CHAPTER 2: THE DIFFERENT METHODS TO MEASURE QUALITY OF LIFE

2.1 INTRODUCTION

In 1991 Stjernswärd wrote: A consensus needs to be drawn on a scientifically valid and reliable method for estimating quality of life (QOL); it should be practical and realistic to use, and with minor modifications, applicable cross-culturally. Can the experts agree on such a method soon? Up to now, few quality of life studies has led to changes in clinical practice.

Despite the widespread acceptance of quality of life as the ideal guideline in health care and thus in clinical research, serious conceptual and methodological problems continue to plague the area. Quality of life has become a key concept in the medical community. The health care provider's treatment and the effect that it has on the patient are two very different perspectives. Connecting these two perspectives is a task for which the quality of life concept is very well suited, in that it comprises both objective and subjective aspects: The personal, subjective experience of one's own life, as well as the more objective assessment of external factors that influence its quality (Ventegodt 1992).

Research designed to measure quality of life, however suffers from various problems relating to theory and method. The lack of theoretical foundation is a cardinal problem. Without an overarching theory of quality of life to guide the design of instruments, it is difficult to determine what to measure and how. Related to this is the problem of validation. Instruments are typically checked only by observation-to-observation cross checks and rarely by reference to theory, let alone to the experience of the respondents: Do they feel their quality of life is gauged correctly by the instrument (Ventegod 1992)?

Historically, the difficulty in assessing more multidimensional, cancer-specific quality of life has been hallmarked by the inability to reach consensus about what dimensions are of importance. This lack of definition has stymied the development of new, more disease-specific, domain-appropriate instruments.

The heterogeneity of QOL instruments and the enthusiasm of arguments advanced in support of each are an indication of incompletely resolved tensions between the requirements of psychometric comprehensiveness and orthodoxy on the one hand and brevity and practicality on the other. Studies that try to compare and cross-validate the various instruments provide a potential means to reduce the confusion.

There is no gold standard for the measurement of quality of life. In this chapter the hypotheses on which quality of life investigations are based and the requirements for the tests with which investigators seek to prove and expand their theories will be discussed. The basis for every hypothesis is a working definition of "Quality of Life" and a survey of such definitions is presented. The multitude of quality of life instruments will also be investigated as to their strengths and weaknesses to demonstrate the applicability of each test. At the end of the chapter a selection of scales and symptom indexes are included for the benefit of students in this field. I have included all the instruments that I encountered, without any specific preferences.

2.2 A THEORETICAL FRAMEWORK FOR QUALITY OF LIFE:

1. It can only be described and assessed by the individual.
2. It must take many aspects of life into account.
3. It must be related to individual aims and goals.
4. Improvement is related to the ability to identify and achieve these goals.
5. Illness and treatment modify these goals.
6. The goals must be realistic.
7. Action is required to narrow the potential gap. This may be by the patient alone or with the help of others.
8. The gap between the expectation and the reality may be the driving force for some individuals.
9. As each goal is achieved new ones are identified, opening the gap again. It is a constantly changing picture (Calman 1984).

According to Barofsky (1986) there are three current approaches to quality of life assessment:

1. Understanding the assessment as a reflection of a judgment process. Judgement-based quality of life assessments investigate how and why a person makes a particular judgement.
2. Population-based assessments (technically the most advanced).
3. Psychosocial assessments (the most prevalent) are concerned with how an individual copes and adjusts. These types of assessments were derived from psychiatric and psychological concepts.

Schipper (1986) identifies four important methodological issues:

1. What is the definition of quality of life and what are its components?
2. Who should measure quality of life?
3. When do you measure quality of life and how do you analyze the data? Quality of life is a continuum and should not be measured at one point in time.
4. How do you ensure that what you are measuring is the quality of life you define?
5. The following criterion should be added: The actual measurement should be done in a uniform and controlled way. The patient should have a private area, the questionnaire should be filled in before being seen by the doctor and the patient should not be influenced by anyone during this time.

Essential minimum criteria for the development of quality of life measures (Schipper 1986):

1. Indices should be disease specific.
2. The index must be functionally oriented.
3. Designed for patient self-administration.
4. Questions should be generally applicable.
   Easy to interpret and exhibit consistent interpretation.
   Few enough questions so that high compliance is maintained.
5. Should be repeatable.
6. Sensitive across the range of clinical practice.
7. Must be validated in the following areas: face, construct, sensitivity, and freedom from social desirability bias and discriminatory function.

According to Ballatori (1993) there is agreement on the following points:

1. We need to measure quality of life of cancer patients and its variations, possibly in relation to the clinical evolution of the disease and to the treatments administered to the patients.
2. We must use measurement scales, such as linear visual analogue scales (VAS) or categorical scales (scores). The former seem preferable to categorical scales from the point of view of analysis of data (they have associated continuous variables instead of the discreteness of categorical scales), although more difficult for the patients to complete.
3. We need multidimensional measurements, as quality of life involves different aspects of the cancer patient's life, such as feeling, psychological condition, social relationships, patient's relationship with his or her disease and treatment toxicity.
4. The patient must perform the evaluation; no other person can have an exact perception of the patient's quality of life, perceptions, and so on.
5. Results of the evaluation must be expressed in a very simple way, so as to use them easily in statistical analysis in combination with survival data, treatment response and therapy toxicity.
6. Any new questionnaire should be tested for reproducibility and validity. Many of the available questionnaires do not meet the above-mentioned criteria and therefore the results of studies on quality of life which employ them are open to criticism.

2.3 CONCEPTUAL FRAMEWORK FOR QUALITY OF LIFE STUDIES

The conceptual arguments relating to the use of categories or domains to measure quality of life have been established previously through the RAND Health Insurance Experiment and are used extensively in measures (e.g. SF36, Nottingham Health Profile, FACT and EORTC QLQ-C30, see addenda). Essentially health is described as a series of discrete yet overlapping areas known as dimensions or domains. The standard approach to measurement of "functioning" in each domain is that a series of questions are developed, which probe that particular area of health. Statistical reliability can be demonstrated by using analyses such as Cronbach's alpha or factor analysis to demonstrate that the questions within the domain correlate with one another and differ between domains (Jenney 1998).

In comparative clinical trials, the *difference* in quality of life between treatments is of primary interest. There are global indicators of well being and functioning (e.g. physical well being) as well as more specific indicators of symptoms of disease and treatment (e.g. appetite).

In large-scale cross-cultural clinical trials, a detailed assessment of numerous aspects of quality of life may be neither appropriate nor feasible. Given that the purpose of such trials is to compare treatment regimens with regard to patients' overall quality of life, not to determine specific reactions associated with a specific drug, global measures are appropriate to assess outcome. Different regimens may have different side effects and effects may vary among various subgroups of patients. The relative importance attached to side effects has been shown to be influenced by patient factors such as age, gender, diagnosis and treatment (Coates 1983a).

Responses on global measures assessed with single items are expected to reflect the summation of the individual meaning and importance of various factors for each patient. Although less precise for specific treatment effects, these measures may be sensitive to the wide spectrum of reactions seen in patients on and off treatment and will detect these changes on single dimensions, allowing for comparison across treatments (Bernhard 1997).

There are two further reasons to include global in addition to specific measures in clinical trials (Hürney 1995). First the perception of a particular aspect and its relative importance (i.e. weight) may vary not only among individuals but also within individuals over time and across different situations (e.g. on or off treatment). Second the measures must be cross-culturally equivalent to the degree that treatment effects can reliably be studied across cultural groups (Bernhard 1996). There may be cultural variation in perception of disease and treatment sequelae and therefore specific aspects may be perceived differently across the multiple cultural and social class groups typically involved in international clinical trials. Because global scales are less affected by this problem, for treatment comparisons across different cultural groups they are an alternative to the predefined weighting system of multi-item scales (Bernhard 1997).

Measures of specific disease and treatment-related symptoms are a useful complement to global outcome measures of well being and functioning. Studying the association between the specific and global measures over time and in relation to the biomedical variables can give insight into the underlying interactions over the different phases of disease and treatment (Bernhard 1997).

Quality of life research within the cancer population must address the separate issues created by both the broad cancer diagnosis and the specific disease presentation. Both aspects contribute to the actual function and quality of life of patients. The former has primarily psychosocial repercussions that concern mortality, social stigma/stereotype and having a long-term, often incurable illness. The latter involves the clinical, functional and psychosocial sequelae of the actual disease course and treatment (Parsons 1998).

2.4 TYPES OF QUALITY OF LIFE STUDIES

Quality of life studies in cancer research can be categorized into three types (de Haes 1985):

1. Discrimination: Comparisons between different groups of cancer patients.
2. Comparisons of cancer patients with controls.
3. Descriptive studies.

There are two basic approaches to measurement of health-related quality of life: Each has advantages and disadvantages. The use of a disease-specific measure allows detailed assessment of symptoms and concerns that are pertinent to a particular group of patients without the measure becoming too cumbersome. The principle aim of this approach is to increase the responsiveness of the measure by including only important aspects of health related quality of life that are relevant to the patients being studied. Such measures do not allow easy comparison between groups of patients (Jenney 1998).

Conversely, generic measures (measures designed for use with any illness group) allow comparisons between groups and peers. Although generic measures may lack sensitivity for some aspects of functioning for individual groups of patients, they provide the only objective means for comparisons between groups, allowing assessment of the impact of the disease and its treatments. The disadvantage of such measures is that they may not focus adequately on particular areas of concern for different groups of patients (Jenney 1998).

A Multitude of methods measuring quality of life has been reported in the literature. Some are simple enough to use in most clinical situations, while many methods are complicated, time-consuming and require the services of psychologists over a long period of time. It appears that many of the current measures of quality of life were designed to investigate relatively specific and perhaps minor nuances in the quality of care. Often, results of such measures are not appropriate in other clinical situations and certain advancements in therapeutic approaches can invalidate the findings based on these measures (Stjernsward 1996).

Butow (1991) compared the PACIS (perceived adjustment to chronic illness scale), 3 one-item LASA (linear analogue self-assessment) scales, the GLQ-8 (general health questionnaire), Bf-S (befindlichkeitsskala von Zerssen), FLIC (functional living index: cancer), HAD (hospital anxiety and depression scale) and the POMS (profile of mood state). He found that, in general, correlations between new and established measures were good, indicating convergent and concurrent validity. The choice of a QOL scale for a particular study depends on the patient groups, the treatments involved and on the available resources. Butows' comparative study favored the use of brief, simple scales. By doing this, the range of situations in which assessment of QOL is feasible is enlarged considerably.

Many different assessment instruments are available. Some measure just one domain and others provide a more global assessment. Alternative methods involve letting patients themselves choose a personal list of items that are important to them (Barraclough 1994).

Health *per se* is difficult to define because of its multidimensional nature. Many indexes exist but they are either based on very general definitions of health that equate health with quality of life or they focus narrowly on some form of illness (Spitzer 1981). Many workers try to measure life's quality, but they use only one or a few aspects that they consider most relevant to the condition of their own primary interest.

Various "domains" can be measured: psychological, social, sexual, occupational, physical, spiritual, satisfaction with care etc. Trying to measure all of these domains is over-ambitious, but measuring just one aspect is a crude approximation. Additionally assessment instruments have to be quick and simple if they are to be given to large numbers of patients (Fallowfield 1990).

2.5 DEFINING QUALITY OF LIFE

Quality of life is difficult to define. Its meaning depends, at least in part, on the context in which it is used. Within the context of health and medical outcome assessments, the impact of health on the quality of life of the individual, is mostly what the observer wishes to measure. This is termed "health-related quality of life". It is useful in that it emphasizes the impact of health on the much broader concept of quality of life but also acknowledges that issues beyond physical functioning are assessed (Jenny 1998). From a psychometric point of view, quality of life is a multidimensional construct that encompasses physical, mental, social, emotional and behavioral components of well being and functioning (Bullinger 1995).

An important aspect of the definition of quality of life is the personal perspective; essentially, one is attempting to assess the uniquely subjective perception of how individual patients feel about their health status and/or nonmedical aspects of their lives (Gill 1994).

It has become fashionable to equate health – defined comprehensively – with quality of life. However, quality of life, as traditionally defined, is a much broader concept than health. In addition to health, quality of life encompasses standard of living, the quality of housing and the neighborhood in which one lives, job satisfaction and many other factors. While health used to be defined primarily in terms of death and the extent of morbidity, the emerging conceptualization of health is far broader. It encompasses how well people function in everyday life, emotional well being and personal evaluations of health in general. To distinguish the new conceptualization from the old, the term "quality of life" has been adopted (Ware 1991).

The World Health Organization (WHO) defined health as a "state of complete physical, mental and social well being and not merely the absence of disease or infirmity". Thus there are clear precedents for the dimensionality of health and specifically for the distinction between physical and mental health. The second criterion for evaluating a health status measure is the range of health levels that are defined. Scales that restrict the range of measurement, other considerations being equal, are inferior to scales that do not (Ware 1991).

Should we emphasize disease-specific or generic measures? Generic scales assess concepts that are relevant to everyone. They are not specific to any age, disease or treatment group. Generic measures focus on such basic human values as the ability to function in everyday life and emotional well being. Generic health consists of three categories namely, physical functioning, mental health and general health. In general, specific measures do not allow for broad comparisons (Feeny 1998). According to Ware (1991), the ideal is to use both generic and disease-specific measures and to analyze them together.

In addressing quality of life in a clinical trial context, it is useful to have both a general definition and an operational definition that guides the measurement of the construct. Most general definitions include physical, mental and social well being. In clinical trials, it was recommended by Moinpour and coworkers (1989) that quality of life be operationally defined with respect to health care and the treatment of disease, i.e. how physical, mental and social well-being are affected by medical intervention. For example, the measurement of physical mobility and the ability to perform a job would be relevant items to measure in a cancer clinical trial. Items that are affected by a number of factors that are mostly unrelated to medical care should not be included, for example job satisfaction.

Quality of life can be measured with a single global instrument that encompasses the three components of the WHO definition, for example the Spitzer Scale, the Functional Living Index-Cancer (FLIC) or Selby's LASA (see 2.8 and 2.9). Use of a global measure allows comparison across a wide variety of trials. The single global measure can also be supplemented with disease-specific and treatment-specific items for that trial. The problem is the lack of a single, global instrument that researchers accept as applicable to measurement of quality of life across many different cancer trials (Moinpour 1989).

Other investigators have described quality of life with a larger number of dimensions: Aaronsen (1986, 1987 & 1988b) recommend that 12 components be included in the assessment of quality of life in clinical trials: pain and pain relief, fatigue and malaise, psychological distress, nausea and vomiting, physical functioning, symptoms and side-effects, body image, sexual functioning, social functioning, memory and concentration, economic disruption and global quality of life.

Conceptually, quality of life is a somewhat vague term. Trying to define it explicitly, so that objective measurement would be possible, is a complicated issue. Fallowfield (1990) adopted a broad approach because certain aspects of quality of life are (at the moment) immeasurable, but nevertheless very important. Campbell (1976a) conducted important research on the components of quality of life and their relationships to one another. The quality of life investigated was however, not health-related. The types of domains that the investigations focused on were: housing, employment, standard of living, marriage etc.

Many researchers and theorists with an interest in the field of quality of life conceptualize it as a multidimensional concept that encompasses all aspects of physical, social and psychological function (Aaronsen 1988a, Cella 1990, Schipper 1985, Knapp 1993). Ware (1984) emphasizes the importance of disease impact on quality of life. He proposes a hierarchy of impacts beginning with the physiological impact of the disease, extending to influences on personal functioning, psychologic distress, general health perceptions and social role functioning. This implies that the interpretation of outcomes of medical treatment by physiological measurement alone, ignore much greater components of disease impact.

The quality of life construct is defined as the individual's subjective assessment of all areas of physical, emotional and social functioning (Calman 1987, Cella 1990).

The need to evaluate subjective morbidity and the impact of both an intervention and disease on a patient's lifestyle is becoming increasingly recognized, this approach has become to be known as measuring quality of life (Bernheim 1987, Holland 1984 & Van Dam 1984).

Quality of life is a frequently used term in the medical literature. The question is: "Does non-health related quality of life, differ from health-related quality of life and if so, how do these concepts differ?" (Bergner 1989). Despite the appeal of material possessions, one of the primary requisites to the enjoyment of a high quality of life is good health (Fallowfield 1990).

The subjective nature of quality of life is illustrated by a patient's insightful comment. She indicated that her quality of life had greatly improved during the preceding week, explaining, "Nothing that is happening to me has improved. In fact, physically I am feeling worse. What is different *is how I am taking it"*. Clearly the subjective nature of quality of life means that it will vary greatly from person to person and even for a given individual over time in the same objective circumstances (Cohen 1996).

Cohen and coworkers (1996) defined quality of life as subjective well being. They reasoned that a single global question asking a person to rate his/her overall quality of life is perhaps the most valid measure, in that it most closely represents what that individual means by quality of life, but such a scale fails to identify the factors contributing to the assessment. To provide the best care possible, health care workers would need to know what contributed to the person's decision to rate his/her quality of life as high or low.

