Spilker B(Ed). Quality of life assessments in Clinical Trials. New York: Raven Press, 1990.

III-11

Quality of Life Assessments in Clinical Trials, edited by B. Spilker. Raven Press, Ltd. New York © 1990.

1
Introduction

Bert Spilker

Project Coordination, Burroughs Wellcome Co., Research Triangle Park, North Carolina 27709

Quality of life has become a relevant measure of efficacy in clinical studies. Its use is spreading and its importance is growing as a valid indicator of whether or not a medical treatment is beneficial. Quality of life may be viewed in terms of the individual, group, or large population of patients. Each of these groups is discussed in this book.

One of the major reasons for confusion when people approach this field is that different groups of authors who write about quality of life issues (and use the same terms) are often speaking about totally different topics that emerge from different perspectives. The purpose of this brief introduction is to provide an overall frame of reference that may be used to approach both the chapters in this book and articles in the literature.

USES OF QUALITY OF LIFE DATA

One of the most important and basic questions about quality of life is why it should be studied or used. This question may be addressed at the patient, physician, pharmacy, company, or country level. At the individual patient level the answer is most obvious, i.e., to improve the quality of that patient's treatment. At the level of an entire drug or therapy, quality of life trials may differentiate between two therapies with marginal differences in survival or different types of morbidity. Quality of life studies may also compare outcomes between two different treatment modalities, such as using a drug or surgery to treat a disease.

After quality of life studies are published, the data might be used for practical or commercial purposes. Certain pharmacies might stock a wider selection of drugs. This greater availability of certain drugs will benefit those patients who desire specific drugs to improve, it is hoped, their quality of life. Physicians might alter their prescribing habits, and companies developing drugs might focus more efforts on finding drugs that improve patients' quality of life. Other commercial advantages for a company, such as getting a drug onto a formulary (e.g., hospital, health maintenance organization), are described in Chapter 15, "An Industry Perspective." For a country, the most important use of quality of life data is to improve the allocation of health care resources.

LEVELS OF QUALITY OF LIFE

Quality of life must be viewed on a number of levels. Although the exact number and definition of levels may vary among authors, the model shown in Fig. 1 provides a basic approach to the topic.

The overall level of assessment is defined by Shumaker et al. in Chapter 9 as "an individual's overall satisfaction with life, and one's general sense of personal well-being." This overall assessment may be measured by summing the scores of an index test that evaluates each individual domain, or by simply asking patients, "On a scale of 1 to 10 (or 1 to 100, or by descriptive categories), how would you assess your overall well-being?" In the clinical trial literature, this is referred to as Clinical Global Impression. Several variations of this question exist. Given the highly personal way that patients judge their quality of life, it may readily be seen that this Clinical Global Impression question is best answered by the patient and not by the physician. A Clinical Global Impression question that assesses disease severity, however, is best answered by the physician. This question lies in the realm of clinical domains and not quality of life domains.

The middle level of broad domains in Fig. 1 is discussed by most authors in this book. The exact number and identity of quality of life domains vary from approximately three to six, depending on which authors are read. Nonetheless, both the number and general identity of these domains are similar. This topic is discussed more fully later in this and other chapters in the book.

The lower level of Fig. 1 includes all aspects of each domain that are specifically assessed by quality of life tests and scales. Choosing how to evaluate these aspects depends on whether a single index or a battery of tests is used to evaluate the

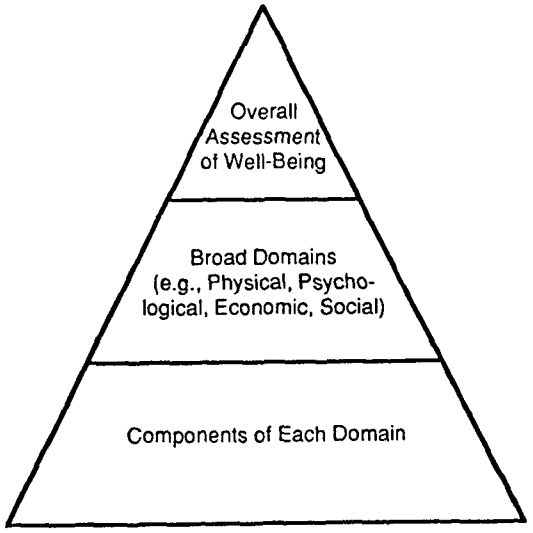

FIG. 1. Levels of quality of life.

components of one (or multiple) domain(s). Even when a single index is created to evaluate a single disease, the developers of validated tests have used widely differing compositions of factors and differing balances of the contributions of each factor. This is well illustrated in Table 3 of Chapter 31 by Barofsky and Sugarbaker.

