A decisive step towards the recognition of Patient Reported Outcomes (PROs) in clinical trials: report of a meeting held at the FDA on February 16, 2001

Catherine Acquadro, MD, Mapi Research Institute, Lyon, France for the ERIQA Group and the PRO Harmonization Group

INTRODUCTION and BACKGROUND

In 1999, four organisations/societies produced supporting guidance documents on the use of Health-related Quality of Life (HRQL) evaluation in drug development: ERIQA, ISOQOL, ISPOR, and PhRMA HOC.
These documents provided suggestions and opinions on different important topics and issues. At the initiative of PhRMA HOC, and Mapi Research Institute, a comparison of the four documents was undertaken. The idea was to compare all recommendations and explore the differences, and points of controversy.

A first meeting, called HRQL Harmonization meeting, was scheduled in March 2000, and gathered representatives from the four organizations above mentioned, and observers from the FDA. One of the conclusion of this meeting was to follow up on this initiative, and set up other Harmonization meetings, under the coordination of a Committee gathering representatives from each organization, and the advise of Laurie Burke (CDER, DDMAC, FDA).

At the occasion of the second meeting (09/2000), the scope was broadened to the notion of Patient-Reported Outcomes (PROs).

Outcomes of the third meeting entitled "Important Issues in Patient-Reported Outcomes", and held on 02/16/2001 at the FDA, are presented here. It was the consensus of the group that the Program should succinctly address specific issues or concerns, rather than present a didactic review of the PRO field.

OBJECTIVES

To answer FDA's concerns. Four key issues were addressed:
1. Conceptual and Definitional Issues
2. The Value of Patient Reported Outcomes
3. Methodological considerations in obtaining Patient Reported Outcomes in clinical trials
4. Interest in and Demand for Patient Reported Outcomes

METHODOLOGY

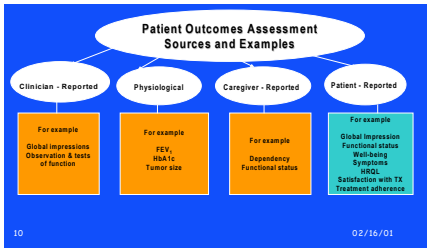
Representatives from the four organizations worked together in 4 subgroups in order to address the four issues described above, and presented their findings to an audience composed of FDA representatives.

FINDINGS

Group 1: Conceptual and Definitional Issues

Team Leader: Margaret Rothman PhD
Members: Ivan Barofsky PhD, Pennifer Erickson PhD, Paul Kind MPhil, Donald Patrick PhD, MSPH

Group 1 was charged with developing a framework for PRO assessment and a conceptual definition of HRQL. The assumptions underlying the framework and definition include the following.
First, PRO assessment, especially in the context of drug evaluation, is an evolving field. Any definition put forward should foster rather than hinder growth of the field. Thus, the framework and definition provided are broad rather than narrow and not intended to be prescriptive.
Second, the framework and definitions are proposed for use within the context of the drug approval and regulatory process. Appropriateness of use beyond this context must be evaluated separately.
While extensive information on the development of patient self-report measures exists, a framework for understanding patient-reported data has not been clearly outlined.
One approach to conceptualizing data collected in clinical trials is to consider the source of the data.



This Figure shows several of these sources and examples of the type of information provided by each source. Each source serves as an umbrella term.

The definition of HRQL that evolved out of Group 1 discussions and was endorsed by the Harmonization Committee is:

HRQL represents the patient's evaluation of the impact of a health condition and its treatment on daily life. HRQL includes multiple domains and/or subdomains that are relevant to the target population and treatment, and an evaluative component.

Clarification of the term is intended to enhance communication among researchers and regulators and to define the patient contribution to the drug evaluation process. It is proposed that HRQL is a more comprehensive concept than other PRO concepts and includes specific attributes. A greater understanding of HRQL will be obtained by further research into the relationship among the different types of PRO. The group did not specifically endorse any of the paradigms that attempt to delineate the relationships among types of PROs and other variables (eg. Wilson and Cleary) as there appeared to be insufficient evidence to support hypothesized relationships.