Most health status and quality of life measures have included the three dimensions of health according to the World Health Organization's definition: The World Health Organization (1946) defines health as physical, psychological and social well being. People with a life-threatening illness, however, define health as a sense of personal integrity and wholeness (Kagawa-Singer 1993) encompassing physical, mental/emotional and spiritual domains (Fryback 1993). Cassel's comments regarding the suffering of persons are relevant to this latter definition of health:

- Our intactness as persons, our coherence and integrity, come not from the intactness of the body, but from the wholeness of the web of relationships with self and others (Cassel 1991).

- Suffering occurs when an impending destruction of the person is perceived; it continues until the threat of disintegration has passed or until the integrity of the person can be restored in some other manner (Cassel 1982).
- Meaning and transcendence offer two additional ways by which the suffering associated with destruction of a part of personhood is ameliorated (Cassell 1982).

Existential concerns are of great importance to people with a life-threatening illness (Fryback 1993) but this domain is not included in most of the quality of life measures. The existential domain (Yalom 1980) includes concerns regarding:

- Death - existential obliteration.
- Freedom - the absence of external structure.
- Isolation - the unbridgeable gap separating self from all else.
- Meaning - the dilemma of meaning-seeking creatures who recognize the possibility of a cosmos without meaning.

If our quality of life measures are to account for important determinants of quality of life such as "how am I taking it" we will need to include measures relating to coping and existential well being, which place the person's interpretation of his/her objective circumstances in the context of his/her world view. Salmon and colleagues (1996) began to do this with their Life Evaluation Questionnaire (LEQ).

Ventegod (1992) defines quality of life as follows: Quality of life resides in the full expression of life's potentials.

Good health is one of the most important requisites to the enjoyment of a high quality of life. Fallowfield (1990) grouped the factors that contribute to quality of life in four core or primary domains as follows:

TABLE 1: DOMAINS OF QUALITY OF LIFE (FALLOWFIELD 1990)

Core domains	Typical items
1. Psychological	Depression
	Anxiety
	Adjustment to illness
2. Social	Personal and sexual relationships
	Engagement in social and leisure activities
3. Occupational	Ability and desire to carry out paid employment
	Ability to cope with household duties
4. Physical	Pain
	Mobility
	Sleep
	Appetite and nausea
	Sexual functioning

Environmental quality, including the quality of community life, may be relevant outcomes especially for health promotion interventions. Dupuis (1988) proposes that quality of life is enhanced as the distance between attained and desired goals diminish. This definition is the same as the definition of Calman (1984): Quality of life therefore, measures the difference, at a particular moment in time, between the hopes and expectations of the individual and that individual's present experiences. These definitions are useful because they set operational limits to quality of life and define quality of life as an internally measured parameter, for which no absolute bounds can be set.

Quality of life is frequently not defined in reports of clinical trials that have appeared. In some instances, quality of life is defined as a level on a measure, for example the Karnofsky Performance Status. Each investigation that purports to investigate quality of life actually examines a very narrow and specific set of factors. Quality of life domains suggested as relevant outcomes of health and medical care are listed in Table 2 (Bergner 1989).

TABLE 2: SUGGESTED DOMAINS OF QUALITY OF LIFE (BERGNER 1989)

- Symptoms
- Functional status
    - Self care
    - Mobility
    - Physical activity
- Role activities
    - Work
    - Household management
- Social functioning
    - Personal interactions
    - Intimacy
    - Community interactions
- Emotional status
    - Anxiety
    - Stress
    - Depression
    - Locus of control
    - Spiritual well-being
- Cognition
- Sleep and rest
- Energy and vitality
- Health perceptions
- General life satisfaction

Some researchers consider quality of life as a risk factor or cause of illness as well as an outcome of medical care (Bergner 1989). Thus, someone who leads a stressful life is seen as a high risk for heart disease. The stress is thought of as quality of life.

There also exists considerable debate as to whether a concept such as universal quality of life exists. Are parameters of quality of life constant across cultures or are certain components seen in one culture and not in another? (Schipper 1986).

2.6 REQUIREMENTS OF QUALITY OF LIFE MEASURES FOR CLINICAL PRACTICE (CONSTRUCT)

- Comprehensive, so that all aspects of health status are included.
- A method for answering the questions that does not involve the clinician.
- Reliable.
- Quick to complete.
- Easy to understand.

The following basic requirements of tests and measurements must be met: reliability, validity and standardization (Fallowfield 1990). If data is available, responsiveness to change over time is also important.

2.6.1 RELIABILITY

One of the most important criteria for determining whether a test has been constructed properly is to examine its reliability. The important question is: "Does this test measure accurately and consistently what it is meant to be measuring?" Many kinds of chance factors in a person's life can influence their score on any self-rating questionnaire. The test developer must be able to indicate how inaccurate any score is likely to be as a result of these chance factors. Sensible interpretations of test scores can only be made if something is known about the test's reliability. This is extremely important when health status is changing over the course of treatment or with disease progression. The *reliability coefficient* of a test is needed to ascertain whether an improvement or deterioration in a patient's quality of life score is due to the therapy been given or due to chance factors.

The *reliability coefficient* can be calculated in different ways:

1. Split-test reliability

Two versions of the same test are given to the sample population. The sample population having been matched for age, social characteristics, sex or disease state. If only one form is available, the test is split into two equal parts and both parts are given to the same individuals in the target population. If the two test scores are similar for the group, then it is likely that the test is consistent and reliable. Perfect reliability would produce a correlation coefficient of 1.00, but coefficients of approximately 0.90 are indicative of a good test.

2. Test-retest reliability

The sample population is given the same test on two different occasions and the correlation coefficient between both scores is calculated. The timing between administrations of the test is very important. A too short time difference will enable respondents to recall their previous answers and reliability may be overestimated. If the time interval is too long, changes in the patient (disease progression etc.) could cause a change in the test score, which could lead to an underestimation of the tests' actual reliability.

3. Standard error of measurement

The standard error provides an estimate of the range of variation in a patient's score if he or she was repeatedly to take the same test on an infinite number of occasions. Therefore it is possible to compute the "zonal" range of inaccuracy on either side of an obtained score.

Reliability is less important than validity. If a test is unreliable the validity will also be low. Any valid test is reliable by definition. However, an instrument can be extremely reliable but not valid. There are quality of life measures, which "reliably" measure only a limited aspect of quality of life. Those that deal only with physical functioning might well suggest that quality of life is very good. For example, following surgery for bowel cancer, a man might have a perfectly functioning colostomy and no sign of metastatic spread of the disease. This would result in a high and reliable score on health performance scales such as Karnofsky (1947). That same patient, however, might be deeply anxious about recurrent disease, severely depressed about impotence and loss of attractiveness to his sexual partner; he might also have stopped working due to fears of odour or leakage from the bag and given up a sporting activity such as swimming. It hardly requires a test to show that such a person has suffered a considerable decline in his quality of life, which is not reflected by an indice that only examines physical functioning. Indices that only measure physical functioning are clearly invalid measures of quality of life.

2.6.2 VALIDITY

Validity is the extent to which a test measures what it should measure. Validity is more difficult to assess than reliability and often involves extensive analysis of many different correlations between measures. There are four main types of validity: face, content, criterion and construct.

Face validity

Do the items in the test, on a subjective evaluation, ask questions relevant to the purpose of the test? For example, in a test measuring memory function following brain injury, one might expect to find questions concerning the name of the current Prime Minister or the capital of France, but such questions are totally invalid in a quality of life scale.

Content validity

How comprehensively were the important constructs of interest covered? For example, in a quality of life questionnaire for use in cancer patients receiving chemotherapy, one might expect to find many items dealing with the potential side effects of treatment.

Traditionally, the way to establish which items should be included in an instrument to ensure good content validity, is to interview typical patients and ask them very open-ended questions to determine the important areas of concern. The problems most frequently cited by patients should then be incorporated into the questionnaire.

Criterion validity

Criterion validity must be studied if a test is designed as a predictive measure. Correlating the test item scores with an established measure and establishing a validity coefficient establishes the criterion validity. These coefficients are usually much lower than those demanded for reliability. Validity coefficients as low as 0.30 are often quite acceptable.

One might predict for example, that high anxiety pre-operatively would correlate with excessive demands for analgesics for pain relief post-operatively. Thus, if the object of the study was to use a psychological test to screen patients who might find their anxiety alleviated by good counseling, it would first be necessary to establish the criterion validity of the test – that is, do highly anxious people, according to the new measure, require more pain relief than those who are not anxious?

Construct validity

Construct validation is an analysis of the meaning of test scores in terms of psychological concepts or "constructs" (Cronbach & Meehl 1955). Every test is to some degree impure and very rarely does it measure exactly what its name implies. Yet the test cannot be interpreted until we know what factors determine scores.

The interpretation of a test is built up very gradually and probably is never complete. As knowledge develops, we arrive at a more complete listing of the influences that affect the test score and at some estimate of the strength of each influence. At present the interpretation of even the best–established psychological tests fall short of the ideal – this, because theories of ability and personality are incomplete and hazy (Cronbach 1970).

Whereas predictive validity is examined in a single experiment, construct validity is established through a long-continued interplay between observation, reasoning and imagination (Cronbach 1970).

The user of the test wants to know how the test can be interpreted and how confidently. The manual should indicate what interpretation the author advises and should summarize the available evidence from all types of studies relevant to this interpretation. If the user wishes to make some other interpretation, he must examine all the evidence on the test in the light of his own theory (Cronbach 1970).

There are three parts to construct validation:

- Suggest what constructs might account for test performance. This is an act of imagination based on observation or logical study of the test.
- Derive testable hypotheses from the theory surrounding the construct. This is a purely logical operation.
- Carry out an empirical study to test one hypothesis after another (Cronbach 1970).

Specificity

Specificity is the proportion of true negatives that are correctly identified by the test (Altman 1991).

Sensitivity

The sensitivity score of an instrument tells us about the accuracy of the measure in picking up changes in a patient's quality of life, due to things such as disease progression or remission and psychological status. Sensitivity is the proportion of true positives that are correctly identified by the test (Altman 1991). Sensitivity is calculated as follows:

Number of true cases ÷ number of true cases plus false negative scores

2.6.3 NORMS AND STANDARDIZATION

When evaluating tests and interpreting their scores, we have to consider, in addition to reliability and validity, the way in which the various scores are being expressed. A numerical score tells us very little about a patient's quality of life, unless we have further information about the scores which most people of a similar age, sex, social class, educational background or disease state would have in similar circumstances. In *standardized* tests, scores are derived or transformed in a manner, which permits the individual scores to be compared with group norms.

When dealing with global scores from tests purporting to measure quality of life, it is very important to know more about the mean and standard deviations from it, in order to analyze the data satisfactorily. Transformations of raw scores into standard deviation-units allow psychologists or persons who know anything about normal distribution curves to see immediately how far above or below average an individual lies. This enables comparisons to be made which are not possible with the raw scores alone (Fallowfield 1990).
More detailed information about these issues are to be found in: Cronbach (1970), Anastasi (1976), Nachmias (1981) and Nunnally (1978).

2.7 THINGS TO CONSIDER WHEN CHOOSING A TEST (FALLOWFIELD 1990):

1. Is it valid and reliable?
2. Are norms available?
3. Is it suitable for the target population?
4. Are the questions easy to read and understand?
5. Is scoring complex or easy?
6. Is the layout of the questionnaire clear?
7. What is the format of the questions?
8. Is it comprehensive but as brief as possible?
9. Does it ask socially loaded questions?
10. Who will complete the questions – the doctor or the patient?

Inclusion of a global quality of life measure is highly recommended if resources permit, because it is important that overall patient distress be measured (Troidal 1987).

Specific instruments for measuring quality of life in cancer patients have been developed, but these sometimes fail to focus adequately on the special problems of a particular cancer, or on the consequence of a particular mode of therapy. There are two main types of instruments to choose from:

- Linear Analogue Self-Assessment (LASA) scales.

LASA scales (or VAS/Visual Analogue Scales) use lines usually ten centimeters long. The length of the line represents the continuum of an experience and the patient marks the line at the point, which corresponds to her perception of that experience. The ends of the lines represent the extremes, from best to worst, of the experience under consideration. LASA scales are easy for patients to complete, but difficult to score.

- Categorical Scales.

Categorical Scales are pre-coded and therefore quick and simple to complete and score. Patients are asked to tick a labeled box, or number, corresponding to their perception of the item in question. A Likert Scale results from the addition of the numerical scores from items of subsets within a rating scale to form a single score.

The categorical scale is more feasible than the visual or linear analogue scale (VAS/LASA) for most large-scale clinical trial research. In theory, the VAS/LASA, by providing a greater range of response choices, is more reliable, valid and responsive to change over time than categorical scales, but comparisons of the two types of scales have not shown this to be the case. The VAS/LASA approach is sometimes difficult for patients to understand and processing is more labor intensive (Selby 1987).

2.8 LINEAR ANALOGUE SELF-ASSESSMENT (LASA) SCALES

LASA scales, also known in social sciences as Visual Analogue Scales (VAS) have been used since early in this century (McCormack 1988). These measures have been widely applied in psychosocial medicine, particularly in pain research. At the beginning of quality of life research in oncology, they were introduced as endpoints in cancer clinical trials by Priestman and Baum (1976).

LASA scales can discriminate between endocrine and cytotoxic treatment and between responders and non-responders to treatment of advanced breast cancer (Baum 1980). Coates confirmed the relationship between LASA scales, performance status and treatment side effects for various cancer sites (1983b & 1990). LASA scales have frequently been used in psycho-oncology, although primarily not as clinical trial endpoints, with the exception of trials in patients with metastatic breast cancer (Coates 1987, Tannock 1988, Fraser 1993b).

Further support for the validity of these scales (including physical well-being, mood and appetite scales used in the International Breast Cancer Study Group form (see Addendum 9) was provided by a trial in metastatic breast cancer, where responsiveness to treatment, discrimination between different chemotherapy regimens (Coates 1987) and significant independent prognostic value for survival (Coates 1992b) was demonstrated.

The LASA methodology, which was first applied in metastatic disease where patients are frequently symptomatic and disease control by effective cytotoxic therapy may more likely produce a measurable effect on QOL, has also been shown to be of clinical relevance in the adjuvant setting, where cytotoxic therapy has a measurable but transient effect (Bernhard 1997).

2.8.1 THE FUNCTIONAL LIVING INDEX: CANCER (FLIC)

Schipper and coworkers developed the FLIC in 1984. It is a good example of a graded linear analogue scale. The 22-item self-report scale (see Addendum 3) has been validated on 837 cancer patients in Canada. The scales are numeric Likert scales, with response options ranging from 1 to 7. The FLIC is a global, cancer-specific, multidimensional quality of life instrument. It measures the following domains: physical, emotional, functional and social/family wellbeing. Items on symptoms and confidence in prescribed treatment (relationship with physician) are also included. There are doubts as to whether or not it has sufficient items for each dimension to accurately detect significant changes in quality of life over a period of time. An example of a study using the FLIC is the analysis of EST 4983: Assessment of quality of life for metastatic lung cancer patients (Finkelstein 1987). This was a pioneering study for the Eastern Coast Oncology Group (ECOG) for the use of quality of life parameters in clinical trials.

Each response on the FLIC is scored to the nearest whole integer. Scores on each of the 22 items, ranges from 1 to 7. For some FLIC question scores, higher scores consistently represent a higher quality of life. Analysis is based on the total score, which is the sum of all the items after they have been recorded.

2.8.2 THE LINEAR ANALOGUE SELF-ASSESMENT SCALE OF PRIESTMAN AND BAUM

Priestman and Baum (1976) measured subjective effects of treatment for advanced cancer of the breast by summing single-dimensional scales (see Addendum 8). This is a self-assessment questionnaire and was developed in the visual analogue scale format. Priestman and Baum developed their test to measure the impact of breast cancer and its treatment on quality of life. Table 3 shows examples of the different categories in which patients produce self-ratings for four main areas:

TABLE 3: THE DIFFERENT CATEGORIES OF PRIESTMAN AND BAUM'S LASA

- The symptoms and effects of disease and treatment.
- Psychological problems.
- Physical indices.
- Personal relationships.

The Priestman and Baum test has been use to compare the quality of life of patients receiving either chemotherapy or endocrine therapy for breast cancer and appears to have good sensitivity and reliability. The same criticisms and limitations that apply to all visual analogue scale tests also apply to this one.

2.8.3 SELBY'S LASA

This scale was specifically designed for use in clinical trials for cancer sufferers. Most of the 32 items (see Addendum 10) were derived from the Sickness Impact Profile (see Addendum 14). Good reliability coefficients and satisfactory discrimination between clinically distinct groups of patients have been documented (Selby 1984).

2.8.4 THE GENERAL LIFE QUESTIONNAIRE (GLQ):

Coates (1992) chose a linear analogue self-assessment (LASA) format because of its simplicity, patient acceptance, reliability and established validity. He developed a quality of life measure based on patients' own ranking of side effects and non-physical problems (see table 4).

TABLE 4: GLQ-8 DESIGN: ITEM TITLES AND CORRELATED SYMPTOMS

Feeling anxious or depressed. Feeling low and miserable; affects family; feeling of having to have unwanted treatment; cannot concentrate; affects work/home duties; feeling anxious or tense.

Feeling sick (nausea or vomiting). Nausea; vomiting.

Numbness or pins and needles. Pins and needles in fingers or toes; numbness in fingers or toes; hot flashes.

Loss of hair. Constipation; diarrhea; hair loss; length of time treatment takes; trouble finding a parking spot.