One or more specific parameters or questions may be used in a clinical trial to evaluate a single component of a domain. Those parameters or questions may be highly important measures of the particular component, but do not represent a validated test of quality of life. Nonetheless, their importance for assessing quality of life is often clear and it is appropriate to include pertinent questions in clinical trials.

DOMAINS OF QUALITY OF LIFE

The major domains of quality of life generally referred to include the following categories:

1. Physical status and functional abilities
2. Psychological status and well-being
3. Social interactions
4. Economic status and factors

Some authors describe their own research or clinical studies as dealing with quality of life issues when in fact they study only one of these broad domains. Others study two or more domains. Although it is not necessary for an investigator to study all domains in any one trial or research program, trials that evaluate only one domain should be distinguished from those that evaluate several domains.

Modifications of these categories are sometimes used by the authors in this book, but there is general agreement in most chapters about the appropriateness of these broad domains. The definitions of these categories are subject to some debate, however, and Chapter 2 discusses this issue further.

COMBINING QUALITY OF LIFE DATA FROM MULTIPLE DOMAINS OR TESTS

A matrix may be described for the four domains and the specific instruments or tests that are used to evaluate them. Quality of life tests measure specific or general aspects of one to four domains. If a single test that measures each of the domains (and is validated for each of those domains) is used, then an aggregate overall assessment of quality of life may generally be obtained to compare different drugs or treatments. One problem with obtaining a single overall score for quality of life is that different domains may yield different results (e.g., treatment A was better than treatment B in two domains, but the opposite result was obtained in the other two domains). Even within a single domain it is common for different components to yield different results. If a battery of validated tests is used to evaluate a single domain (or all domains), it is impossible to combine all test score results. Individual test results may be aggregated, however, by presenting them in a comparative manner. Investigators must establish the relative importance of each individual test used to measure one or more aspects of quality of life prior to conducting the trial. This practice insures that data obtained from tests defined as minor are not later used to claim that a certain treatment is more (or less) effective than another.

Different types of tests and scales may be required to measure specific aspects of each category, depending on the type of patients being evaluated and the interests of the investigators. Moreover, different weights may be assigned to each of the four broad categories based on the patients' beliefs as influenced by their disease severity and nature, background, religion, plus many other factors. In addition, there is no *a priori* reason to state that each of these (or other) categories must be measured and combined to understand changes in a patient's quality of life. One domain or component of a domain may reflect a clinical situation better than the combination of several or many separate measures.

Assessment of quality of life requires input from patients to insure that the patients' perceptions are included and are accurate. A recent study compared physician and patient perceptions of quality of life using several different scales and found that correlation between the two was poor (1). This supports the view that physicians cannot accurately assess a patient's quality of life in all, or perhaps most, situations. This may result from the fact that physicians usually judge patients' clinical responses rather than how clinical responses are filtered through a patient's values and beliefs. This topic is discussed later in this introduction.

DEFINITION OF QUALITY OF LIFE

In editing this book it was necessary to decide whether to insist on a common definition of quality of life. The alternative was for each author to define quality of life on his or her own terms. The problem with the first approach is that no single, universally accepted definition exists. Moreover, because the field is diverse and changing, it would be unfair to limit the authors to a specific, narrow definition. Besides, a single definition would likely yield a stilted book that could not reflect the richness of diversity present in the field.

