in 2 steps. First, the titles of all documents were independently reviewed by 2 of the authors (AG, MB) to identify those that were most likely to contain HR-QOL recommendations in the text; disagreements between reviewers were resolved by closer examination of the document. Secondly, the content of the documents judged likely to contain HR-QOL recommendations were then read and evaluated by 1 of the 2 reviewers. Each reviewer evaluated half of the documents looking for explicit statements on the use of HR-QOL measures. Subsequently, to check the

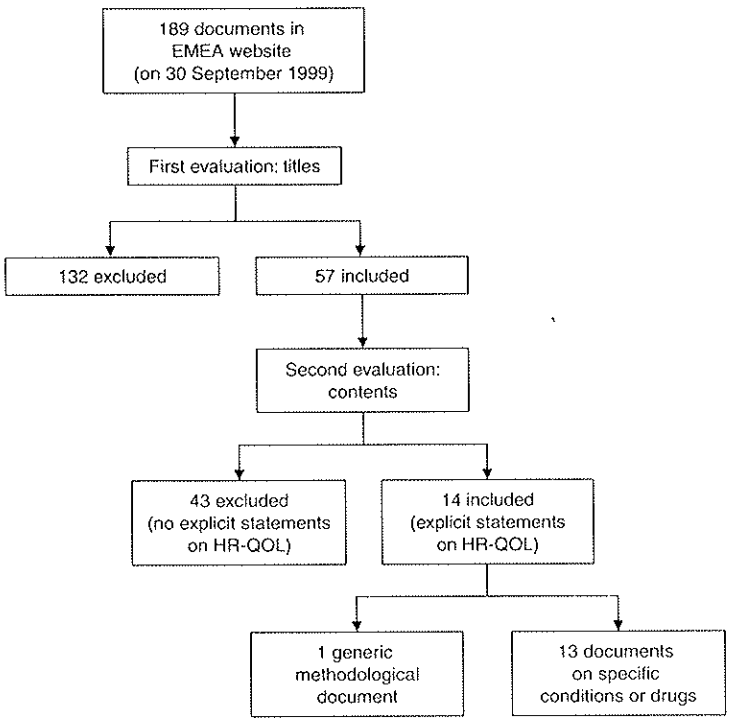

Fig. 1. Overview of data collection and evaluation. **EMEA** = European Agency for the Evaluation of Medicinal Products; **HR-QOL** = health-related quality of life.

accuracy of the selection made by the 2 reviewers, a random sample of 10% of the documents excluded after the first and second evaluations were evaluated by a third author (GD).

2.3 Results

Of the 189 documents that were identified in the EMEA website, 57 were selected through the independent evaluation of titles by the 2 initial reviewers. 90% agreement was reached between these reviewers. The subsequent evaluation by the independent reviewer did not identify any another eligible documents.

Assessment of the content of these 57 documents revealed that 14 contained statements about HR-QOL assessment (see figure 1 for an overview of the data and analysis and table I for a complete list of documents). Of these 14 documents, 13 addressed specific conditions or drugs, such as anti-cancer drugs, cardiac failure and stable angina pectoris, and 1 was an ICH document on general principles (note for guidance on statistical principles for clinical trials).

The ICH document was intended to give directions on trial design, conduct and analysis to sponsors and scientific experts preparing applications and summaries or assessing evidence about the value of drugs. The focus was on general methodological and statistical principles and not on the use of specific statistical procedures and methods. In section 2.2.2 of the document (Considerations for Overall Clinical Development. Trial Context. Scope of Trial. Primary and Secondary Variables), in which the characteristics of primary (target) variables and the criteria to be satisfied were defined, it was stated that '... measurements relating to quality of life

Table I. European Agency for the Evaluation of Medical Products (EMEA) documents containing health-related quality-of-life statements[29]