Tiredness. Constantly tired; giddiness on standing up; sore throat; shortness of breath; difficulty sleeping; general aches and pains.

Appetite or sense of taste. Taste change; weight loss; weight gain; appetite loss; easy bruising; increased thirst; increased appetite.

Sexual interest or ability. Loss of sexual feeling; loss of sexual ability.

Thought of actually having treatment. Dry skin; thought of coming for treatment; having to have a needle.

2.8.5 THE QUALITY OF LIFE CORE QUESTIONNAIRE:

The International Breast Cancer Study Group (IBCSG) developed and tested the Quality of Life Core Questionnaire (see Addendum 9). It takes the form of a Linear Analogue Self-assessment or LASA scale. It differs from other breast cancer and cancer specific questionnaires in respect to conceptual, methodological and practical issues. The restriction to a few key indicators is in contrast to other study settings where quality of life must be assessed more comprehensively, as, for example, in health surveys. This form is therefore neither a generic substitute for other QOL instruments, nor a "definitive" measure of QOL, but a tool designed for a specific purpose (Bernhard 1997).

The IBCSG questionnaire uses global measures based on single-item-direct patient estimation instead of numerical summation of various specific items. In contrast to the classical psychometric approach a global single-item measure is expected to be less valid because different individuals may to a certain extent interpret it in different ways. However, given that global health measures reflect the disease and treatment-related issues that are salient for each individual patient, they are an appropriate endpoint, especially for treatment comparisons in repeated measurement designs where each patient is compared with herself. Indicators of specific symptoms or side effects, such as hot flashes, have more obvious face validity (Bernhard 1997).

2.9 CATEGORICAL SCALES

2.9.1 MEASURES BASED ON PHYSICAL ASPECTS

When people become ill, one of the very first aspects to be influenced is their physical functioning. Clinical researchers have used systematic measures of functional status for more that 50 years (Bergner 1989). The first measures were developed to assess the baseline performance status of a patient. Functional status assessments are routinely used to determine patient eligibility for clinical trials and to aid treatment decisions. WHO or Karnofsky performance status indices are routinely used in the cancer clinic to decide whether or not to administer chemotherapy.

The distinguishing characteristics of the WHO and Karnofsky Performance Status measures are:

- They are brief.
- A physician completes them on the basis of observation and history of a patient.

The ECOG and Karnofsky performance status measures were developed by physicians to systematize the collection and recording of information that was thought to be relevant for the diagnosis and treatment of patients. Rigorous development and testing was not done and the reliability is poor (Hutchinson 1979, Mor 1984). This severely limits the use of these measures for monitoring patient progress and assessing outcome.

TABLE 5: THE WHO PERFORMANCE STATUS SCALE

GRADE	DESCRIPTION	KARNOVSKY
0	Fully active, able to carry on all pre-disease performance without restriction.	90 – 100
1	Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature.	70 – 80
2	Ambulatory and capable of all self care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	50 – 60
3	Capable of only limited self care, confined to bed or chair more than 50 % of waking hours.	30 – 40
4	Completely disabled. Can not carry on any self-care. Totally confined to bed or chair.	10 – 20

The Karnofsky Performance Status (KPS):

This index was already published in 1948 for use in cancer research and is based on an interpretation of quality of life in terms of physical ability (Karnofsky 1948). It is one of the most frequently cited "quality of life" measures found in the medical literature. Frequency of usage is, however, no indication of appropriateness. Karnofsky and

Burchenal actually developed the performance scale as a means of determining nursing requirements in a ward. The Karnofsky performance status is a useful method to determine physical functioning and has been shown to correlate well with survival, but it is a very crude method for assessing quality of life. The most important difficulty is that the physician fills it in and that it makes no assessment of a patient's psychosocial status.

Clark and Fallowfield (1986) point out some absurdities of the scale, in particular the assumption that a patient with a low score due to immobility is considered to have a poor quality of life and that a patient with a higher score necessarily has a better quality of life. Additionally, all observation scales have the problem that they involve an entirely subjective evaluation made by a clinician. Bias inevitably arises and there are studies to show unacceptable variability between raters. The strength of both the Karnofsky and WHO performance status scales is their simplicity and the fact that a useful assessment of physical function can be made without complicated and time-consuming tests. The fact that clinical decisions about the treatment of cancer patients are made on a daily basis as a result of these two indices, show their usefulness in the oncology field.

TABLE 6: THE KARNOFSKY INDEX

100	Normal, no complaints, no evidence of disease.
90	Able to carry on normal activity, minor signs or symptoms of disease.
80	Normal activity with effort, some signs or symptoms of disease.
70	Cares for self, but unable to carry on normal activity or do work.
60	Requires occasional assistance but is able to care for most of personal needs.
50	Requires considerable assistance and frequent medical care.
40	Disabled; requires special care and assistance.
30	Severely disabled; hospitalization is indicated although death is not imminent.
20	Very ill, hospitalization and active supportive care necessary.
10	Moribund.
0	Dead.

Other functional status measures are the Index of Activities of Daily Living (ADL; Katz 1976), the Sickness Impact Profile (SIPS; Bergner 1981), the Cancer Inventory of Problem

Situations (CIPS; Schag 1983) and the Barthel Index (Mahoney 1965), which assess performance of activities of daily living. These measures assess activities such as walking, eating and dressing. They are not meant to be used for designated conditions and have been developed with some attention to reliability of measurement, validity and scoring. The patient or someone completes these measures, without the doctor's involvement.

Patrick (1973) measured the perceived social values of defined functional levels of health. Hochberg (1979) determined the physical function of glioblastoma patients. Grogono and Woodgate (1971) developed a 10-item scale focussing mainly on physical function. Kaplan (1979) created a health index with two components: level of well being and prognosis, the latter being the probability of attaining a level of well being by a certain time.

The problem with unifunctional measures of quality of life is that they may provide a very distorted outcome evaluation (Schipper 1986). Functional status measures miss much that is important in quality of life, because less that one third of patients who have a serious chronic illness have measurable limitations in personal or role functioning. Moreover, functional status measures do not adequately assess mental health (Ware 1984).

The Katz Index: Activities of Daily Living (1963):

Its primary use was in the assessment of functional status of elderly patients in long-term care settings. The Katz index measures basic socio-biological functions (see Addendum 4). Nurses or doctors rate patients on six items: bathing, dressing, toileting, mobility, continence and feeding. It is a good example of a scale created for a variety of diagnoses, but is not very valid as a quality of life measure.

Patients are rated as either dependent or independent for each item and then graded from A to G on the basis of these judgements. As with the Karnofsky performance status, high grades on the Activities of Daily Living do correlate well with survival (Katz 1970). The Katz index has been shown to be of prognostic value in determining the long-term course of adaptation in stroke victims or patients with hip fractures. A major problem limiting the scale's usefulness is its inability to discriminate well between differences in functioning at the upper end of the scale, as about 80% of the elderly do not experience functional limitations.

This scale has good validity and reliability and is helpful in measuring the functional status of elderly, institutionalized patients, but the application of the scale in general population studies of quality of life is not appropriate.

2.9.2 MEASURES BASED ON PSYCHOLOGICAL/EMOTIONAL FACTORS

An apparently mobile, well-functioning and physically fit person may be experiencing debilitating emotions and consequently an extremely poor quality of life. It is therefore of paramount importance to include a thorough evaluation of the patient's mood in any good quality of life instrument. A selection of measures measuring the emotional wellbeing of people will be discussed.

Post mastectomy depression and loss of self-esteem was assessed by Worden and Weisman (1977) using several instruments restricted to emotional factors.

The befindlichkeitsskala von Zerssen (Bf-S):

The Bf-S is a specific and precise standard scale. This 28-item, one-dimensional adjective checklist is very sensitive to anxiety and especially depression. It was initially developed by von Zersssen for serial assessments of mood in longitudinal psychopharmacological studies and has become a standard measure for mood alterations in different clinical settings. It has been validated in German and French-speaking populations and used in cancer patients (Hürney 1992).

The profile of mood states (POMS) of Pollock (1979) and McNair (1981):

Asking them to rate how applicable 65 different mood descriptions are to them assesses individuals' current emotional state. Patients may choose responses ranging from "not at all" to "extremely". Good specificity has been shown for the POMS. The Profile of Mood States contains six different subscales (see Addendum 15):

Tension
Anger
Depression :SUBSCALES OF POMS
Vigor
Fatigue
Confusion

The hospital anxiety and depression scale (HAD):

Developed by Zigmond and Snaith (1983) specifically for use with physically ill populations. There are two subscales namely, anxiety and depression, but items of a somatic nature, for example fatigue, which could also be attributed to physical disease as much as mood disturbance, are not included (see Addendum 16).

There are fourteen items, half for each of the two subscales, and the items are rated on a four-point scale. The Hospital Anxiety and Depression Scale has the advantage that it is very easy and quick to administer, complete and score. It takes about two minutes to complete and two minutes to score. It has been shown to be sensitive and specific and has been translated into many languages. Its validity has been confirmed in many studies. A score of 7 or less implies normality, 8 to 10 is borderline and 11 or more suggests significant anxiety or depression.

The perceived adjustment to chronic illness scale (PACIS):

The Perceived Adjustment to Chronic Illness Scale (PACIS) is a global indicator designed to capture the patient's view of her effort to cope with illness. In a study by Hürney (1993) a large proportion of PACIS variance was explained by disease and treatment burden suggesting that this indicator does reflect psychological adjustment.

The Rand Mental Health Inventory (MHI):

The Mental Health Inventory is a validated, 38-item instrument designed to assess psychological state.

2.9.3 MEASURES BASED ON SOCIAL FUNCTION

There is increasing evidence that social support may predict survival in breast cancer patients (Maunsell 1995, Hürney 1993). Social relationships influence subjective evaluation of quality of life. Social functioning and social support however, have been reported to be the most problematic areas for investigators to measure. Investigators must be aware that the construct for social functioning is a powerful one with respect to explaining variance in the measurement of quality of life (McMillen 1989).

The social support questionnaire (SSQ6):

A promising brief instrument for measurement of social functioning is the six-item Social Support Questionnaire (SSQ6). Validation however, was carried out with college students instead of patients and there was a ceiling effect regarding social support (McMillen 1989).

2.9.4 MEASURES BASED ON SYMPTOMS

Westaby (1979) focussed on symptoms, drug use and work capability in patients who have had surgery for coronary artery disease.

The Brief Fatigue Inventory (BFI) Mendoza 1999

Several scales have been created to measure fatigue, but many are too long and difficult for very ill patients to complete. The Brief Fatigue Inventory was developed for the rapid assessment of fatigue severity. The BFI was shown to be an internally stable (reliable) measure that tapped a single dimension, best interpreted as severity of fatigue. It has been correlated highly with similar measures.

The McGill/Melzack Pain Questionnaire (MPQ)

Chronic, unremitting pain imposes a severe deleterious effect on quality of life. Consequently, a satisfactory pain inventory, despite its apparent specificity, does constitute an important element of quality of life assessment. The McGill Pain Questionnaire (MPQ), a systematic and objective measure of pain, was developed in 1971 (Melzack). It was the most widely used pain inventory in clinical practice and research. It was however, possibly, superseded by the Brief Pain Inventory in the late 1990's. The MPQ comprises groups of adjectives, some of which are shown in Addendum 5, and these rank values are scored to provide a pain rating index. Melzack (1975) has shown the MPQ to be highly reliable and valid, even with patients as young as 12 years old. Many questionnaires using Visual Analogue Scales have been developed using items adapted from the MPQ to assess pain.

The Memorial Pain Assessment Card (MPAC):

The MPAC is a validated instrument designed to assess pain intensity and pain relief. It includes three 100 mm visual analog scales (VAS) for pain intensity, pain relief and mood and an eight-item categorical verbal rating scale (VRS).

The Memorial Symptom Assessment Scale (MSAS) and Global Distress Index (GDI):

The Memorial Symptom Assessment Scale is a 32-item, patient-rated instrument that was developed at the Memorial Sloan-Kettering Cancer Center. It assesses 26 symptoms in terms of three dimensions – frequency, intensity and distress – and six symptoms in terms of two dimensions – intensity and distress. Each symptom characteristic is scored reflecting frequency, intensity and distress.

TABLE 7: SCORING FOR THE MEMORIAL SYMPTOM ASSESSMENT SCALE

Frequency	1= rarely	2= occasionally	3= frequently	4= almost constantly
Intensity	1= slight	2= moderate	3= severe	4= very severe
Distress	0= not at all			
	1= a little bit	2= somewhat	3= quite a bit	4= very much

Its validity and reliability have been confirmed in patients with solid tumors, including advanced breast, colon, prostate and ovarian carcinomas. The Memorial Symptom Assessment Scale- Global Distress Index (MSAS-GDI) is a ten-item subscale that reflects global symptom distress (Seidmann 1995).

The FACT fatigue and anemia scales (Yellen 1997)

Using the 28-item Functional Assessment of Cancer Therapy-General (FACT-G) questionnaire as a base, 20 additional questions related to the symptoms and concerns of patients with anemia were developed. Thirteen of these 20 questions dealt with fatigue, while the remaining 7 covered other concerns related to anemia. Using semi-structured interviews with 14 anemic oncology patients and 5 oncology experts, two instruments were produced: The FACT-Fatigue (FACT-F), consisting of the FACT-G plus 13 fatigue items, and the FACT-Anemia (FACT-An), consisting of the FACT-F plus 7 nonfatigue items.

The 41-item FACT-F and the 48-item FACT-An scores showed good stability and the fatigue subscales showed strong internal consistency. Convergent and discriminant validity testing revealed a significant positive relationship with other known measures of fatigue, a significant negative relationship with vigor, and a predicted lack of relationship with social desirability. The total scores of both scales differentiated patients by hemoglobin level and patient-rated performance status.

The FACT-F and the FACT-An are useful measures of quality of life in cancer treatment, adding more focus to the problems of fatigue and anemia. The Fatigue Subscale may also stand alone as a very brief, but reliable valid measure of fatigue.

2.9.5 MEASURES BASED ON SUBJECTIVE EFFECTS

Clinical observation, systematic research and popular anecdote indicate that, when confronted by death, people change the criteria by which they evaluate their lives. Questionnaires used routinely to assess quality of life in people with poor-prognosis cancer tend to be symptom-based and do not assess factors, which become important to patients when confronted by fatal illness, such as the meaning of life and the degree to which life has been enriched by the illness. Principal component analysis identified five dimensions:

- Clearer perception of the meaning of life.
- Freedom versus restriction of life.
- Resentment of the illness.
- Contentment with past and present life.
- Past and present social integration.

The life evaluation questionnaire (LEQ) of Salmon (1996):

Only the most symptom-oriented scales (freedom, resentment) correlated with the Rotterdam Symptom Checklist. Scale scores showed that younger patients were more resentful of their illness, but also gained a clearer perception of the meaning of life. The Life Evaluation Questionnaire (LEQ) developed by Salmon and coworkers (1996) can evaluate psychological needs of people with incurable cancer, which are neglected by existing instruments.

The Life Evaluation Questionnaire does not provide a complete assessment of a patient's psychological reaction to illness. References to illness-specific symptoms were excluded at the outset and anxiety and depression items were excluded on the basis of the analysis. The questionnaire focuses on patients' evaluation of the effect of their symptoms on their lives. More conventional scales, based on physical and emotional symptoms, should also be included if a complete assessment of quality of life is sought. The reliability values are high and indicate that the aspects of life evaluation that the Life Evaluation Questionnaire does measure are measured accurately.

The Life Evaluation Questionnaire should be useful to assess treatments targeted to adaptation to, and the meaning of, illness such as counseling and psychotherapy. The scale could also be used to identify areas of concern on which psychological treatments could focus. The questionnaire was also beneficial to many patients, who welcomed the opportunity to voice concerns, which they had not previously expressed.

2.9.6 MULTIDIMENSIONAL GENERIC MEASURES

Much of the early research relied on more generalized, health related, quality of life instruments that were developed for use within the general population. The benefits of using generalized instruments for a disease population are that the scores may be compared with the standardized norms of the general population. In this manner, differences between healthy and ill populations may be identified, clarifying domains that are affected by disease (Parsons 1989). However Najan and Levine (1981) have suggested that quality of life measures that are focused on disease or treatment can miss critical aspects of quality of life for a particular patient.

There is a strong interaction between physical condition and the psychological sphere of the patients: functional status is closely related to all social and psychological dimensions of life. Therefore, the questionnaire, though divided in sections, must regard the patient in his of her entirety (Ballatori 1993). The successful studies in the field view quality of life in functional terms and as a construct consisting of: vocational, physical, psychological and social function (Schipper 1986).

The Alameda County Human Population Laboratory:

The Alameda County Human Population Laboratory (Hochstim 1970, Breslow 1972) yields three separate scores for physical, mental and social health. It is comprehensive but lengthy.

The Cancer Rehabilitation Evaluation System-Short Form (CARES-SF):

The Cancer Rehabilitation Evaluation System was developed specifically to address illness-related dysfunction. For use in clinical trials, rather than for use in needs assessment, a shorter 59-item version, the CARES-SF was extracted from the 139-items CARES (see Addendum 2). The CARES-SF was tested for reliability and validity by te Velde and co-workers (1996). In general, the CARES-SF was found to be feasible. It required 11 minutes to complete (on average) and mostly could be filled out by the patients themselves without assistance. Problems were found from items related to sexuality or intimate relationships, which were sometimes considered to be too intrusive.

