The role of patient reported outcomes in the regulatory process needs to be better defined

Promote group: Patient-Reported Outcomes MOving Toward Evidence, coordinate by Istituto Superiore di Sanità

We read the editorial with great interest and we strongly support its conclusions on the necessity to standardise the patients reported outcomes (PROs) measures and stimulate their appropriate use. The growing amount of applications in clinical research of these outcomes has stimulated the regulatory agencies, in the United States and Europe, to take into consideration PROs in the regulatory process and to produce documents where this topic is addressed.

In 2004 the European Medicines Agency’s (EMEA) Committee for Medical Products in Human Use published a “Reflection Paper on the Regulatory Guidance for the Use of Health-Related Quality of Life Measures in the Evaluation of Medicinal Products” 1. In 2006 a draft guidance for industry, the “Patient-Reported Outcome Measures: Use in Medical Product Development to Support Claims”, was published by the Food and Drug Administration (FDA)2. The two documents have some agreement points and several different aspects.

- Agreement points between the agencies: both documents not only have recognized the usefulness of patient-centred measures for health outcomes assessment, but also have expanded on methodological aspects, such as study design, statistical analysis and hypothesis testing, reliability and validity of patient centred measures.
- Disagreement points: FDA stated that all PROs, including health related quality of life (HRQoL), can be used as “effectiveness endpoints” in clinical trials, and in particular for drugs to be licensed for chronic diseases (e.g., cancer, HIV). EMEA does not assign at the moment the same weight to all the PROs measures. In fact, whereas the core symptoms of a disease (e.g. pain, migraine, …), assessed by the patient himself, are well-accepted
as primary and secondary efficacy endpoints in registration trials, the HRQoL assessment is regarded to be an optional endpoint of drugs efficacy, as “the basis for the approval of a new medicinal product is its clinical efficacy and safety in a given condition”1.

In 2005, a review analysing the use of PROs measures for the approval of new pharmaceutical products was published3 by the EMEA. According to the authors, the regulatory decision-makers should develop and update harmonized procedures to adequately use PROs information in the regulatory decision processes. They concluded that the reflection paper released by EMEA1 on HRQoL research is a promising step towards achieving this aim.

As a multidisciplinary group of health care researchers and physicians (PROmote group), coordinated by the Italian National Institute of Health (Istituto Superiore di Sanità), it is our opinion that the EMEA reflection paper is based on preliminary assumptions but needs an urgent update. We strongly encourage both the International and National regulatory authorities to align their documents with the current thinking that all PROs, including HRQoL, should have a significant role in the evaluation of efficacy and safety of medicines.

References


The complete assessment of the benefits of an intervention must include evidence of the effect on the patient’s health status and quality of life. Such evidence is usually based on self administered or interview administered questionnaires, which are increasingly referred to as patient reported outcome measures. Two linked papers (doi:10.1136/bmj.a1190; doi:10.1136/bmj.a3006) raise important questions regarding the standardised application of these measures in randomised controlled trials. The first used several patient reported outcome measures as end points in an international study of combined hormone replacement therapy. The second is a systematic review of randomised trials that included the short form 36 item (SF-36) health survey questionnaire as an outcome measure. Two broad types of patient reported outcome measures exist—those that are specific to a disease or population and those that are generic and can be applied across populations, regardless of any underlying health problems. The two are complementary, the first type gives detailed information about specific health problems and the second type give more general information on health and quality of life. Specific measures are usually more responsive to changes in health after care for the health problem being investigated. Generic measures have greater potential to measure any unforeseen effects or side effects of health care, and the results can be compared with those for other populations. Generic measures are also more suitable for use in economic evaluation. These features have led to recommendations that both types of measure are used in healthcare evaluations, including randomised trials.

The SF-36 is a generic measure that was first tested in the United Kingdom in the early 1990s and has since become the most widely evaluated patient reported outcome measure, with hundreds of published studies presenting the results of testing for data quality, reliability, validity, and responsiveness to changes in health. It is also the most widely reported measure within randomised controlled trials. Numbers of published studies related to disease specific measures have also grown immensely. Multiple measures exist for common health problems. This has led to confusion and different primary end points being selected across trials, which limits generalisability. Given the evidence for the measurement properties of the SF-36, and its widespread acceptance and use, it makes a good generic measure of choice in randomised trials of health care that may affect health and quality of life. However, its use in randomised trials is not standardised, perhaps because potential users have to choose between eight scale scores and two summary scores. Many disease specific measures give a single score, but we still have the problem of defining what is an important or meaningful level of change that is needed for sample size calculations in randomised trials.

The exponential growth in patient reported outcome measures has not been matched by adequate consideration of their appropriate use and standardisation in randomised controlled trials. Recommendations that are based on expert consensus and systematic reviews of research evidence relating to outcome measures can promote standardisation. This work should follow the COSMIN (consensus based standards for the selection of health measurement instruments) standards for the selection of measures, which draws on existing recommendations and expert opinion. Many systematic reviews of patient reported outcome measures for different patient populations can now inform recommendations. Primary research that compares existing measures, which can further inform appropriate selection, should take precedence over developing new measures. Funding bodies should ask for documentation supporting the choice of patient reported outcomes, including evidence that the literature and available recommendations were consulted. The CONSORT statement should be amended to require supporting information on the selection of patient reported outcome measures and the proposed important level of change. These initiatives will contribute to the appropriate and standardised application of measures that include aspects of health and quality of life, end points that are of genuine importance to patients.