Do We Need a New End Point in Clinical Trials Today?1

Moinpour and colleagues from the Southwest Oncology Group should be congratulated for preparing a thorough but concise review of the use of quality of life end points in cancer clinical trials (1). Perhaps their most important contributions are the listing of sources from the large body of developing literature on this subject (2-10) and the pragmatic synthesis of the findings. They have also shared important information about the decision-making process used to initiate patient-rated quality of life end points within their cooperative group. One minor concern is the group's decision to make the quality of life assessment a companion protocol rather than an integral part of the clinical trial. Unfortunately, this approach may limit clinician involvement in implementation of the research and the data collection process, thereby giving a subtle message that these end points are not as important as the traditional measures of response and survival. Nevertheless, the preparatory work of the Southwest Oncology Group investigators is impressive, and we look forward to hearing more from them as their carefully thought out plans are activated.

In his editorial (11), Skeel astutely pointed out that we have a lot of catching up to do before quality of life assessments will be effectively used as reliable and valid end points in cancer clinical trials. During the past decade, many cancer-specific, patient-rated tools for assessment of quality of life and treatment toxicity have been created and scientifically evaluated (2-10). Investigators in the United Kingdom, Europe, Canada, and Australia have played a leading role in the development and utilization of these measures in clinical trials (2,12-14). American investigators have lagged behind.

Moinpour et al. (1) reviewed the many candidate instruments. Some complex tools may be better suited for highly functional patients (e.g., those receiving adjuvant chemotherapy for breast cancer) (15), and simpler tools may be necessary for patients who are more seriously ill (16,17). Nevertheless, the American oncology community must be willing to accept the introduction of these measures into the clinical trial on equal footing with the repeated laboratory or radiographic studies used to monitor tumor response. In addition, social scientists must be willing to compromise and deal with the practical problems inherent in the clinical trial setting (18).

How can these goals be accomplished? Although the initial work of the cooperative groups is laudable (1,11), these efforts will probably be inadequate to move this endeavor forward at more than a snail's pace. To expedite and direct this important process, the National Cancer Institute (NCI) should sponsor a consensus development conference on quality of life end points in clinical trials. The conference should bring together national and international experts in this field, including clinical investigators, social scientists, and other professionals with a research interest in this problem. The spectrum of reliable and valid patient-rated measures of quality of life and treatment toxicity should be reviewed, and a plan should be developed to rapidly accomplish the following:

(a) identify which measurement approaches should be used in specific clinical trial situations;
(b) formulate guidelines for teaching oncologists to routinely include a patient-rated quality of life measurement as part of clinical practice;
(c) develop strategies for obtaining high-quality data from patients participating in clinical trials; and
(d) map a plan for the prompt introduction of patient-rated assessments into all NCI-sponsored clinical trials.

Why should progress in this research area be pressed for now? As Skeel (11) noted, the magic bullet has not been found for most of the common cancers treated by oncologists. Additional end points in clinical trials are badly needed to help resolve important debates. For example, the addition of quality of life end points in phase II trials could do much to influence the more rapid approval of new drugs by the Food and Drug Administration. A similar argument applies to the evaluation of new drugs for human immunodeficiency virus (HIV) infection. Lastly, the traditional end points used in recent clinical trials for adjuvant treatment of node-negative breast cancer patients (19-22) have serious limitations, leading to considerable controversy over how the results from these trials should be applied to current clinical practice. There are persuasive arguments from both sides (23,24), but these studies lack even the most minimal patient-rated assessment of quality of life, which might have quickly resolved the debate.

The time has come to integrate some form of patient-rated assessment of treatment outcome into the clinical trial. We need to make a concerted effort to include this important variable in our assessment equation. The tools are at hand to accomplish this goal, but a design and commitment are required.

PATRICIA A. GANZ
University of California, Los Angeles
San Fernando Valley Program,
VAMC (111B)
Department of Medicine (1118)
16111 Plummer St.
Sepulveda, CA 91343

1This letter was written while Dr. Ganz was on the Veterans Administration's Extended Educational Leave Program and was the recipient of an American Cancer Society-Eleanor Roosevelt International Cancer Fellowship working with members of the Swiss Group for Clinical Cancer Research (SAKK) on quality of life evaluation in clinical trials.
References


Response

We read with great interest the remarks of Drs. Roland Skeel (1) and Patricia Ganz on quality of life measurement in clinical trials. We are heartened by the considerable agreement emerging in the literature with respect to the following major issues addressed in our review (2):
(a) supplementation of the physician’s report with the patient’s report of quality of life;
(b) development of a component-based view of quality of life, with components measured separately (as opposed to a more global construct) and modules tailored to different protocols (e.g., treatment-specific symptoms); and
(c) consideration of the quality control issues that affect successful implementation in a clinical trial setting.

While emphasizing the mutual agreement about these broad issues, we would like to address three minor clarifications in response to points raised by Drs. Skeel and Ganz.

First, use of separate or companion protocols for quality of life assessment in Southwest Oncology Group trials is an administrative device currently mandated by the National Cancer Institute. It primarily serves as a mechanism for distinguishing credits for cancer control research from those for therapeutic research. We have no reason to believe that this approach will “limit clinician involvement in implementation of the research and the data collection process,” a concern noted by Dr. Ganz. To the contrary, Drs. Ian Thompson and Stephen Smalley, investigators for two Southwest Oncology Group therapeutic trials, have contributed to all aspects of the design of these companion protocols—for example, development of treatment-specific items for the questionnaire, discussions regarding expected effects on different components of quality of life over time, and identification of meaningful times for assessment.

An earlier experience with quality of life assessment as an add-on end point in a breast cancer therapeutic trial resulted in poor data collection compliance. We believe this was due to group inexperience with collection of patient-based quality of life data and with insufficient quality control procedures. Physician interest and a substantial investment in data management are key variables in successful quality of life assessment in a cooperative group study.

Second, given sufficient physician involvement, we would be interested in assessing quality of life in phase II trials. Limited resources and greater physician interest in such assessment for phase III trials led to our decision to begin with comparative trials. We agree with Dr. Skeel that studying quality of life in patients on a combined-modality regimen for head and neck cancer at the phase II level could yield informative data on trade-offs relating to treatment response and toxicity prior to the design of the phase III trial.