The General Health Questionnaire (GHQ):

Goldberg developed his questionnaire as a technique for the identification and assessment of non-psychotic psychiatric illness. The questionnaire is useful for identifying patients with affective neuroses, i.e. minor depressions, anxiety states and what was previously called "neurasthenics". Golberg's General Health Questionnaire comes in three different versions, containing 28, 30 or 60 items (Goldberg 1972). The 28-item test is most generally used and will be discussed. It has four sub-scales assessing depression, anxiety, social functioning and physical symptoms. Patients underline the response that is the closest to how they have been feeling about each of the 28 statements (see Addendum 11). Scoring is quick and simple and can be done either by using a Likert-type score of zero to three, or a bimodal response scale with "less" or "no more" than usual scoring zero and "rather" or "much more than usual" scoring one. This is a way of avoiding "end-users" or "middle users", that is the patients who always respond at the extremes of scales or always use the middle options.

The General Health Questionnaire has good reliability and has been validated against the Clinical Interview Schedule. Its also performs well against other psychiatric screening tests. Because it has been used in many different clinical settings and in community studies with large numbers of people, it is a useful instrument for quality of life assessment. Unfortunately it only assesses physical functioning and psychological status, so the whole spectrum of quality of life is not investigated.

The Integrative Quality of Life Theory (Ventegod 1998):

According to Ventegod there are seven criteria that a quality of life instrument must meet in order to become a scientifically sound construct:

1. A definition of quality of life.
2. An embedding philosophy of human life.
3. A theory that operationalizes this philosophy by deriving questions that are unambiguous, non-overlapping and jointly exhaustive and assigning relative weights to these questions.
4. Quantifiable response alternatives.
5. Technical checks (reproducibility, sensitivity, well- scaledness, etc.)
6. Validation through meaningfulness to investigators, respondents and users.
7. Aesthetic appeal of the questionnaire.

The integrative quality of life theory is a meta-theory that integrates six actual quality of life theories by organizing them from a subjective to an objective spectrum. The subjective quality of life items are quality of life as immediate, self-experienced well being; as satisfaction in life and as happiness ad modum Aristotle. According to Aristotle human happiness consists of living in conformity with nature. Objective quality of life concerns items such as: Does the respondent have a partner, children, a job, and hobbies?

The two remaining theories are about human nature: Maslow's theory about human needs and expanded by Aggems and a theory of human beings seen as striving to express life' potentials. Two additional theories blend the subjective and the objective ends of the spectrum: The temporal organization of life refers to the way in which life is divided between work, family and leisure. And spatial organization refers to the socio-spatial domains:

Subjective

1. Immediate self-experienced well being
2. Satisfaction
3. Happiness
4. Fulfillment of needs
5. Experience of objective temporal domains
6. Experience of objective spatial domains
7. Expression of life's potential
8. Objective factors

Objective

These theories are global: covering all aspects of an individual's life and not just one aspect thereof, and generic: applicable to all persons, not just those with a certain type of disease.

The McMasters Health Index (MHIQ):

The Health index from McMaster University (1977) measures the social, emotional and physical function of persons with a wide range of health problems. This instrument has been found to be reliable in a variety of clinical settings. The McMasters Health Index Questionnaire consists of 59 questions. The scores derived from the answers to these questions are added to give the three above mentioned indices as well as a global index of perceived quality of life.

The MOS Short-Form General Health Survey:

Ware suggested the measurement of physical and mental health, social and role functioning and general health perceptions. He and his coworkers developed the MOS Short-form General Health Survey to measure these five constructs plus pain (Stewart 1988).

The Nottingham Health Profile (NHP):

This health profile was developed in 1980 by Hunt and McEwen as a survey tool, but has been used increasingly in the United Kingdom to evaluate the outcome of medical interventions (Hunt 1985). Evidence for reliability and validity has been provided by an enormous amount of research.

In part one of the NHP (Addendum 6) the following problem areas are investigated: energy, pain, emotional reactions, sleep, social isolation and physical mobility. In part two (Addendum 7) seven statements are covered, concerning the areas of daily life that are often affected by ill-health: paid employment, jobs around the house, social life, personal relationships, sex life, hobbies and interests and holidays. Respondents must answer "yes" or "no" to statements such as "things are getting me down". The statements are weighted in order to reflect the relative importance or severity of each item. A high score is indicative of severe problems and the maximum score is 100 for part one and part two of the test respectively.

The Nottingham Health Profile discriminates well between healthy and physically ill people. Unfortunately it only focuses on negative aspects of health, so that patients cannot indicate well being accurately. Zero scores don't necessarily reflect the absence of problems and the test is insensitive to small but significant areas of distress. It is however, well-researched, acceptable, cheap and easy to score.

Psychosocial Adjustment to Illness Scale (PAIS) of Morrow (1978):

Morrow (1978) developed this impressive test which can be used to evaluate quality of life in a variety of patient populations (see Addendum 13). The Psychosocial Adjustment to Illness Scale was specifically developed to address illness-related dysfunction. The experience of the authors gained from studying the psychosocial impact of illness has resulted in an extremely comprehensive instrument. It was originally a semi-structured interview, administered by trained doctors, nurses, psychologists or social workers, but became available later as a self-report questionnaire. The test has 45 questions looking at a patient's global adjustment to illness in seven important areas affecting quality of life:

1. Health care orientation – their attitudes towards and expectations concerning physicians and treatments.
2. Vocational environment – satisfaction with job performance and adjustment to work.
3. Domestic environment – the impact of illness on family finances and communication.
4. Sexual relationships – effect illness has had on frequency, satisfaction and pleasure from sexual activity.
5. Extended family relationships – problems with extended family members since illness.
6. Social environment – the maintenance of interest in social activities.
7. Psychological distress – anxiety, depression and other sequelae.

The core domains according to Fallowfield (1990) that should be included in any adequate quality of life instrument are all found covered very well in the Psychosocial Adjustment to Illness Scale. It is unfortunately very long, taking patients about 30 minutes to complete and it is also difficult to score. Ratings for each question are made on a four-point scale. Scores are converted to standardized T-scores found in tables in the handbook, providing a PAIS total score, which can be compared to published norms. Unlike many other measures, norms are available for different patient populations, also for cancer patients. The test has good reliability coefficients and correlates well with other tests measuring psychological dimensions (has good criterion validity). This test measures the adjustment to the fact, that illness and its treatment, exerts an important influence on quality of life, especially in chronic diseases, extremely well.

The Sickness Impact Profile (SIP):

The Sickness Impact Profile (SIP), based on the concept of health-related dysfunction, is an outcome measure derived from quantitative estimates of changes in the behavior of respondents (see Addendum 14). It has 312 items in 14 categories and is therefore comprehensive but time-consuming (Bergner 1981). This is a widely used and well-known quality of life questionnaire.

The selected statements can be divided into independent categories: physical function and psychosocial function. The questions are answered with a "yes" or "no". All statements answered in the affirmative have their scale values added up to yield a percentage overall score. An overall score or scores for the two main dimensions can be computed. Validity and reliability have been proven and the questionnaire has been updated to improve it. Few quality of life instruments have undergone such extensive work on validation and reliability and it has therefore often been used to evaluate treatments. It is however, cumbersome and time-consuming both for extremely ill patients and for busy clinicians. These limitations make it unacceptable for routine use but it is an important instrument to consider for use in clinical trials.

The WHOQOL-100

The WHOQOL-100 (World Health Organization's Quality of Life questionnaire) was used in a two-part study by Tazaki (1998). The purpose of the study was to evaluate quality of life among cancer patients to see if any significant differences were seen in cancer stages, treatment status and prognosis. For the qualitative study, two focus groups were conducted by medical professionals to establish the applicability of the WHOQOL instrument in evaluating the quality of life of cancer patients, but most participants were negative about using a generic instrument such as WHOQOL. For the quantitative study, 197 cancer patients were analyzed, using the WHOQOL. There was high reliability and a high correlation between the psychological and environmental domains, the physical domain and the level of independence and social relations and the environment and between health conditions perceived by patients and quality of life scores. Differences by gender, treatments and cancer sites were also found to be significantly different at the 5% significance level. The results indicated that the WHOQOL core instrument was sensitive enough to evaluate the quality of life of cancer patients. It is however, very lengthy and time-consuming and a shorter version the WHOQOL-Bref. Consisting of 26 questions, is currently being developed.

2.9.7 MULTIDIMENSIONAL DISEASE-SPECIFIC MEASURES

Generalized tools are useful for the comparison of individuals to the general population. It may be inappropriate however, to assume that cancer patients exist within the same context as the general population. Cancer patients' lives are very different from those of normal individuals due to the enormous physical and emotional burdens that cancer survivors must endure. Thus, the significance and value of experiences/healthstates/compromise in functioning for the cancer patient may be markedly different from generalized population norms. The information gathered must be sensitive to differences within the disease population (Parsons 1998).

Several multi-dimensional, disease-specific questionnaires have been developed and validated specifically for use within the adult cancer population:

The Ability Index:

The Ability Index of Izsak and Medalie (1971): This index integrates 21 items covering physical, emotional, social and economic factors into a single score. It is modified for each type of cancer.

The Breast Cancer Chemotherapy Questionnaire (BCQ) of Levine 1988:

This questionnaire was developed for use as an outcome measure in clinical trials of adjuvant chemotherapy in women with stage II breast cancer. The BCQ consists of 30 questions that focus on loss of attractiveness, fatigue, physical symptoms, inconvenience, emotional distress and feelings of hope and support from others. The BCQ was validated by its correlation with other questionnaires. The BCQ correlated more strongly with global ratings of both physical and emotional function by the patients and their physicians than the other instruments (Spitzer, Karnofsky and Rand Physical & Emotional Health Status).

A comparison between the quality of life outcomes of patients in the two treatment groups in the period when one group had completed treatment and the other had not, showed that the BCQ and Karnofsky scale, were the only instruments able to demonstrate differences between the groups.

The BCQ was administered to the patient by a trained nurse-interviewer. The use of questionnaires administered by personal interview, as compared with those that are self-administered is controversial. Interviewer-administered questionnaires are more expensive to use and with such questionnaires it has been suggested that a patient may respond more favorably than truth in order to please the interviewer. On the other hand, the nurse in the study of Levine (1988) was occasionally able to identify particular treatment-related problems amenable to intervention, because of the personal interview.

The EORTC QLQ-C30:

The EORTC QLQ-C30 questionnaire is a multidimensional QOL scale for use with breast cancer patients (see Addendum 17). In 1986, the European Organization for Research and Treatment of Cancer (EORTC) initiated a research program to develop an integrated, modular approach for evaluating the quality of life of patients participating in international clinical trials.

The QLQ-C30 incorporates nine multi-item scales:

- Five functional scales: physical, role, cognitive, emotional and social.
- Three symptom scales: fatigue, pain and nausea & vomiting.
- A global health and quality of life scale.
- Several single-item symptom measures are also included.

During development and validation studies it was found that the average time required to complete the questionnaire was approximately 11 minutes. Most patients could complete the questionnaire on their own. The reliability and validity of the questionnaire were highly consistent across the three language-cultural groups studied. The results (Aaronsen 1993b) support the EORTC QLQ-C30 as a reliable and valid measure of the quality of life of cancer patients in multicultural clinical research settings.

Sprangers et al. (1996) constructed a breast cancer- specific quality of life questionnaire module to be used in conjunction with the EORTC QLQ-C30. The module, the QLQ-BR23, consists of 23 items covering symptoms and side effects related to different treatment modalities, body image, sexuality and future perspective. This module was tested in 170 Dutch, 168 Spanish and 158 American cancer patients at two points in time. Multitrait analysis confirmed the hypothesized structure of four of the five scales. Cronbach's alpha coefficients were, in general, lowest in Spain (range 0.46 to 0.94) and highest in the United States (range 0.70 to 0.91). On the basis of known-groups comparisons, selective scales distinguished clearly between patients differing in disease stage, previous surgery, performance status and treatment modality, according to expectation. Additionally, selective scales detected change over time as a function of changes in performance status and treatment-induced change.

The results supported the clinical and cross-cultural validity of the QLQ-BR23 as a supplementary questionnaire for assessing specific quality of life issues relevant to patients with breast cancer (Sprangers 1996).

The Functional Assessment of Cancer Scales (FACT):

The Functional Assessment of Cancer Therapy Scales is a modular approach to quality of life assessment. It includes a core instrument, the FACT-G (general), which can be used, for any type of cancer. Subscales or modules for specific subgroups of patients supplement the core instrument. FACT-B is the instrument for use with breast cancer patients. (Cella 1993).

The FACT-G is constructed out of the following domains: physical well being, family/social well being, relationship with doctor, emotional well being and functional well being. The FACT scale is reliable and has been validated. For a more detailed description of the FACT scale see Chapter 4. Updates of the FACT are available, but the questionnaire available at the time that the research was initiated, was used and a discussion is provided in chapter 4.

The Rotterdam Symptom Checklist (RSCL):

This instrument was developed by De Haes (1983) to measure the toxicity and impact of treatment for cancer on psychosocial functioning (see Addendum 12). Respondents rate different items on a four-point scale by ticking a box opposite the reply which comes closest to how they have been feeling over the previous three days. The two primary subscales measure physical and psychosocial dimensions by means of thirty questions.

Additional items for assessment of treatment or illness-related variables are often included for use with patients who have breast cancer.

Good sensitivity, validity and specificity for psychosocial items on the scale have been established. The test is very easy to understand, is well accepted by patients, simple to administer and quick to complete (five to ten minutes). Additionally, scoring is straightforward and easy to compute. It has been suggested that this scale does not adequately cover sexual or social dimensions of quality of life and additional physical items have been proposed for use with specific groups of cancer patients.

The Spitzer Scale or Quality of Life Index (QLI):

Spitzer and co-workers developed this scale in 1981 for use with cancer patients (see Addendum 18). It is a physician-scored scale but can also be scored by patients themselves. The test had to be quick to complete, simple to administer and more comprehensive than only testing for simple physical functioning. The five key areas that Spitzer identified were activity, daily living, perception of health, social support and outlook on life. These domains are rated on a three-point scale from naught to two, resulting in a maximum score of ten.

Good inter-rater reliability between physicians and good correlations between patients' self-ratings and those of their clinicians has been established. It had been validated on patient populations in Australia and Canada and discriminates well between patients with different illnesses and at different stages of disease. A limitation is the fact that the scale gives equal weighting to all items, which could be unrealistic. Specificity of problems is also not addressed adequately, because there are not enough items in each key area. The primary strength of this scale is its simplicity and speed.

This scale can be more accurately termed a quality of life measure than the Karnofsky of WHO performance status measures, because it assesses more than physical functioning, although the total score correlates more substantially with measures of physical functioning as opposed to psychosocial functioning (Spitzer 1981).

2.10 THE QUALITY OF TIME GAINED

Curing a cancer may be achieved with or without the loss of normal functions. The direct dimensions that can be measured according to these definitions are the years of life gained and the quality of the gained life years. These two dimensions, length and quality of life, can be expressed as quality adjusted life years (QALYs) or quality adjusted time without symptoms of disease and toxicity of treatment (Porzsolt 1993). In order to express benefits of adjuvant therapies for breast cancer that incorporate aspects of quality of life for treatment decision-making, Gelber (1993) has developed a quality-adjusted survival analysis, called Q-TWiST. This method involves determining the time without symptoms of the disease and toxicity of treatment (TWiST).

Porzsolt (1993) also advocates the use of QALYs (quality adjusted life years) and Q- TWiST (quality adjusted time without symptoms of disease and toxicity of treatment). For the palliative treatment of patients with incurable disease he finds the aforementioned two parameters to be more realistic goals to strive for than remission.

2.10.1 TwiST: TIME WITHOUT SYMPTOMS OR TOXICITY

A very important concept in the adjuvant setting is a global indicator of subjective health estimation, namely time without symptoms or toxicity (TwiST). A key goal in the International Breast Cancer Study Group (IBCSG) treatment evaluation is to link patient-rated quality of life and physician-rated toxicity to derive values to be used as weights in the Q-TwiST model. It partitions time from treatment to death into three periods: the toxicity of initial treatment (TOX), time without symptoms or toxicity (TwiST) and a post-recurrence period with disease symptoms (REL). Treatments are then compared by overall survival duration, subtracting some of the time spent in TOX and REL according to measures of utility (Bernhard 1997).

TwiST is however, largely a symptom measure. It does not fully evaluate the psychosocial dimensions typically included in quality of life evaluation (Schipper 1985).

A quality-adjusted survival (Q-TwiST) analysis of EORTC Trial 30853, comparing goserelin acetate and flutamide with bilateral orchiectomy in patients with metastatic prostate cancer, was performed by Rosendahl and coworkers (1999). Although orchiectomy had a survival benefit when quality-adjusted survival is not taken into account, orchiectomy translated into a disadvantaged quality of life in real terms. The Q-TwiST analysis resulted in a 5.2-month difference in favour of goserelin and flutamide. The Q-TwiST analysis showed that a subjective definition of health states reflects the differences in quality of life better than so called "hard" measures such as ordinary survival benefit.