CPMP/EWP/281/96 note for guidance on the clinical investigation of drugs used for weight control
CPMP/EWP/553/95 note for guidance on medicinal products in the treatment of Alzheimer's disease
CPMP/EWP/205/95 note for guidance on evaluation of anticancer medicinal products in man
CPMP/EWP/233/95 note for guidance on the clinical investigation of medicinal products in the treatment of chronic peripheral arterial occlusive disease
CPMP/EWP/235/95 note for guidance on the clinical investigation of medicinal products for the treatment of cardiac failure
CPMP/EWP/234/95 note for guidance on the clinical investigation of anti-anginal medicinal products in stable angina pectoris
CPMP/EWP/563/95 note for guidance on clinical investigation of medicinal products in the treatment of Parkinson's disease
CPMP/EWP/561/98 note for guidance on clinical investigation of medicinal products for the treatment of multiple sclerosis
CPMP/ICH/363/96 note for guidance on statistical principles for clinical trials
CPMP/EWP/784/97 points to consider on clinical investigation of medicinal products in the treatment of osteoarthritis
CPMP/EWP/562/98 points to consider on the clinical investigation of medicinal products in the treatment of patients with chronic obstructive pulmonary disease
CPMP/556/95 draft points to consider on the clinical investigation of slow-acting antirheumatic medicinal products in rheumatoid arthritis
CPMP/EWP/565/98 concept paper on the development of a committee for products. Points to consider on the clinical investigation of medicinal products for the treatment of amyotrophic lateral sclerosis
CPMP/EWP/560/98 concept paper on the development of a CPMP. Points to consider on clinical investigation of medicinal products for the treatment of acute ischemic stroke

CPMP = Committee for Proprietary Medical Products; **EWP** = Efficacy Working Party; **ICH** = International Conference on Harmonisation.

and health economics are further potential primary variables.'

In 12 of the 13 specific documents, the assessment of health-related quality of life was recommended with varying cautions and warnings. For example, in the case of Alzheimer's dementia (AD), it was stated that '. . . although quality of life is an important dimension of the consequences of diseases, the lack of validation of its assessment in AD does not allow specific recommendations. . .'.

As shown in table II, health-related quality of life was always recommended as an efficacy outcome, and assessment in phase III trials was usually recommended. Nine of the 13 specific documents were actually 'notes for guidance', i.e. official recommendations that came into operation before[4] or after[5] 1998.

Among the 43 documents that had no explicit statements on health-related quality of life, there were conditions or drugs for which recommendations about the use of HR-QOL measures were expected i.e. there was a large consensus about the value of HR-QOL instruments in clinical research and a large number of published papers providing examples of their use (of HR-QOL measures) in pharmacological randomised controlled trials. This is the case for antihypertensive and anti-HIV/AIDS drugs.

Among the 13 specific documents, we identified 2 examples in which questionnaires were recommended – one in chronic cardiac failure and the other in chronic obstructive pulmonary disease. The questionnaires were, respectively, the Minnesota Living with Heart Failure Questionnaire and the Saint George's Respiratory Questionnaire, 2 psychometric, disease-oriented instruments. In both cases they were cited as examples of measures that might be used. The second was recommended for primary variables (together with the forced expiratory volume in 1 second) and the first as a supportive endpoint only.

In general, recommendations were vague and had poor reliability. In all of the cases where health-related quality of life was recommended as a potential (primary or supportive) variable to describe the efficacy of medicinal products, recommendations were usually very vague, such as 'quality of life assessment should be performed by using general or disease-specific questionnaires' or 'quality of life measurement can provide valuable information about the effect of therapy on the general health status.' Warnings and cautions also were usually

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.' Two examples were completely inconsistent with the taxonomy usually adopted in the literature.

In the document on chronic obstructive pulmonary disease, a well known specific HR-QOL questionnaire (the Saint George's Respiratory Questionnaire) was recommended as a primary end-point. However, when discussing whether to choose secondary end-points, quality of life assessment was offered as an example of a potential additional variable. The implicit underlying concept is that the Saint George's Respiratory Questionnaire is not a HR-QOL measure, but something else, maybe a 'mere' measure of (disease-specific) symptomatic benefit.

In the document on anticancer medicinal products '. . . symptom control supported by quality of life data. . .' is considered an additional efficacy end-point in studies that assess the symptomatic effect of the compound under evaluation, '. . . provided that . . . established quality of life questionnaires (including for example the level of hospitalisation) are used. . .'. In this case, the assumption is that the HR-QOL concept comprises all the data reported by patients including health and nonhealth outcomes, such as health resources utilisation.