The problem with allowing each author carte blanche to use his or her own definition is that the book could lose the unity and cohesiveness desired. It would become merely a collection of loosely connected chapters. A compromise was reached where a general definition, based on that of Schipper et al. (see Chapter 2), was proposed to each author as a basis for his or her chapter. The fact that some authors adopted this definition while others used alternatives is viewed as a strength of the book.

RELATIONSHIP OF CLINICAL SAFETY AND EFFICACY DATA TO QUALITY OF LIFE

How does a medical treatment's benefits or adverse reactions affect quality of life?

On first consideration it appears that adverse reactions diminish a patient's quality of life and beneficial effects enhance it. But, either positive or negative clinical changes are generally judged in comparison with other benefits or problems of the treatment and with other treatments the patient has received. The patient's values and beliefs determine how a few or many different factors of a treatment's benefits and problems sum together and also whether the net change represents a positive or negative effect on his or her quality of life. The net result of a treatment on a patient's quality of life often cannot be predicted by the physician. The assessment of whether the change in quality of life is positive or negative is often a complex

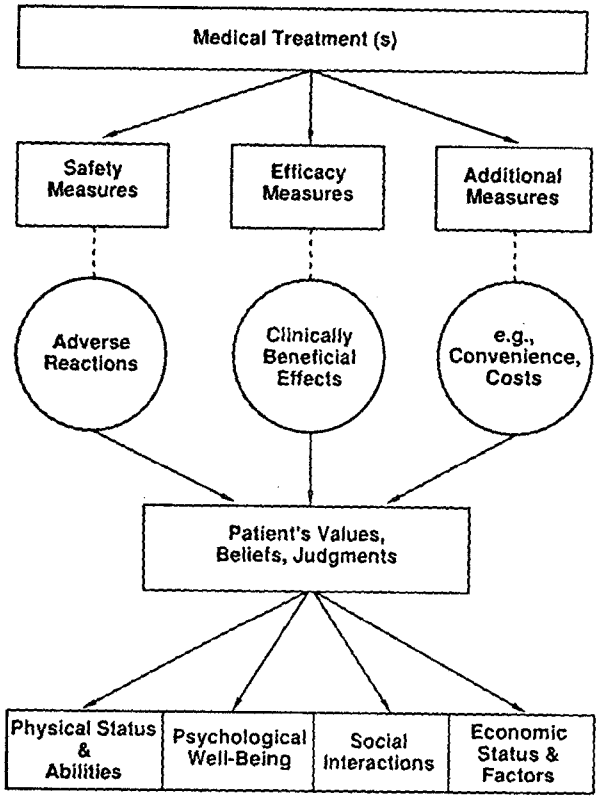

FIG. 2. Model of how clinical aspects of efficacy (i.e., benefits), safety (e.g., adverse reactions), or other factors filter through the patient's values and beliefs to influence his or her quality of life domains.

judgment that may differ for each of the broad domains or for each component of a single domain. Moreover, within each domain some components may be more positive as a result of a specific treatment, whereas other components become more negative.

Severe adverse reactions usually decrease a patient's quality of life and marked efficacy benefits usually increase it. But there are exceptions to both situations because of the patient's values that influence this assessment. For example, severe adverse reactions that are accompanied by clinical improvement may result in a net improvement in quality of life as judged by one patient, and the opposite conclusion may be reached by another patient experiencing similar effects. These points are illustrated in the model shown in Fig. 2. A corollary of this model is that one cannot simply measure adverse reactions or assess clinical benefits of a medical treatment and reach any firm conclusions about how a patient's quality of life is affected. It

is necessary to measure one or more quality of life domains for a specific patient, or group of patients, to assess and document how the benefits and/or adverse reactions have been filtered through the patient's values, beliefs, and judgments. Some parameters of clinical efficacy are very closely related to quality of life (e.g., chronic pain), whereas others have an extremely weak association (e.g., reduction of nonsymptomatic risk factors).

Although only one direction of arrows has been used in Fig. 2, there is a bidirectional flow under certain circumstances. For example, changes in one or more quality of life domain(s), independent of medical treatment a patient is receiving, may affect the patient's compliance with treatment and thereby influence its effectiveness. A person who loses a job or is hurt in an accident also may not have enough money to purchase medical treatment.