One can plot the amount of quality-adjusted survival time associated with more and less intensively treated groups over time. This Q-TwiST gain function elegantly displays the future gains to be expected on average from an initial investment in toxic therapy (Coates 1993).

2.10.2 QUALITY ADJUSTED LIFE YEARS (QALYs)

Quality Adjusted Life Years (QALYs) is based on the principle that benefits of treatment are measured not only in years of survival gained, but also in their quality. Discussions about the economic impact of cancer clinical trials must therefore be based on three outcomes: survival, morbidity and the quality of life. If healthcare policy could potentially rely on quality of life research for decision making regarding resource allocation, that research had better be methodically sound. Quality of life is multidimensional in nature and includes at minimum, physical, social and emotional concepts. A scientifically tested quality of life instrument must be used in the way in which it was intended to be used. Quality of life research often provides a continuum of response relating a symptom, behavior or emotion to its impact on daily living. Adequate statistical analysis is therefore called for. Quality of life analysis is more frequently concerned with correlations, analysis of variance and more complex analysis that provide data on Quality Adjusted Life Years (QALYs) and Time Without Symptoms and Toxicity (TWIST) (Watkins Bruner 1995).

2.11 THE QUALITY OF QUALITY OF LIFE DATA

Cancer clinical trials are primarily designed to assess the effect of treatment on response and survival. There is, however, increasing recognition among investigators that a comprehensive understanding of the effect of cancer therapies requires consideration of patient quality of life (Klar 1998). Goodyear and Fraumeni (1996) reported that the number of publications concerned with patient quality of life doubles every three years.

A continuing challenge in all trials measuring quality of life is the timely completion of scheduled assessments. Low rates of compliance can compromise the interpretation of results particularly if compliance depends on patient characteristics (e.g. patient health). The baseline assessment is included to provide a benchmark against which later assessments can be compared. There are many possible explanations for low rates of compliance (e.g. patient was too ill, staff oversight).

During the assessment of quality of life of metastatic lung cancer patients it was found that the dropout rate was considerable (Finkelstein 1987).

2.12 METHODOLOGICAL CONSIDERATIONS

2.12.1 FACTORS ASSOCIATED WITH MISSING DATA

In a number of trials for the International Breast Cancer Study Group, Bernhard and coworkers (1997) found that the factors most highly associated with missing quality of life forms were institution and chemotherapy compliance. Patients who did not receive the full course of assigned chemotherapy had lower submission rates than those who did: the major reason for stopping therapy early was patient refusal.

Results of the assessment of QOL for metastatic lung cancer patients EST 4983 must be interpreted with caution, since there is a bias in the selection of patients who completed the QOL questionnaire over several months compared to those who only completed the initial and possibly one or two questionnaires during therapy. Both morbidity and mortality were selection factors. Further, it is possible that compliance was itself correlated with quality of life (Finkelstein 1987).

1.12.2 TIMING

The consideration of timing and clinical status is particularly germane to oncology research given the variability of the clinical course during and after cancer therapy. Patients' issues during therapy in the acute phase tend to be very different from their issues in the long term, reflecting the transition from acute concerns for mortality and treatment-induced morbidity to long-term concerns about normalcy and reintegration into normal functioning (Parsons 1998).

In the literature, the patient's response to chemotherapy is described primarily from the health professional's perspective. Most studies do not address inherent changes as the disease progresses. Although cancer is a disease of multiple stages, frequently data collection is based on one interview at a particular stage rather than many interviews done over time and during various stages of treatment. The one-shot approach ignores the changing nature of the disease progression. Thus there is a scarcity of longitudinal information regarding day-to-day management of chemotherapy for the patient (Wilson & Morse, 1991).

Individual patients can be surveyed at several points over time (longitudinal study), or a randomly distributed sample of the patients may be surveyed at one time as a snapshot of time across a population (cross-sectional study). The advantages of the cross-sectional snapshot often include access to a larger population and the ability to conduct the assessment in a relatively shorter research window. The most striking disadvantage is that patients will be in the treatment and/or recovery period at variable times. The interpretation of results from a cross-sectional study must be made judiciously, because it is so dependent on case mix. The longitudinal study allows for intra-reporter comparison across time as well as linkage to the clinical state (Parsons 1998).

The timing of the assessment is an important consideration for research. Studies may be cross sectional or longitudinal. Clearly, determining the timing of assessment is dependent on the overall purpose of the study and the availability of suitable measures. Chronic illness outcomes research, mandates longitudinal testing to capture the dynamics of an illness with multiple sequelae, spanning a range of time. Cross-sectional research facilitates the accumulation of larger numbers of subjects and is appropriate for the assessment of a finite outcome at a fixed point in time. Cross-sectional studies do not offer causative or comparative data (from baseline to endpoint) for an individual patient, but they can be used to establish general trends in the population (Parsons 1998).

In adjuvant trials for the International Breast Cancer Study Group (IBCSG), Bernhard (1997) found that for patients receiving tamoxifen alone, quality of life improved as time from surgery increased, but the start of tamoxifen had no effect. In contrast, for chemotherapy patients, appetite, physical well-being and, in premenopausal patients, coping were worse one to five days after the start of CMF (cyclophosphamide, methotrexate and fluorouracil), but chemotherapy had little effect on mood and emotional well-being.

In a phase III trial of a sixteen-week multidrug regimen versus cyclophosphamide, doxorubicin and fluorouracil (CAF) as adjuvant therapy for node-positive, receptor negative breast cancer, the timing of the questionnaire proved problematic: Quality of life at the time of the during-treatment evaluation was significantly lower with the 16-week regimen than with CAF. The greater reduction in quality of life with the 16-week regimen than CAF during treatment might reflect, in part, the timing of the during-treatment evaluations after the most recent treatment. The Breast Chemotherapy Questionnaire (BCQ) asks the patients about the previous 2 weeks. During this time the patients on the 16-week regimen had received weeks 11 and 12 of treatment, whereas patients who were on the CAF regimen had gone 2 weeks without treatment. The lower scores with the 16-week regimen than CAF might reflect the fact that the patients on the former had actually received treatment in the previous 2 weeks, whereas patients on the latter had had a 2-week break. This shows the difficulties with choosing the best time to evaluate quality of life: evaluation of quality of life on day 15 of a CAF cycle provides a better measure of CAF toxicity but fails to evaluate the effects of a 2-week break between treatment on quality of life (Fetting 1998).

2.12.3 IMPACT OF LANGUAGE AND CULTURAL GROUPS

In the studies that Bernhard and coworkers (1997) conducted for the International Breast Cancer Study Group (IBCSG), they found that language or cultural groups had the biggest effect on the variance of baseline quality of life scores than any socio- demographic or biomedical factor. The impact of language or cultural group also exceeded that of adjuvant treatment modalities in subsequent assessments. Patterns of scores were however, similar in the different language groups.

2.13 STATISTICAL CONSIDERATIONS

2.13.1 SELF-RATING VERSUS OBSERVER-RATED SCALES

Patient-based measures of quality of life should supplement physician judgements of treatment-related toxic effects routinely reported in most trials. Aaronsen and coworkers (1988a) distinguished between subjective response criteria as judged by observers and quality of life assessments provided by patients.

According to Fallowfield (1990) and Barraclough (1994) quality of life is by definition about the patient's own perceptions and it is therefore better to measure it with self-rating rather than observer-rating scales. In a large number of cases the doctors' ratings of the severity of patients' physical and psychological symptoms, do not agree with the patients' own ratings thereof. In comparing the correlation of the patient's and the doctor's evaluations of the patient, Ballatori (1993) found that physicians are not able to judge a patient's psychological condition reliably. Maguire and coworkers (1999) found that the rate of false positive reporting by carers was high. In their study thirteen of the 59 patients were suffering from an affective disorder. This had been recognized by the general practitioner in only five cases and six patients who had a normal mood were wrongly diagnosed as being depressed. It was concluded that it is unreliable to rely on carers' proxy reports of the symptoms experienced by patients and that more accurate personal assessments are needed where possible. It is likely that this will only be achieved by ensuring that those health professionals involved in palliative care have training in the relevant assessment skills.

The aim of a study by Sneeuw (1998) was to examine whether significant others can provide useful proxy information on health-related quality of life. The level and pattern of agreement between patient and proxy ratings of the EORTC QLQ-C30 (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire), the reliability and validity of both types of information and the influence of several factors on the extent of agreement, was assessed. Quality of life ratings were obtained for 307 and 224 patient-proxy pairs (at baseline and at follow-up respectively). Agreement was moderate to good. Multi-trait multi-method analysis showed good convergence and discrimination of specific quality of life domains. Comparison of mean scores revealed a small but systematic bias between patient and proxy ratings. The maximum level of disagreement was found at intermediate levels of quality of life, with smaller discrepancies noted for patients with either a relatively poor or good quality of life. Both patient and proxy ratings were reliable and responsive to changes over time. Several characteristics of the patients and their significant others were found to be associated with the level of agreement, but explained less than 15% of the variance in patient-proxy differences. It was found that significant others as proxy respondents of cancer patients' quality of life where this is necessary, is a viable method.

Aaronsen (1990), Campbell (1976b), Cohen (1992) and Guyatt (1993) all state that quality of life is a subjective evaluation rather than an objective reality and so can only be assessed with reliability by the person whose quality of life is being evaluated. Brunelli (1998) found that the percentages of agreement between patients' ratings and proxy-ratings were higher for physical than for psychological and cognitive symptoms and that there was a greater agreement on the absence rather than the presence of a problem. Their results suggest that caution is needed in the use of health-care workers as alternative sources of information regarding patients' quality of life.

Sneeuw and coworkers (1997) used the COOP / Wonca charts to investigate the value of caregiver ratings in evaluating quality of life in patients with cancer. One important starting point in quality of life research is that the assessment is essentially subjective, with the patient being the primary source of information on his or her quality of life. There are several reasons why it is important to study the value of proxy quality of life ratings provided by the patient's caregivers at home (family or close companions) and in the clinic (physicians or nurses).

Firstly it might be useful in helping to resolve the problem of poor compliance rates in the collection of self-report quality of life data that has been encountered frequently in cancer clinical trials. Patient loss to follow-up is often related to patients' poor health (i.e. it is non-random). Unfortunately, it is precisely at this point of disease progression or acute symptom experience that we are intensely interested in assessing changes in the quality of life. Unacceptable levels of missing data, especially if it is non-randomly missing data, may lead to substantial bias in the analysis of quality of life data. Secondly, proxy judgements of patients' quality of life can and often does play a role, at least implicitly, in decisions regarding treatment and patient care. Especially in oncology, where many patients are treated with palliative rather than curative intent, quality of life considerations may weigh heavily in delivering the most adequate patient care. It is therefore important to understand the extent to which caregivers can assess accurately the patients' level of functioning and well being.

The accuracy of proxy ratings is usually assessed by examining the extent to which proxy ratings correspond to those of the patient's self-assessment. A lot of heterogeneity in research methodology and a diversity of results characterize the literature in this field. In spite of this, the prevailing opinion is that the capacity of caregivers to accurately rate the patients' quality of life is limited.

Sneeuw's investigation (1997) found close agreement between patient and caregiver ratings. Relative to the patients, the physicians were more efficient in detecting changes over time in physical fitness and overall health, but less so in relation to social function and pain.

2.13.2 THE USE OF SUMMARY MEASURES AND STATISTICS

Assessment of health related quality of life has become an important endpoint in many clinical trials of cancer therapy. Most of these studies entail multiple quality of life scales that are assessed repeatedly over time. As a result, the problem of multiple comparisons is a primary analytical challenge with these trials. The use of summary measures and statistics both reduces the number of hypotheses tested and facilitates the interpretation of trial results where the primary question is "Does the overall quality of life differ between treatment arms?" (Fairclough 1997).

2.14 AUTOMATED COLLECTION OF QUALITY OF LIFE DATA

Velikova and coworkers (1999) assessed alternative automated methods of collecting data on quality of life in cancer patients. After initial evaluation of a range of technologies, they compared computer touch-screen questionnaires with paper questionnaires. Cancer patients completed the European Organization for Research and Treatment of Cancer Quality of life questionnaire (EORTC QLQ-C30) and the Hospital Anxiety and Depression Scale (HADS) on paper and on a touch-screen. The quality of the data collected with the touch-screen was good, with no missed responses. It was concluded that computer touch-screen quality of life questionnaires were well accepted by cancer patients, with good quality and reliability.

2.15 CLINICAL BENEFIT RESPONSE

Although the ultimate aim of treating the cancer patient is cure, in most metastatic solid tumors this, unfortunately, can only infrequently be achieved with chemotherapy. However, potential benefits such as palliation of symptoms or prolongation of survival, are other reasons for using chemotherapy for solid tumors. The evaluation of some of these benefits is problematic (Verweij 1996).

For many diseases, objective regression of disease is not appropriately reflected in a prolongation of survival. The justification for nevertheless administering chemotherapy in these cases is that most medical oncologists believe that objective tumor regression also results in a decrease of tumor-related symptoms. Therefore, additional tools for properly investigating the palliation of symptoms are of importance. For many years quality of life assessment with all of its limitations, has been used for this purpose (Verweij 1996).

Rothenberg (1996) uses a new "clinical benefit response" method in a phase II trial of gemcitabine in patients with refractory pancreatic cancer. Despite the fact that objective tumor regression was scarcely mentioned, the authors report that a considerable number of patients benefited from treatment in other respects. The use of clinical benefit response as an endpoint of phase II studies is new and very interesting, but the data must be interpreted carefully.

TABLE 8: DEFINITION OF CLINICAL BENEFIT RESPONSE (Rothenberg 1996)

≥ 50% reduction in pain intensity

≥ 50% reduction in analgesic consumption

≥ 20% improvement in the Karnofsky performance scale that was sustained for ≥ 4 consecutive weeks

≥ 7% weight gain

The first two parameters are considered together and the other two as independent factors. If one of the factors is judged to be negative the patient is a non-responder.
If only one of the factors is positive and all of the others are stable, the patient is a responder.

Reduction in pain has a subjective element. Recording of daily analgesic consumption is dependent on patient compliance and patients sometimes misinform their physicians. Even the Karnofsky performance score can be awarded very subjectively.

The potential clinical gain should be balanced against the potential negative effects of chemotherapy, namely the side effects. Accurate reporting of side effects is another difficult issue. This is another reason for being cautious in evaluating assessment tools with a subjective element.

Clinical benefit response may well become a very important and relatively simple tool for measuring the effects of chemotherapy. Randomized studies are required and comparisons with quality of life measurements should be performed (Verweij 1996).

2.16 CLINICAL FINDINGS

2.16.1 RESULTS OF ADJUVANT TRIALS

Results of the international breast cancer study group trials (IBCSG) VI and VII were analyzed for biomedical and sociodemographic factors that impact on baseline quality of life (QOL) scores. Among premenopausal patients, those with poor prognostic factors showed a tendency to report worse QOL, with estrogen receptor status as an independent predictor for mood. Older postmenopausal patients reported better emotional well being, mood and less effort to cope compared with younger premenopausal patients. Co-morbidity, type of surgery, treatment assignment and sociodemographic factors showed a statistically significant impact in postmenopausal patients only (Bernhard 1997).

There was an impressive improvement of all QOL scores with time, which reflects patients' adaptation to disease and treatment in the adjuvant setting. QOL scores at time points when patients were assigned to receive CMF (cyclophosphamide, methotrexate and fluorouracil) therapy were systematically lower, although the difference diminished over time. Overall, chemotherapy has a measurable adverse effect on patients' QOL, but this is transient and minor compared to patients' adaptation following diagnosis and surgery. (Bernhard 1997).

In trial IX patients undergoing chemotherapy (CMF) reported worse physical well-being and mood and more effort to cope with their disease (perceived adjustment to chronic illness scale PACIS) than patients receiving endocrine therapy only. There were no treatment differences in social support at any of the time points
(Bernhard 1997).

Recurrence had a major impact on QOL. There was a significant drop in all QOL scores between the pre- and post-recurrence assessments, with the post-recurrence scores approaching the scores recorded at baseline. Recurrence was perceived as a major event and the drop to baseline scores reflects a significant loss of patients' adaptation (Bernhard 1997).

The indicators of symptoms/side effects showed different profiles of changes over time, reflecting the different side effects of chemotherapy, endocrine therapy and surgery. In addition, the relative impact of the various specific indicators on physical wellbeing changed over time, suggesting that a global multi-item scale using weights, which are constant across time, may not be optimal. The strong association between physical wellbeing and mood under chemotherapy (Bernhard 1997) emphasized the overall emotional burden of cytotoxic side effects.

2.17 ANALYSIS

Researchers should have a basic understanding of elementary statistics, as the adequate analysis of quality of life data is extremely important. The sorts of analyses applied depend mainly on the purpose of the study.

Single-item scores or looking at variables within key domains which appear to be causing difficulty is sufficient if the aim is to use the information to tailor therapy for the individual or to apply appropriate ameliorative interventions when necessary.

Comparison of group "means" between patients receiving different therapies is more problematic and the difficulties are compounded when the total number of patients in each group is small. Patients with extreme scores can skew the results of overall quality of life for the majority of the other patients.

Pooling of all scores from different sections or domains of the questionnaire is also problematic. Patients with low scores in one area can be compensated by high scores in other areas, with a resultant confounding of the results.