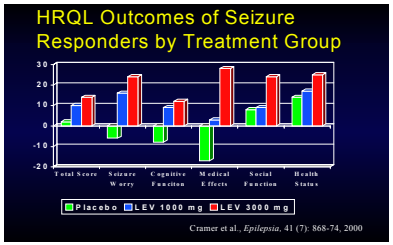
Group 2: The Value of Patient Reported Outcomes

Team Leader: Nancy Kline Leidy PhD
Members: Asha Hareendarn MD, Charlotte McMillan PhD, David Miller PhD, Dennis Revicki PhD, Pierre Sagnier MD, Ingela Wiklund PhD

Group 2 was charged with studying the Added Value of PROs.
The presentation focused on two key issues:
1. Patient-reported data are unique and complementary indicators of disease activity and treatment effectiveness
2. Professional organizations recognize the key role patient-reported data play in diagnosis and treatment, as evidenced by professional practice guidelines

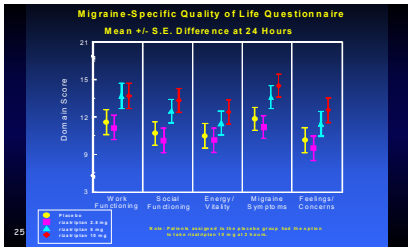
Patient- reported outcomes (PROs) are essential endpoints in any clinical trial in which:
(1) the patient's self-report is the primary or sole indicator of disease activity;
(2) the treatment has a small impact on survival but may have a significant impact (positive or negative) on health-related quality of life;
(3) the treatment may adversely affect patient functioning and well-being;
(4) the treatment arms offer equal clinical efficacy but differential PRO benefits;
(5) treatment-related decisions are based on a combination of objective and subjective (patient-reported) parameters.

Several examples were presented to back up the first key issue. Among them:



Example 1:
Result of a trial examining the efficacy of leveiracetam (LEV) in reducing seizure frequency in patients with epilepsy is a case in point (Cramer et al., 2000). In this study, the HRQL outcomes of patients categorized as "responders", i.e., patients for whom the treatment was efficacious, differed across the three treatment groups, suggesting a differential HRQL benefit of treatment distinct from the primary endpoint.

Example 2:
Results of a trial examining the efficacy of rizatriptan for the treatment of migraine is an example of the importance of data provided by the patient in evaluating optimal dosing regimens (Santanello et al., 1997). In this trial, the 5.0 and 10 mg doses of rizatriptan were each found to be significantly more efficacious than placebo in relieving pain.



However, patients randomized to the 10mg group showed significantly better responses on three of five domains of HRQL assessed in the study. These additional data suggest 10 mg is the dose of choice for achieving pain relief sufficient to improve functioning and well-being.

A number of speciality groups and organizations recommend the use of PROs in clinical trials and have published guidelines for selecting outcome measures specific to the unique characteristics and evaluation needs of the underlying disease. The Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) Group, for example, has recommended that clinical trials include a comprehensive appraisal of symptoms such as pain and joint stiffness, and the HRQL effects of treatment (Boers et al., 1998; Strand et al., 2000).
GREES (Group for the Respect of Ethics and Excellence in Science) recommendations for the registration of drugs used in the treatment of rheumatoid arthritis suggests that generic and disease-specific measures of HRQL be included as secondary efficacy endpoints for clinical trials of symptom-modifying drugs (GREES, 1998).

Group 3: Methodological considerations in obtaining Patient Reported Outcomes in clinical trials

Team Leader: Patrick Marquis MD
Members: Olivier Chassany MD, Dominique Dubois MD, Joseph Jackson PhD, Nancy Santanello MD, MS, Rhys Williams PhD

Group 3 was charged with presenting methodological issues.
They showed that: PROs are scientific measures that can evaluate change in outcomes, based on a recognized psychometric theory and methods *(Likert 1932, Nunnally 1978, 2nd edition),* and supported by empirical validation: reliability, validity, responsiveness *(Lohr 1996, Cronbach 1955, Goodwin 1997).*
They should be handled like any other measures used in clinical trials. Moreover, methods for selecting, developing, validating, measuring, reporting, PROs are the same as other clinical measures.