A figure similar to Fig. 2 could be constructed for a broad patient population or health care sector. This level is of paramount importance to health care planners who allocate resources to those medical treatments that provide the greatest benefit in clinical terms and, it is hoped, in terms of quality of life. In a population-oriented model, consideration of resource availability, allocation, and consumption would have to be included, as well as the impact of a patient's quality of life on the community.

FUTURE ISSUES TO ADDRESS

The quality of life field is a rapidly changing and developing medical area. The standards developed over the next several years will probably have a major influence on this area for a long period. It is presently premature to define many golden rules of this field, though one of the most important is that only validated scales should be used in clinical studies. A few major issues for future discussion are mentioned briefly in this section.

Using disease-specific versus general non–disease-specific scales to evaluate quality of life has proponents on both sides. This issue is currently being debated, and many experts challenge the view that each disease should be ideally evaluated with validated instruments specific to that disease. They state that well-validated general instruments may be used to evaluate patients with many types of diseases. Several chapters present views on this subject.

Specific scales used to evaluate quality of life are not always disease-specific. Some are function-specific (e.g., sexual or emotional function) or population-specific (e.g., geriatric). Many disease-specific scales are fairly general in the type of information they elicit and therefore bridge the gap between general and disease-specific scales (e.g., Health Assessment Questionnaire for arthritis, Quality of Life Index for cancer). This topic is discussed in greater detail by Patrick and Deyo (2). The choice of using a single index test to evaluate two or more domains versus using a battery of tests may never be settled by consensus. A number of authors in this book discuss this issue and many of the trade-offs involved (e.g., see Chapter 9 by Shumaker et al.).

The number of scales available for incorporation into clinical trials to evaluate quality of life issues is huge. Many of these tests have been validated in one or more patient populations. A consensus may be reached in the future on a few widely accepted scales for each domain. Other scales may be viewed as less credible, and many may eventually be rejected for quality of life assessments. Several authors in this book have already honed down the large number of possible scales and tests to a small number that are reviewed in their chapters.

A related subject is obtaining better identification of specific conditions under which individual scales should be used. At a more detailed level, specific questions relate to whether tests should (a) quantitate events or assess how patients value those events; (b) measure what patients *actually do* (i.e., activities) versus what they *can do* (i.e., capabilities); (c) use concomitant control groups, historical controls, or use the patient as his own control; and (d) assess the last 24 hours for evaluation versus considering the previous week (or other period).

If several people administer a test in one clinical trial, interrater reliability must be assessed. Some experts have also questioned whether it is necessary to train and certify individuals who administer various quality of life tests. If this is perceived to be a problem, then more attention will likely be paid to this issue. The qualifications and training of those who interpret test results is a related issue that should be discussed, especially for those scales involving subjective responses (e.g., given through interview methods).

A final issue concerns choosing which aspects of quality of life should be measured and which parameters should be used to assess these aspects. This is an important issue, because it is often possible to choose for measurement just those aspects and parameters that are most likely (or even known) to show the changes desired. This is stacking the deck before the game is played. This quasi-ethical approach to evaluating quality of life will be prevented when some or all of the earlier issues mentioned in this section are resolved. An example involves the choice of parameter(s) to demonstrate cost-effectiveness. Many different parameters exist and may be used to show that almost any treatment is better than a comparison under certain conditions. Once standards are established that describe appropriate means of evaluating cost-effectiveness, people will not be able to stack the deck in their favor as readily.

It is hoped that this book will help advance quality of life assessments by (a) helping to standardize definitions and approaches, (b) indicating which tests are validated, (c) identifying the state-of-the-art for measuring quality of life in many patient populations, and (d) stimulating wider use of these measures in clinical trials.

REFERENCES

1. Slevin MR, Plant H, Lynch D, Drinkwater J, Gregory WM. Who should measure quality of life, the doctor or the patient? *Br J Cancer* 1988;57:109–112.
2. Patrick DL, Deyo RA. Generic and disease-specific measures in assessing health status and quality of life. *Med Care* 1989;27:S217–S232.