Within the context of generic instruments, there are two theoretical approaches to measurement and presentation of the scores obtained: health profiles and summary scores. The former allows more detailed assessments within domains and is therefore more responsive to change. Subscale or domain scores can be provided that allows identification of specific areas of functioning that may be impaired. They may be essential for assessment of interventions that are designed to improve specific aspects of health-related quality of life (Jenney 1998).

A single summary score, or health index, may also be used that reflects overall health-related quality of life. All of the items in the instrument are summed to provide an overall score. Such scores are useful for population comparisons and in cost-benefit analyses. However, they do not provide details of specific areas of impairment of health-related quality of life (Jenney 1989).

Utility measures provide a single summary score of health related quality of life but also takes into account the preferences of individuals of different health states. They reflect both the health status of the individual and the value that the individual puts upon that health state (Jenney 1998).

2.18 CONCLUSION

There are currently many good tests available for quality of life measurement. These can help doctors determine the impact of their therapies on more that just the physical and functional aspects of their patients' lives. Failure to attempt to monitor quality of life is not good medical practice, nor is it good science.

TABLE 9: COMPARISON OF SOME QUALITY OF LIFE INSTRUMENTS

INSTRUMENT	DOMAIN	ADVANTAGES	DISADVANTAGES
Ability Index: Izsak & Medalie	E M P R	Modified for different cancer types	Single score
Alameda County Human Population Laboratory	E P R	Comprehensive	Generic & too long
BCQ: Breast Cancer Chemotherapy Questionnaire: Levine	E I P R S	Specifically for adjuvant stage II breast Valid & responsive	Not global Interviewer administered
BFI: Brief Fatigue Inventory: Mendoza	S	Reliable, brief, self-report	Measures a single dimension
Bf-S: Befindlichkeitsskala von Zerssen	E	Sensitive to anxiety & depression. Valid.	Not validated for English patients
BPI: Brief pain Inventory	S		Measures only one domain
CARES-SF Cancer Rehabilitation Evaluation System-Short Form: te Velde	C D E F H I P R S	Reliable & valid. Quick to complete. For patient self-assessment & clinical trials.	Lack of disease-specific questions
COOP/WONCA charts	E F H P Q R S	Sensitive to changes over time. Brief. Caregivers or patients complete it	Generic
EORTC QLQ-C30	C E F P R S	Reliable & valid. Categorical. Applicable across cultures Disease specific modules available Translations available in 24 languages Responsive to changes in patients' health status over time	Certain cultures may have problems with sexual items
FACT Functional Assessment of Cancer Therapy	D E F P R S	Reliable & valid Applicable across cultures Disease specific modules available Translations available Sensitive to change	Certain cultures may have problems with sexual items
FLIC: Functional Living Index Cancer: Shipper	D E F P S R	Quick self-report graded valid LASA test Cancer specific & multidimensional	? Sensitivity, single score. Labor intensive. Not for large-scale clinical trials research.
GHQ: General Health Questionnaire: Goldberg	E S R	Easy to score, reliable & valid	Does not cover all domains adequately
GLQ-8: General Life Questionnaire: Coates	E S R	Simplicity, patient acceptance, reliability & validity	Does not cover all domains adequately Same disadvantages as other LASA scales See Priestman & Baum
Grogono & Woodgate	P	Sensitive & specific. Translations	Poor reliability
HAD: Hospital Anxiety & Depression Scale	E	Quick and easy to use and score	Measures only one domain
IQL: Integrative Quality of Life: Ventegodt	M	Valid and reliable	Very long and difficult to score
Kaplan	P	Measures level of well-being & prognosis	Uni-dimensional and generic
Karnofsky Performance Status	F	Quick & useful to determine physical functioning Widely used	Measures only one domain Entirely subjective evaluation made by a clinician

LEQ: Life Evaluation Questionnaire Salmon	E	Evaluates psychological needs very well Helps patients to voice their concerns	Measures only one domain
Katz Index: Activities of Daily Living	F	Applicable for a variety of diagnoses Correlates well with survival Has prognostic value	Not valid for quality of life measurement Focus is on severe disability thus inappropriate for most outpatient purposes
McMaster Health Index Questionnaire MHIQ	E P R	Global, good psychometric properties, Categorical, brief and patient rated.	Reliability not as high as the Nottingham Health Profile.
MOS Short-form General Health Survey: Ware 36 item & 20 item versions	E H P R S	Reliable, convergent & discriminant validity. Norms available.	Generic
MPQ: McGill/Melzack Pain Questionnaire	S	Reliable, specific & valid	Measures only one domain
NHP: Nottingham Health Profile Part I has 38 items	E P R S	Good psychometric properties & easy to score. Patient reported & categorical.	Well being cannot be indicated Accurately
PACIS: Perceived Adjustment to Chronic Illness Scale: Hürney	E	Reflects psychological adjustment Global	Generic
PAIS: Psychological Adjustment to Illness Scale	E D F H R S	Comprehensive & reliable Norms available. Has a global measure. Good criterion validity	Difficult to score and very long (46 items). Lack of disease-specific questions
POMS: Profile of Mood States – Brief	E	Patient self-report. Brief. Categorical. Acceptable psychometric properties.	Measures only one domain
Priestman & Baum: LASA	E F P R S	Sensitive, specific & reliable Self-assessment	Time-consuming to score Scores may not relate well to the specific domain Discrimination may not be "real" Meaning of changes in scores is Obscure
QOL Core Questionnaire of the IBCSG LASA scale	E H P R S	Global single-item measure. Treatment comparisons of the same patient	Restricted to a few domains. LASA Interpretation of questions
Rand Personal Functioning Index (21 items)	F P	Patient self-report. Brief. Categorical. Acceptable psychometric properties.	Not comprehensive enough
RSCL: Rotterdam Symptom Checklist: de Haes	E F P R S	Sensitive, specific, valid & easy to understand. Quick to complete & easy to score	? Availability of norms Sexual and social dimensions are possibly inadequate
Selby's LASA	E F R S	Reliable, valid & breast cancer specific. Self or observer scored. Quick	As for Priestman & Baum
Spitzer's QLI-Index	E F H P R	Brief, reliable, valid Physician or patient scored Measure of mostly physical functioning	Response variation on social functioning was minimal. Very low composite scores (0-3) were rarely obtained.

SIP: Sickness Impact Profile: Bergner	E F R S	Widely used, valid & reliable	Single score and / or 12 categories Cumbersome & time-consuming (136 questions). Not disease-specific
SSQ6 Social Support Questionnaire	R	Promising and brief (six items)	Validation done with college students Does not discriminate among patients with high scores. One domain
WHO Performance Status	F	Quick & useful to determine physical functioning Widely used	Measures only one domain Entirely subjective evaluation made by a clinician
WHOQOL-100	E F P R S	Reliable, specific & sensitive, with high construct validity WHOQOL-Bref. Is being tested (26 items)	Generic instrument & too long Some vague questions

KEY:

C	cognitive	D	relationship with doctor
E	emotional	F	functional
H	health	I	inconvenience
M	meta-theory	P	physical
Q	quality of life	R	relationships
S	symptoms		

2.19 BIBLIOGRAPHY

Aaronsen NK. Methodological issues in psychosocial oncology with special reference to clinical trials. In: Proceedings of the International Workshop on quality of life assessment and cancer treatment. Ventafridda V, van Dam FSAM, Yanick R & Tamburini M, editors. Amsterdam: Excerpta Medica, 29 – 41, 1986.

Aaronsen NK, Bakker W, Stewart AL, van Dam FSAM, van Zandwijk N, Yarnold JR & Kirkpatrick A. Multidimensional approach to the measurement of quality of life in lung cancer clinical trials. In Monograph series of the European Organization for Research and Treatment of cancer. Aaronsen NK, Beckman JH, editors, vol 17. New York: Raven Press, 63 – 82, 1987.

Aaronsen NK, Calais da Silva F & de Voogt HJ. Subjective response criteria and quality of life. Progress in clinical and biological research, 269, 261 – 273, 1988a.

Aaronsen NK, Bullinger M & Ahmedzai S. A modular approach to quality of life assessment in cancer clinical trials. Recent Results Cancer Res, 111, 231 – 249, 1988b.

Aaronsen NK. Quality of life research in cancer clinical trials: a need for common rules and language. Oncology, 4, 59 – 66, 1990.

Aaronsen NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez N, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: A quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst, 85, 365 – 376, 1993b.

Altman DG. Practical statistics for medical research. London: Chapman and Hall, 1991.

Anastasi A. Psychological Testing, 4th ed., New York: Macmillan Publishing Co. Inc., 1976.

Ballatori E, Roila F, Basurto C, Bracarda S, Picciafuoco M, Soldani M et al. Reliability and validity of a quality of life questionnaire in cancer patients. Eur J Cancer, 29A (Suppl 1), S63 – S69, 1993.

Barofsky I. Quality of life assessment. Evolution of the concept. In Ventafridda V, van Dam FSAM, Yancik R & Tamburini M eds. Assessment of quality of life and cancer treatment. Amsterdam: Excerpta Medica, International Congress Series 702, 1986.

Baum M, Priestman T, West RR & Jones EM. A comparison of treatment responses in a trial comparing endocrine with cytotoxic treatment in advanced carcinoma of the breast. Euro J Cancer, 16 (Suppl): 223 – 226, 1980.

Bergner M, Bobbitt RA, Carter WB & Gilson BS. The sickness impact profile: Development and final revision of a health status measure. Medical Care, 19, 787 – 805, 1976.

Bergner M. Quality of life, health status and clinical research. Medical care, 27, Suppl., S148 – S156, 1989.

Bernhard J, Hürney C, Coates AS & Gelber RD. Applying quality of life principles in international cancer clinical trials. In Spilker B (ed): Quality of life and pharmacoeconomics in clinical trials. Philadelphia: Lippincott-Raven, 693 – 705, 1996.

Bernhard J, Hürny C, Coates AS, Peterson HF, Castiglione-Gertsch M, Gelber RD, et al. Quality of life assessment in patients receiving adjuvant therapy for breast cancer: The IBCSG approach. Ann Oncol, 8, 825 – 835, 1997.

Bernheim JL. Measurement of quality of life: An imperative for experimental cancer medicine. In: Aaronson NK and Beckman V, editors. The quality of life in cancer patients. Monograph series of the European Organization for Research and Treatment of Cancer. New York: Raven, 11 – 18, 1987.

Breslow L. A quantitative approach to the world health organization definition of health: physical, mental and social well being. Int J Epidemiol, 1, 347 – 355, 1972.

Brunelli C, Costatini M, Di Giulio P, Gallucci M, Fusco F, Miccinesi G et al. Quality of life evaluation: when do terminal cancer patients and health-care providers agree? J Pain Symptom Manage, 15, 151 – 158, 1998.

Bullinger M & Ravens-Sieberer U. Health related quality of life assessment in children: a review of the literature. Rev Eur Psychol App, 45, 245 – 254, 1995.

Butow P, Coates A, Dunn S, Bernhard J & Hurny C. On the receiving end IV: Validation of quality of life indicators. Ann of Oncol, 2, 597 – 603, 1991.

Calman KC. Quality of life in cancer patients – a hypothesis. J Medical Ethics, 10, 124 – 127, 1984.

Calman KC. Definitions and dimensions of quality of life. In Aaronsen NK & Beckman JH, editors. The quality of life of cancer patients, New York: Raven Press, 1 – 9, 1987.

Campbell A, Converse PE & Rogers WL. The Quality of American life. New York: Russell Sage Foundation, 1976a.

Campbell A. Subjective measures of well being. American Psychology, 31, 117 – 124, 1976b.

Cassell EJ. The nature of suffering and the goals of medicine. N Engl J Med, 306, 640 – 644, 1982.

Cassell EJ. The nature of suffering and the goals of medicine. New York, Oxford University press, 40, 1991.

Cella DF & Tulsky DS. Measuring quality of life today: Methodological aspects. Oncology, 4, 29 – 38, 1990.

Cella DF, Tulsky DS, Gray G, Sarafian B, Linn E, Bonomi A, et al. The functional assessment of cancer therapy scale: Development and validation of the general measure. J ClinOncol, 11, 570 – 579, 1993.

Clark AW & Fallowfield. Quality of life measurements in patients with malignant disease: a review. JRSM, 79, 165 – 169. 1986.

Coates A, Abraham S, Kaye SB, Sowerbutts T, Frewin C, Fox RM et al. On the receiving end – patient perception of the side effects of cancer chemotherapy.
Eur J Cancer Clin Oncol, 19, 203 – 208, 1983a.

Coates A, Dillenbeck CF, McNeil DR, Kaye SB, Sims K, Fox RM et al. On the receiving end II. Linear analogue self-assesment (LASA) in evaluation of aspects of the quality of life of cancer patients receiving chemotherapy. Eur J Cancer Clin Oncol, 19, 1633 – 1637, 1983b.

Coates A, Gebski V, Bishop JF, Jeal PN, Woods RL, Snyder R et al. Improving the quality of life during chemotherapy for advanced breast cancer. A comparison of intermittent and continuous treatment strategies. N Engl J Med, 317, 1490 – 1495, 1987.

Coates A, Glasziou P & McNeil D. On the receiving end III. Measurement of quality of life during cancer chemotherapy. Ann Oncol, 1, 213 – 217, 1990.

Coates A. Application of quality of life measures in health care delivery. Journal of Palliative care, 8, 18 – 21, 1992a.

Coates A, Gebski V, Signorini D, Murray P, McNeil D, Byrne M & Forbes JF. Prognostic value of quality-of –life scores during chemotherapy for advanced breast cancer.
J Clin Oncol, 10, 1833 – 1838, 1992b.

Coates A. Quality of life considerations in the adjuvant setting: Critical review. Recent results in Cancer Research, 127, 243 – 245, 1993.

Cohen SR & Mount B. Quality of life assessment in terminal illness: defining and measuring subjective well being in the dying. Journal of Palliative Care, 8, 40 – 45, 1992.

Cohen SR, Mount BM & MacDonald N. Defining quality of life. Eur J Cancer, 32A, 753 – 754, 1996.

Cronbach LJ & Meehl PE. Construct validity in psychological tests. Psychological Bulletin, 52, 281 – 302, 1955.

Cronbach LJ. Essentials of psychological testing, 2nd ed., New York: Harper & Roe, 1970.

De Haes JCJM, Pruyn JFA & van Knippenberg FCE. Klagtenlijst voor kankerpatienten. Eerste ervaringen. Nederlands Tijdschrift voor de Psychologie, 38, 403 – 422, 1983.

De Haes JCJM & van Knippenberg FCE. The quality of life of cancer patients: A review of the literature. Social Science in Medicine, 20, 809 – 817, 1985.

Dupuis G. International perspectives on quality of life and cardiovascular disease: the quality of life systemic inventory. Presented at the Workshop on Quality of Life in Cardiovascular Disease, Winston-Salem, NC, June 1988.

Fairclough D. Summary measures and statistics for comparison of quality of life in clinical trial of cancer therapy. Statist. Med., 16, 1197 – 1209, 1997.

Fallowfield L. The quality of Life. The missing measurement in health care. London: Souvenir Press, 1990.

Fayers P, Aaronsen NK, Bjordal & Sullivan M. EORTC QLQ-C30 Scoring Manual. Brussels: EORTC Study Group on Quality of Life, 1995.

Feeny D, Furlong W & Barr RD. Multiattribute approach to the assessment of health-related quality of life: Health Utilities Index. Medical and Pediatric Supplement 1, 54 – 59, 1998.

Fetting J. Evaluating quality and quantity of life in breast cancer adjuvant trials. J Clin Oncol, 6, 1795 – 1797, 1988.

Fetting JH, Gray R, Fairclough D, Smith TJ, Margolin KA, Citron ML et al. Sixteen-week multidrug regimen versus cyclophosphamide, doxorubicin and fluorouracil as adjuvant therapy for node-positive, receptor-negative breast cancer: an intergroup study. J Clin Oncol, 16, 2382 – 2391, 1998.

Finkelstein D. Analysis of EST 4983. Assessment of quality of life for metastatic lung cancer patients. ECOC final reports terminated studies, 294 – 322, 1987.

Fraser SC, Dobbs HJ, Ebbs SR, Fallowfield LJ, Bates T & Baum M. Combination of mild single agent chemotherapy for advanced breast cancer? CMF vs. epirubicin measuring quality of life. Br J Cancer, 67, 402 – 406, 1993b.

Fryback PB. Health for people with a terminal diagnosis. Nursing Science Questions, 6, 147 – 159, 1993.

Gelber RD, Goldhirsch A & Cole BF. Evaluation of effectiveness: Q-TwiST. Cancer Treatment Reviews, 19 Suppl A, 73 – 84, 1993.

Gill TM & Feinstein AR. A critical appraisal of the quality of quality-of-life measurements. JAMA, 272, 619 – 626, 1994.

Goldberg D. The detection of psychiatric illness by questionnaire. London: Oxford University Press, 1972.

Goodyear MDE & Fraumeni MA. Incorporating quality of life assessment into clinical cancer trials. Chapter 104 in Spiker B, editor. Quality of life and pharmacoeconomics in clinical trials. New York: Lippincott-Raven, 1996.

Grogono AW & Woodgate DJ. Index for measuring health. Lancet, 1024 – 1026, 1971.

Guatt GH, Feeney DH & Patrick DL. Measuring health-related quality of life. Basic Science Review, 118, 622 – 629, 1993.