Group 4: Interest in and Demand for Patient Reported Outcomes

Team Leader: Rick Berzon PhD
Members: Joyce Cramer PhD, Greg Boyer PhD, Haim Erder PhD, Albert Wu MD, PhD, Jean-Paul Gagnon PhD, Richard Willke PhD

Group 4 demonstrated that the interest in and demand for PRO information continues to intensify. A variety of trends—demographic, social and technologic—are driving this phenomenon. Over the past decade, illnesses have become more chronic in nature, patient empowerment has been on the rise, and the explosion in information technology has contributed to the increasing interest in and demand for PRO data.

DISCUSSION

The audience did not question the definitions of PROs and HRQL, and expressed a great interest in the presentation of PROs added value. The group recognized that reliable and valid instruments are available to measure PROs, but deplored the lack of quality of some studies. The interest of including PROs in clinical trials was recognized as adding value for decision-making. Concerns about PROs were also expressed.

There is a need to clarify:

a) the uniqueness of PROs methodology;
b) the meaning of clinical significance,
c) when are the data meaningful,
d) the methods to handle missing data;
e) the level of evidence needed to support a claim,
f) how should results be presented in the label.

CONCLUSIONS AND NEXT STEPS

Although additional research is needed, this meeting could be considered as a crucial step in the future recognition of PROs as relevant evaluation criteria of drugs in clinical trials. The meeting was a seen by many participants as a turning point and an encouraging sign for the future of the field.

Following this meeting (02/2001), the four organizations agreed to formalize the PRO Harmonization Group and to meet at regular periods with observers from the FDA and other agencies if possible (e.g. EMEA), and set up a program of meetings with overall and specific objectives (meeting-related).

The main objectives of the PRO Harmonization Program are therefore:
1. to clarify areas of concern or confusion about PRO evaluation;
2. to explain the added value of PRO outcomes among all key players, i.e. academics, regulators, industry researchers, and prescribers;
3. to open and maintain communication between key players; and
4. to disseminate meeting outcomes

The next meeting "Important Issues in Patient Reported Outcomes Research: Continued Discussion", will address the following issues:
1. Instrument development: what are the standards?
2. Instrument selection: demonstrating hypothesis, relationships to measurement
3. Statistical Issues: focus on handling missing data
4. Interpretation: interpreting changes that are not consistent between outcomes

References

Boers M, Brooks P, Strand V, Tugwell P. The OMERACT filter for outcome measures in rheumatology. J Rheumatol 1998;25 198-199
Cramer JA, Arrigo C, Van Hammee G et al. The effect of levetiracetam on epilepsy-related quality of life. Epilepsia 2000;41:868-874
Cronbach LJ, Meehl PE. Construct validity in psychological tests. Psychological Bulletin 1955;52:281-302
Goodwin LD. Changing conceptions of measurement validity. J Nurs Educ 1997 Mar; 36(3):102-7
Group for the Respect of Ethics and Excellence in Science (GREES) Rheumatoid Arthritis Section. Recommendations for the registration of drugs used in the treatment of rheumatoid arthritis. British J Rheumaology 1998;37:211-215
Lohr KN, Aaronson NK, Alonso J et al.Evaluating quality of life & health status instruments: development of scientific review criteria; Clinical Therapeutics 1996;18(5):979-992
Likert R. A technique for the measurement of attitudes. Archives of Psychology 1932;140:1-55
Nunnally JC. Psychometric Theory, 2nd Edition. New York, McGraw Hill 1978
Santanello NC, Polis AB, Hartmaier SL, Kramer MS, Block GA, Silberstein SD. Improvement in migraine-specific quality of life in a clinical trial of rizatriptan. Cephalalgia 1997; 17 (8): 867-72.
Strand V, Gladman D, Isenber D, Petri M. Smolen J, Tugwell P. Endpoints: consensus recommendations from OMERACT IV. Lupus 2000; 9: 322-327.
Wilson IB, Cleary, PD. 1995. Linking clinical variables with health-related quality of life; a conceptual model of patient outcomes. JAMA 1995;273:59-65.