It is worth mentioning that the terminology used was not consistent in the different documents. In at least one document (the note for Guidance for chronic cardiac failure), however, details were provided about dimensions to be included and assessed, and validity and reliability criteria to be satisfied.

3. Discussion

Despite the continuing debate about the true objective for measuring health status or happiness and satisfaction with life, the focus that should be taken (general or disease-tailored values) and the terminology used (quality of life or health-related quality of life), interest in measuring relevant qualitative aspects of life that are most closely related to health and healthcare has grown in recent years. In addition to the genuine goal of increasing patients' involvement in medical decision-making through the use of measures based on patients' perceptions (thereby introducing the patients' point of view into clinical research), not infrequently HR-QOL measures are included as a therapeutic efficacy end-point in several industry-sponsored studies, both to assist the industry in the regulatory process and for

Table II. Overview of European Agency for the Evaluation of Medicinal Products recommendations on health-related quality of life assessment

Title/subject	Study phase	Type of outcome	Type of end-point	Instruments recommended?
Weight control	III	E	S	No
Anticancer medicinal products in humans	II/III	E	S	No
Chronic peripheral arterial occlusive disease	III	E	S	No
Cardiac failure	III	E	S	Yes
Stable angina pectoris	III	E	S	No
Amyotrophic lateral sclerosis	–	E	S	No
Osteoarthritis	III	E	S	No
Rheumatoid arthritis	III	E	S	No
Chronic obstructive pulmonary disease	III	E	P	Yes
Ischaemic stroke	–	E	–	No
Multiple sclerosis	III	E	S	No
Alzheimer's disease	–	–	–	–
Parkinson's disease	–	–	–	–

E = efficacy; P = primary; S = secondary; – = not available/not applicable.

marketing purposes. Nevertheless, the regulatory agencies such as the US Food and Drug Administration (FDA) and EMEA currently do not require this kind of data. However, there are indications that the present situation may change. Several of the draft guidelines intended to serve as a starting point for discussions on the use of pharmacoeconomic data to support claims, drafted by a subdivision of the FDA (Division of Drug Marketing, Advertising and Communications), contain statements and recommendations on HR-QOL issues.

One of the first objectives of the ERIQA Project was to review existing information on HR-QOL assessment to highlight points to be improved or developed. After a preliminary search among the several documents produced by national and international regulatory agencies on the specific issue of the use of HR-QOL, a formal evaluation of the official EMEA documents was conducted to clarify the position of the agency on the use of such measures in registrative studies.

We found no documents that directly focused on HR-QOL measures, and very few explicit recommendations; most of them were generic and vague, using nonstandard terminology. In addition, terminology and recommendations were not consistent across documents. The only document that included details about the dimensions to be included and assessed, and the validity and reliability criteria to be satisfied was the note for guidance for chronic cardiac failure, an indication for which the FDA has also drafted guidelines. As already reported by Wiklund and other ERIQA investigators,[30] the 2 documents show striking differences with respect to some important points, suggesting difficulties in conducting studies suitable for both Europe and the US and, thus, the need for harmonisation or, at least, collaboration between the 2 agencies.

Although harmonisation might be useful for all counterparts involved in the regulatory process, particularly pharmaceutical firms, the key issue is the quality of the standards required. The present review of the EMEA recommendations clearly shows that current recommendations are general, vague and not consistent across documents. There are clear dangers involved; the field of health outcomes assessment and outcomes research[17,18] has already witnessed negative effects with the uncritical widespread adoption of tools that have ended up being both appropriately and inappropriately used.

4. Conclusion

EMEA guidelines incorporating quality-of-life outcomes are welcomed but it is obvious that more valid and detailed guidance is required. Closer collaboration between the EMEA and the FDA is also recommended.

Outcomes research experts should be involved in the preparation of such documents to assure the necessary technical expertise (statistics, epidemiology, psychometry, economics, decision science, clinimetrics, etc.) and the representativeness of the various counterparts (scientific societies, public agencies, the pharmaceutical industry). The main questions that need to be answered are whether (do we need these measures to assess the efficacy, activity and safety of medical products in addition to the established traditional measures of clinical benefits?), when (in which phase of the drug development plan?) and how (what methods should be adopted and which criteria need to be satisfied?) such measures should be integrated into studies for registration purposes.

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