Hochberg FH, Linggood R, Wolfson L, Baker WH & Kornblith A. Quality and duration of survival in glioblastoma multiforme. J Am Med Assoc, 241, 1016 - 1018, 1979.

Hochstim JR. Health and ways of living. In: The community as an epidemiological laboratory. Kessler II & Levin ML, editors. Baltimore: John Hopkins Press, 149 – 175, 1970.

Holland JCB. Need for improved psychosocial research methodology: Goals and potentials. Cancer, 53, 2218 – 2220, 1984.

Hunt SM & McEwen J. The development of a subjective health indicator. Sociology of Health and Illness, 2, 231 – 246, 1980.

Hunt SM, McEwen J & McKenna SP. Measuring health status: a new tool for clinicians and epidemiologists, Journal of the Royal College of General Practitioners, 35, 185 – 188, 1985.

Hürny C, Bernhard J, Gelber RD, Coates A, Castiglione M, Isley M et al. Quality of life measures for patients receiving adjuvant therapy for breast cancer: an international trial. Eur J Cancer, 28, 118 – 124, 1992.

Hürny C, Bernhard J, Bacchi M, van Wegberg B, Tomamichel M, Spek U et al. The Perceived Adjustment to Chronic Illness Scale (PACIS): A global indicator of coping for operable breast cancer patients in clinical trials. Swiss Group for Clinical Cancer Research (SAKK) and the International Breast Cancer Study Group (IBCSG). Support Care Cancer, 1, 200 – 208, 1993.

Hürny C, Bernhard J, Coates A, Peterson HF & Gelber RD. The quality of quality of life measurements. JAMA, 273, 843, 1995.

Hürney C, Wegberg BV & Bacchi M. Time trade-off (TTO) interviews vs. subjective health estimations (SHE) in metastatic breast cancer patients. Development and validation of a self-rated linear analogue scale. Submitted 1997.

Hutchinson TA, Boyd NF & Feinstein AR. Scientific problems in clinical scales, as demonstrated in the Karnofsky Index of Performance Status. J Chronic Dis, 32, 661 - 666, 1979.

Izsak FC & Medalie JH. Comprehensive follow-up of carcinoma patients. J Chron Dis, 24, 179 – 191, 1971.

Jenney MEM. Theoretical issues pertinent to measurement of quality of life. MPO, Suppl 1, 41 – 45, 1998.

Kagawa-Singer M. Redefining health: living with cancer. Soc Sci Med, 37, 295 – 304, 1993.

Kaplan RM, Bush JW & Berry CC. Health status index. Category rating versus magnitude estimation for measuring levels of well being. Med Care, 17, 501 – 525, 1979.

Karnofsky DA, Abelmann WH, Craver LF & Burchenal HJ. The use of nitro mustards in the palliative treatment of carcinoma. Cancer, 1, 634 – 656, 1948.

Katz ST, Ford AB, Mosowitz RW, Jackson, BA & Jaffe MW. Studies of illness in the aged. JAMA, 185, 914 – 919, 1963.

Katz ST, Downs TD, Cash HR & Grotz RC. Progress in the development of the index of ADL. The Gerontologist, 10, 20 – 30, 1970.

Katz ST & Akpom CA. A measure of primary sociobiological functions. Int J Health Serv, 6, 493 – 507, 1976.

Klar N. The quality of quality of life data. ECOG Update 3, 4 – 6, 1998.

Knapp JE. Dispositional optimism, control, control beliefs and quality of life in recurrent cancer patients. Michigan: UMI Dissertation Services, 1993.

Maguire P, Walsh S, Jeacock J & Kingston R. Physical and psychological needs of patients dying from colo-rectal cancer. Palliative Medicine, 13, 45 – 50, 1999.

Mahoney FI & Barthel DW. Functional evaluation: the Barthel Index. Md State Med J, 14, 61, 1965.

Maunsell E, Brisson J & Deschenes L. Social support and survival among women with breast cancer. Cancer, 76, 631 – 637, 1995.

McCormack HM, de L. Horne DJ & Sheather S. Clinical applications of visual analogue scales: A critical review. Psych Med, 18, 1007 – 1019, 1988.

McMillen Moinpour C, Feigl P, Metch B, Hayden KA, Meyskens FL & Crowley J. Quality of life end points in cancer clinical trials. J Natl Cancer Inst, 81, 485 – 495, 1989.

McNair DM, Lorr M & Doppelmann LF. EITS manual for the profile of mood states. San Diego: Educational and Industrial Testing Service, 1981.

Melzack R & Torgerson WS. On the language of pain. Anaesthesiology, 34, 50 – 59, 1971.

Melzack R. The McGill pain questionnaire: major properties and scoring methods. Pain, 1, 277 – 299, 1975.

Mendoza TR, Wang XS, Cleeland CS, Morrissey M, Johnson BA, Wendt JK, et al. The rapid assessment of fatigue severity in cancer patients: use of the Brief Fatigue Inventory. Cancer, 85, 1186 – 1196, 1999.

Mor V, Laliberte L, Morris JN, Wiemann M. The Karnofsky performance status scale: an examination of its reliability and validity in a research setting. Cancer, 53, 2002,1984.

Morrow GR, Chiarello RJ & Derogatis LR. A new scale for assessing patient's psychosocial adjustment to medical illness (PAIS). Psychol Med, 8, 605 – 610, 1978.

Nachmias C & Nachmias D. Research Methods in the social sciences. London: St Martin Press, 1981.

Nunally JC. Psychometric theory, 2nd edition, New York: McGraw-Hill, 1978.

Parsons SK & Brown AP. Evaluation of quality of life of childhood cancer survivors: A methodological conundrum. MPO, suppl. 1, 46 – 53, 1998.

Patrick DL, Bush JW& Chen MM. Toward an operational definition of health. J Health Soc Behav, 14, 6 – 23, 1973.

Pollock V, Cho DW & Reker D. Profile of mood states: the factors and their physiological correlates. Journal of Nervous and Mental Disorders, 167, 612, 1979.

Porzsolt F, Goals of Palliative cancer therapy: scope of the problem. Cancer Treatment Reviews, 19 (Suppl. A), 3-14, 1993.

Priestman TJ & Baum M. Evaluation of quality of life in patients receiving treatment for advanced breast cancer. Lancet, April, 899 – 901, 1976.

Rosendahl I, Kiebert GM, Curran D, Cole BF, Weeks JC, Denis LJ & Hall RR. Quality-adjusted survival (Q-TwiST) analysis of EORTC trial 30853: Comparing goserelin acetate and flutamide with bilateral orchiectomy in patients with metastatic prostate cancer. The Prostate, 38, 100 – 109, 1999.

Sackett DL, Chambers LW, MacPherson AS, Goldsmith CH & Mcauly RG. The development and application of indices of health: General method and a summary of results. Am J Public Health, 67, 423 – 428, 1977.

Salmon P, Manzi F & Valori RM. Measuring the meaning of life for patients with incurable cancer: The life evaluation questionnaire. Eur J Cancer, 32A, 755 – 760, 1996.

Schipper H, Clinch J, McMurray A & Levitt M. Measuring the quality of life of cancer patients: The functional living index- cancer (FLIC). Development and validation. J Clin Oncol, 2, 472 – 483, 1984.

Schipper H & Levitt M. Measuring the quality of life: Risks and benefits. Cancer treatment Reports, 69, 1115 – 1123, 1985.

Seidmann AD, Portenoy R, Yao TJ, Lepore J, Mont EK, Kortmansky J et al. Quality of life in phase II trials: A study of methodology and predictive value in patients with advanced breast cancer treated with Paclitaxel plus Granulocyte colony stimulating factor. J Natl Cancer Inst, 87, 1316 – 1322, 1995.

Selby PJ, Chapman JAW, Etazadi-Amoli J, Dalley D & Boyd NF. The development of a method for assessing the quality of life of cancer patients. Br J Cancer, 50, 13 – 22, 1984.

Selby P & Robertson B. Measurement of quality of life in patients with cancer. Cancer Surv, 6, 521 – 543, 1987.

Sneeuw KCA, Aaronsen NK, Sprangers MJ, Detmar SB, Wever LDV & Schornagel JH. Value of caregiver ratings in evaluating the quality of life of patients with cancer. J Clin Oncol, 15, 1206 – 1217, 1997.

Sneeuw KC, Aaronsen NK, Sprangers MA, Detmar SB, Wever LD & Schornagel JH. Comparison of patient and proxy EORTC QLQ-C30 ratings in assessing the quality of life of cancer patients. Journal of Clinical Epidemiology, 51, 617 – 631, 1998.

Spitzer WO, Dobson AJ, Hall J, Chesterman E, Levi J, Shepherd, et al. Measuring the quality of life of cancer patients. A concise QL-index for use by physicians. Journal of Chronic Diseases, 34, 585 – 597, 1981.

Sprangers MAG, Groenvold M, Arraras JI, Franklin J, te Velde A, Muller M et al. The European Organization for research and treatment of cancer, breast-cancer specific quality-of-life questionnaire module: First results from a three-country field study. J Clin Oncol, 14, 2756 – 2768, 1996.

Stewart AL, Hays RD & Ware JE Jr. The MOS Short-form General Health Survey. Reliabilitay and validity in a patient population. Med Care, 26, 724 – 735, 1988.

Stjernswärd J, Stanley K & Koroltchouk. In Ventafridda V, van Dam FSAM, Yancik R & Tamburini M, editors. Assessment of quality of life and cancer treatment. Amsterdam: Excerpta Medica. International Congress Series 702, 1986.

Stjernswärd J & Teoh N. Perspectives on quality of life and the global cancer problem. In Osoba D, editor. Effect of cancer on quality of life. Boston: CRC Press, Inc., 1991.

Tannock IF, Boyd NF, DeBoer G, Erlichman C, Fine S, Larocque G et al. A randomized trial of two dose levels of cyclophosphamide, methotrexate and fluorouracil chemotherapy for patients with metastatic breast cancer. J Clin Oncol, 6, 1377 – 1387, 1988.

Tazaki M, Nakane Y, Endo T, Kakikawa F, Kano K, Kawano H et al. Results of a qualitative and field study using the WHOQOL instrument for cancer patients. Jpn J Clin Oncol, 28, 134 – 141, 1998.

Te Velde A, Sprangers MAG & Aaronsen NK. Feasibility, psychometric performance, and stability across modes of administration of the CARES-SF. Ann Oncol, 7, 381 – 390, 1996.

Troidl H, Kusche J & Vestweber KH. Quality of life: An important endpoint in surgical practice and research. J Chronic Dis, 40, 523 – 528, 1987.

Van Dam FSAM, Linssen CA & Couzijn AL. Evaluating quality of life in cancer clinical trials. In: Buyse ME, Staquet MJ & Sylvester RJ, editors. Cancer clinical trials, methods and practice. Oxford: Oxford University Press, 26 – 43, 1984.

Velikova G, Wright EP, Smith AB, Cull A, Gould A, Forman D, et al. Automated collection of quality of life data: a comparison of paper and computer touch-screen questionnaires. J Clin Oncol, 17, 998 – 1007, 1999.

Ventegodt S, Aldrup Poulsen D & Hilden J. 5 Teorier for livskvalitet. Ugeskr Laeger, 154, 585 – 586, 1992.

Watkins Bruner D. In search of the quality in quality of life research. Int J Radiation Oncology Biol Phys, 31, 191 – 192, 1995.

Ware JE. Conceptualizing disease impact and treatment outcomes. Cancer, 53, 2316 – 2326, 1984.

Ware JE. Measuring functioning, well being and other generic health concepts. In: Osoba D, editor. Effect of cancer on quality of life. Boston: CRC Press, Inc., 1991.

Westaby S, Sapsford RN & Bentall HH. Return to work and quality of life after surgery for coronary artery disease. Br Med J, 2, 1028 – 1031, 1979.

Wilson,S & Morse,J.M. Living with a wife undergoing chemotherapy. Image, 23, 78-84, 1991.

World Health Organization. Preamble of constitution of the WHO. Geneva, World Health Organization, 1946.

Worden JW & Weisman AD. The fallacy of postmastectomy depression. Am J Med Sci. 273, 169 – 175, 1977.

Yalom ID. Existential Psychotherapy. New York: Basic Books, 1980.

Yellen SB, Cella DF, Webster K, Blendowski C & Kaplan E. Measuring fatigue and other anemia-related symptoms with the Functional Assessment of Cancer therapy (FACT) measurement system. Journal of Pain & Symptom Management, 13, 63 – 74, 1997.

Zigmund AS & Snaith RP. The Hospital Anxiety and Depression Scale.
Acta Psychiatry Scandanavia, 67, 361 – 370, 1983.

ADDENDUM 1: BREAST CHEMOTHERAPY QUESTIONNAIRE

(BCQ LEVINE 1988) (Seven-point scale, initial questionnaire)

This questionnaire is designed for women who are receiving or have in the past received chemotherapy for breast cancer. I will be asking you about how you have been feeling, physically and emotionally, during the last 2 weeks. The questions I will ask you, focus on some of the problems and some of the feelings that may be experienced by women who have been given chemotherapy for breast cancer. The table below states the possible numbered responses for each color card. In the second table, there is a column in which you must show your response number to each question (for which the color card to be used is indicated). For example, for question number one, a blue card is to be used. If your response to question number one is "some of the time", you must enter number 4 into the appropriate space.

BLUE CARD	YELLOW CARD	GRAY CARD	GREEN CARD
1. All of the time	1. None of the time	1. A great deal of trouble or inconvenience	1. A great deal of trouble
2. Most of the time	2. A little of the time	2. A lot of trouble or inconvenience	2. A lot of trouble
3. A good bit of the time	3. Some of the time	3. A fair bit of trouble or inconvenience	3. A fair bit of trouble
4. Some of the time	4. A good bit of the time	4. Some trouble or inconvenience	4. Some trouble
5. A little of the time	5. Most of the time	5. A little trouble or inconvenience	5. A little trouble
6. Hardly any of the time	6. Almost all of the time	6. Hardly any trouble or inconvenience	6. Hardly any trouble
7. None of the time	7. All of the time	7. No trouble or inconvenience	7. No trouble

QUESTION	CARD	RE-SPONSE
1. How often during the past 2 weeks have you felt worried or upset as a result of thinning or loss of your hair?	Blue	
2. How often during the past 2 weeks have you felt optimistic or positive regarding the future?	Yellow	
3. How often during the past 2 weeks have you felt that your fingers were numb or falling	Blue	

asleep?		
4. How much trouble or inconvenience have you had during the last 2 weeks as a result of having to come or stay at the clinic or hospital for medical care?	Gray	
5. How often during the last 2 weeks have you felt low in energy?	Blue	
6. In general, how often during the last 2 weeks have you felt tearful or down in the dumps?	Blue	
7. How much trouble have you had in the last 2 weeks as a result of feeling nauseated?	Green	
8. How often during the last 2 weeks have you been troubled or upset as a result of feeling unattractive?	Blue	
9. How much of the time during the last 2 weeks have you felt the future looks hopeful and promising?	Yellow	
10. How often during the last 2 weeks have you had trouble getting a good night's sleep?	Blue	
11. How much trouble or inconvenience have you had during the last 2 weeks as a result of waiting to see a physician while visiting the clinic or hospital?	Gray	
12. How often during the last 2 weeks have you felt tired of fatigued while hurrying?	Blue	
13. In general, how often during the last 2 weeks have you felt worried or tense?	Blue	
14. How often during the last 2 weeks have you had an upset stomach?	Blue	
15. How often during the last 2 weeks have you felt uncomfortable or embarrassed as a result of thinning or loss of your hair?	Blue	
16. How much help and support have you received from people outside your family during the last 2 weeks?	Yellow	
17. How often during the last 2 weeks did you have the sensation that you smelled of chemicals?	Blue	
18. How much trouble or inconvenience have you had during the last 2 weeks as a result of sitting in the waiting room at the clinic or hospital?	Gray	
19. How often during the last 2 weeks have you had problems with fatigue or tiredness which interfered with your housework?	Blue	
20. In general, how often during the last 2 weeks have you felt frustrated or irritable?	Blue	
21. How much of the time during the last 2 weeks have you been troubled by increased production of gas?	Blue	
22. How often during the last 2 weeks have you been sad or tearful as a result of thinning or loss of your hair?	Blue	
23. How often during the last 2 weeks have you felt good about yourself?	Yellow	
24. How much of the time during the last 2 weeks have you felt drowsy during the day?	Blue	
25. How much trouble or inconvenience have you had during the last 2 weeks as a result of waiting for treatment at the clinic or hospital?	Gray	
26. How much of the time during the last 2 weeks have you had problems with fatigue or tiredness which limited your usual social activities?	Blue	
27. How much of the time during the last 2 weeks would you say that your family has been worried about you and about your health?	Blue	
28. How much of the time during the last 2 weeks have you been troubled by constipation?	Blue	
29. How much trouble or distress have you had as a result of pain, soreness, or sores in your mouth, during the last 2 weeks?	Green	

30. How much of the time during the last 2 weeks have you been troubled by burning, watery or sore eyes?	Blue	

ADDENDUM 2: ITEM CONTENT OF THE CARES-SF (TE VELDE 1996)

The response categories for all items are expressed in terms of perceived applicability, with response choices ranging: Not At All, A Little, A Fair Amount, Much, Very Much.

---

1. I have difficulty bending or lifting.
2. I do not have the energy I used to.
3. I have difficulty doing household chores.
4. I have difficulty bathing, brushing my teeth, or grooming myself.
5. I have difficulty planning activities because of the cancer or its treatments.
6. I cannot gain weight.
7. I find food unappealing.
8. I find that cancer or its treatments interfere with my ability to work.
9. I frequently have pain.
10. I find that my clothes do not fit.
11. I find that doctors don't explain what they are doing to me.
12. I have difficulty asking doctors questions.
13. I have difficulty understanding what the doctors tell me about the cancer or its treatments.
14. I would like to have more control over what the doctors do to me.
15. I am uncomfortable with the changes in my body.
16. I frequently feel anxious.
17. I have difficulty sleeping.
18. I have difficulty concentrating.
19. I have difficulty asking friends and relatives to do things for me.
20. I have difficulty telling my friends or relatives about the cancer.
21. I find that my friends or relatives tell me I'm looking well when I'm not.
22. I find that my friends or relatives do not visit often enough.
23. I find that my friends or relatives have difficulty talking with me about my illness.
24. I become nervous when I'm waiting to see the doctor.
25. I become nervous when I get my blood drawn.
26. I worry about whether the cancer is progressing.
27. I worry about not being able to care for myself.
28. I do not feel sexually attractive.
29. I am not interested in having sex.

30. I sometimes don't follow my doctor's instructions.

31. I have financial problems.

32. I have insurance problems.

33. I have difficulty with transportation to and from my medical appointments and/or other places.

34. I am gaining too much weight.

35. I have frequent episodes of diarrhea.

36. I have times when I do not have control of my bladder.

Do you have children?

37. I have difficulty helping my children cope with my illness.

Are you working or have you been employed during the last month?

38. I have difficulty talking to the people who work with me about the cancer.

39. I have difficulty asking for time off from work for medical treatments.

40. I am worried about being fired.

Did you look for work during the past month?

41. I have difficulty finding a new job since I have had cancer.

Have you attempted sexual intercourse since your cancer diagnosis?

42. I find that the frequency of sexual intercourse has decreased.

Are you married or in a significant relationship?

43. My partner and I have difficulty talking about our feelings.

44. My partner and I have difficulty talking about our wills and financial arrangements.

45. I do not feel like embracing, kissing, or caressing my partner.

46. My partner and I are not getting along as well as we usually do.

47. My partner spends too much time taking care of me.

48. I have difficulty asking my partner to take care of me.

Are you single and not in a significant relationship?

49. I have difficulty initiating contact with potential dates.

50. I have difficulty telling a date about the cancer or its treatments.

Have you had chemotherapy treatments in the last month?

51. I become nervous when I get chemotherapy.

52. I become nauseated during and/or before chemotherapy.

53. I feel nauseated after I receive chemotherapy.

54. I vomit after chemotherapy.

55. I have other side effects after chemotherapy.

Have you had radiation therapy treatments in the last month?

56. I get nervous when I get radiation treatments.

57. I feel nauseous or vomit after my radiation treatments.

Do you have an ostomy?

58. I have problems with ostomy care and maintenance.

Do you have a prosthesis?

59. I have difficulty with my prosthetic device (artificial limb, breast prosthesis, etc.).

ADDENDUM 3:FUNCTIONAL LIVING INDEX: CANCER (FLIC) SCHIPPER 1984

PLEASE INDICATE WITH AN X YOUR RATING

1. Most people experience some feeling of depression at times. Rate how often you feel these feelings.

1 2 3 4 5 6 7

never continually

2. How well are you coping with your everyday stress?

1 2 3 4 5 6 7

not well very well

3. How much time do you spend thinking about your illness?

1 2 3 4 5 6 7

constantly never

4. Rate your ability to maintain your usual recreation or leisure activities.

1 2 3 4 5 6 7

able unable

5. Has nausea affected your daily functioning?

1 2 3 4 5 6 7

not at all a great deal

6. How well do you feel today?

1 2 3 4 5 6 7

extremely extremely
poor well

7. Do you feel well enough to make a meal or do minor household repairs today?

1 2 3 4 5 6 7

very not
able able

8. Rate the degree to which your cancer has imposed a hardship on those closest to you in the past weeks.

1	2	3	4	5	6	7
no hardship						tremendous hardship

9. Rate how often you feel discouraged about your life.

1	2	3	4	5	6	7
always						never

10. Rate your satisfaction with your work and your jobs around the house in the past month.

1	2	3	4	5	6	7
very dissatisfied						very satisfied

11. How uncomfortable do you feel today?

1	2	3	4	5	6	7
not at all						very uncomfortable

12. Rate in your opinion, how disruptive your cancer has been to those closest to you in the past 2 weeks.

1	2	3	4	5	6	7
totally disruptive						no disruption

13. How much is pain or discomfort interfering with your daily activities?

1	2	3	4	5	6	7
not at all						a great deal

14. Rate the degree to which your cancer has imposed a hardship on you (personally) in the past 2 weeks.

1	2	3	4	5	6	7
tremendous hardship						no hardship

15. How much of your usual household tasks are you able to complete?

1	2	3	4	5	6	7
all						none

16. Rate how willing you were to see and spend time with those closest to you, in the past 2 weeks.

1	2	3	4	5	6	7
unwilling						very willing

17. How much nausea have you had in the past 2 weeks?

1	2	3	4	5	6	7
none						a great deal

18. Rate the degree to which you are frightened of the future.

1	2	3	4	5	6	7
constantly terrified						not afraid

19. Rate how willing you were to see and spend time with friends, in the past 2 weeks.

1	2	3	4	5	6	7
unwilling						very willing

20. How much of your pain or discomfort over the past 2 weeks was related to your cancer?

1	2	3	4	5	6	7
none						all

21. Rate your confidence in your prescribed course of treatment.

1	2	3	4	5	6	7
no confidence						very confident

22. How well do you appear today?

1	2	3	4	5	6	7
extremely poor						extremely well

Please check to see if you have completed all questions. Thank you for your valuable assistance in this project.

ADDENDUM 4: SOME DEFINITIONS AND GRADES FOR THE KATZ INDEX OF ACTIVITIES OF DAILY LIVING (KATZ, 1963)

Index of Independence in Activities of Daily Living

The index of independence in activities of daily living is based on an evaluation of the functional independence or dependence of patients in bathing, dressing, going to the toilet, transferring, continence, and feeding. Specific definitions of functional independence and dependence appear below the index.

A	Independent in feeding, continence, transferring, going to toilet, and bathing.
B	Independent in all but one of these functions.
C	Independent in all but bathing, and one additional function.
D	Independent in all but bathing, dressing and one additional function.
E	Independent in all but bathing, dressing, going to toilet, and one additional function
F	Independent in all but bathing, dressing, going to toilet, transferring, and one additional function.
G	Dependent in all six functions.
Other	Dependent in at least two functions, but not classifiable as C, D, E, or F.

Independence means without supervision, direction, or active personal assistance, except as specifically noted below. This is based on actual status and not on ability. A patient who refuses to perform a function is considered as not performing the function, even though he is deemed able.

Eg bathing (sponge, shower or tub)

Independent: assistance only in bathing a single part (as back or disabled extremity) or bathes self completely.

Dependent: assistance in bathing more than one part of body: assistance in getting in or out of tub or does not bathe self.

ADDENDUM 5: McGILL PAIN QUESTIONNAIRE (MELZACK, 1971)

What does pain feel like?

Tell which words best describe your present pain

Use only a single word in each appropriate group the one that applies best

Indicate answer with (▯)

1		2		3		4	
1. flickering		1. jumping		1. pricking		1. sharp	
2. quivering		2. flashing		2. boring		2. cutting	
3. pulsing		3. shooting		3. drilling		3. lacerating	
4. throbbing				4. stabbing			
5. beating				5. lancinating			
6. pounding							
5		**6**		**7**		**8**	
1. pinching		1. tugging		1. hot		1. tingling	
2. pressing		2. pulling		2. burning		2. itchy	
3. gnawing		3. wrenching		3. scalding		3. smarting	
4. cramping				4. searing		4. stinging	
5. crushing							
9		**10**		**11**		**12**	
1. dull		1. tender		1. tiring		1. sickening	
2. sore		2. taut		2. exhausting		2. suffocating	
3. hurting		3. rasping					
4. aching		4. splitting					
5. heavy							
13		**14**		**15**		**16**	
1. fearful		1. punishing		1. wretched		1. annoying	
2. frightful		2. grueling		2. blinding		2. troublesome	
3. terrifying		3. cruel				3. miserable	
		4. vicious				4. intense	
		5. killing				5. unbearable	
17		**18**		**19**		**20**	
1. spreading		1. tight		1. cool		1. nagging	
2. radiating		2. numb		2. cold		2. nauseating	
3. penetrating		3. drawing		3. freezing		3. agonizing	

4. piercing		4. squeezing				4. dreadful	
		5. tearing				5. torturing	

ADDENDUM 6: NOTTINGHAM HEALTH PROFILE (HUNT 1980)

(Some items from Part 1)

Listed below are some problems people may have in their daily life.

Look down the list and put a tick in the box under "yes" for any problem you have at the moment.

Tick the box under "no" for any problem you do not have.

Please answer every question. If you are not sure whether to say yes or no, tick whichever answer you think is more true at the moment.

	YES	NO
I'm tired all the time		
I have pain at night		
Things are getting me down		
	YES	NO
I have unbearable pain		
I take tablets to help me sleep		
I've forgotten what it's like to enjoy myself		
	YES	NO
I'm feeling on edge		
I find it painful to change position		
I feel lonely		
	YES	NO
I can only walk about indoors		
I find it hard to bend		
Everything is an effort		

ADDENDUM 7: NOTTINGHAM HEALTH PROFILE (HUNT, 1980)

(Part 2)

Now we would like you to think about the activities in your life which may be affected by health problems.

In the list below, tick "yes" for each activity in your life which is being affected by your state of health. Tick "no" for each activity which is not being affected, or which does not apply to you.

Is your present state of health causing problems with your…	YES	NO
JOB OF WORK (That is, paid employment)		
LOOKING AFTER THE HOME (Examples: cleaning and cooking, repairs, odd jobs round the home, etc.)		
SOCIAL LIFE (Examples: going out, seeing friends, going to the pub, etc.)		
HOME LIFE (That is: relationships with other people in your home)		
SEX LIFE		
INTERESTS AND HOBBIES (Examples: sports, arts and crafts, do-it-yourself, etc.)		
HOLIDAYS (Examples: summer or winter holidays, weekends away, etc.)		

ADDENDUM 8: SOME ITEMS FROM PRIESTMAN AND BAUM'S LASA (PRIESTMAN 1976)

DIFFICULTY WITH SLEEP

Most nights ______________________________| Never

FEELING OF WELL BEING

Very bad ______________________________| Very good

RELATIONSHIP WITH PARTNER

Impossible ______________________________| Excellent

RELATIONSHIP WITH OTHER PEOPLE

Impossible ______________________________| Excellent

SEXUAL RELATIONSHIPS

Total loss ______________________________| Better than ever

DECISION MAKING

Impossible ______________________________| Excellent

ABILITY TO PERFORM HOUSEWORK

Impossible ______________________________| Better than ever

ADDENDUM 9: QUALITY OF LIFE CORE QUESTIONNAIRE (BERNHARD, 1997)

International Breast cancer Trials VI, VII, VIII, IX, 10–93 to 14-93
Quality of Life Core Questionnaire

Patient instructions:

We would like to know how strongly you are affected by your illness and treatment. Please answer all of the following questions by **placing a vertical mark on the line** depending on how you assess yourself.

For example: Have you had trouble sleeping?

None ______________________________|_____ A lot

This mark would indicate considerable sleeping difficulties since your last assessment.

Your information will be treated as strictly confidential. Thank you for replying!

Please turn over for the questionnaire

How have you been within the last two weeks?

Physical Well Being Good ____________________ Lousy

Mood Happy ____________________ Miserable

Tiredness None ____________________ A lot

Appetite Good ____________________ None

Hot Flushes None ____________________ A lot

Feeling sick (nausea and vomiting) None ____________________ A lot

How much effort does it cost you to cope with your illness?

No effort at all ____________________ A great deal of effort

Do you feel supported by the people close to you?

Very much ____________________ Not at all

Does the operation restrict the use of your arm?

Not at all ____________________ A lot

Imagine that you would have to live the rest of your life in your current condition. Please indicate, on the line below, how you would rate a life in your current condition between perfect health and worst health.

Make a vertical mark according to your estimate.

Perfect health ____________________ Worst health

Please check that all questions are answered. Thank you!

ADDENDUM 10: PART OF SELBY'S LASA (1984)

Please score how you *feel* each of these aspects of your life was affected by *the state of your health,* during *today* (24 hours)

☐ ***Depression***

extremely depressed ______________________________ not depressed at all

☐ ***Appearance of your body***

extremely dissatisfied (because of the state of my health, disease or treatment) ______________________________ completely satisfactory for me at my age

☐ ***Family relationships and marriage/cohabitation***

extremely bad relationships because of the state of my health ______________________________ normal family life for me

☐ ***Housework***

no housework because of the state of my health ______________________________ normal house-hold duties for me

☐ ***Eating* (increased or decreased)**

COMPLETE (a) or (b)

(a)

not eating ______________________________ normal eating for me

(b)

greatly increased eating ______________________________ normal eating for me

ADDENDUM 11: THE GENERAL HEALTH QUESTIONNAIRE (GHQ 28) PART A – (DAVID GOLDBERG, 1972)

Please read this carefully:

We should like to know if you have had any medical complaints and how your health has been in general, *over the past few weeks*. Please answer ALL the questions on the following pages simply by underlining the answer which you think most nearly applies to you. Remember that we want to know about present and recent complaints, not those that you had in the past.

It is important that you try to answer ALL questions.

Thank you very much for your co-operation.

Have you recently:

	Better than usual	Same as usual	Worse than usual	Much worse than usual
A2 been feeling in need of a good tonic?	Not at all	No more than usual	Rather more than usual	Much more than usual
A3 been feeling run down and out of sorts?	Not at all	No more than usual	Rather more than usual	Much more than usual
A4 felt that you are ill?	Not at all	No more than usual	Rather more than usual	Much more than usual
A5 been getting any pains in your head?	Not at all	No more than usual	Rather more than usual	Much more than usual
A6 been getting a feeling of tightness or pressure in your head?	Not at all	No more than usual	Rather more than usual	Much more than usual
A7 been having hot or cold spells?	Not at all	No more than usual	Rather more than usual	Much more than usual

ADDENDUM 12:ITEMS IN THE ROTTERDAM SYMPTOM CHECKLIST (RSCL) (DE HAES, 1983)

Name ____________________ Title ____________________ Date of Birth ____________________

Date ____________________ Occupation ____________________ Hospital ____________________

In this questionnaire you will be asked about your symptoms.

Read each item and place a firm tick in the box opposite the reply which comes closest to how you have been feeling during the last three days.

Please turn over for: Section 1

ROTTERDAM SYMPTOM CHECKLIST

1. Lack of appetite		**2. Irritability**		**3. Worry about my health**	
Not at all		Not at all		Not at all	
A little		A little		A little	
Somewhat		Somewhat		Somewhat	
Very much		Very much		Very much	
4.Tiredness		**5. Worrying**		**6. Sore muscles**	
Not at all		Not at all		Not at all	
A little		A little		A little	
Somewhat		Somewhat		Somewhat	
Very much		Very much		Very much	
7. Depressed		**8. Lack of energy**		**9. Pain**	
Not at all		Not at all		Not at all	
A little		A little		A little	
Somewhat		Somewhat		Somewhat	
Very much		Very much		Very much	
10. Nervousness		**11. Nausea**		**12. Feel desperate about the future**	
Not at all		Not at all		Not at all	
A little		A little		A little	
Somewhat		Somewhat		Somewhat	
Very much		Very much		Very much	
13. Difficulty in falling asleep		**14. Headache**		**15. Vomiting**	
Not at all		Not at all		Not at all	
A little		A little		A little	
Somewhat		Somewhat		Somewhat	
Very much		Very much		Very much	
16. Feeling self-conscious		**17. Dizziness**		**18. Lack of sexual interest**	
Not at all		Not at all		Not at all	
A little		A little		A little	
Somewhat		Somewhat		Somewhat	
Very much		Very much		Very much	
19. Feel lonely		**20. Dissatisfied with my appearance**		**21. Feel tense**	
Not at all		Not at all		Not at all	
A little		A little		A little	
Somewhat		Somewhat		Somewhat	
Very much		Very much		Very much	

ADDENDUM 13: SOME ITEM FROM SECTION VI OF THE PAIS – SOCIAL ENVIRONMENT (MORROW, 1978)

(1) INDIVIDUAL LEISURE INTEREST

Are you still as interested in your leisure time activities and hobbies as you were prior to your illness (i.e. watching TV, sewing, bicycling, etc.)?

[ ] 0 = same level of interest as previously
[ ] 1 = slightly less interest than before
[ ] 2 = significantly less interest than before
[ ] 3 = little or no interest remaining

(2) INDIVIDUAL LEISURE ACTIVITIES

How about actual participation? Are you still actively involved in doing those activities?

[ ] 0 = participation remains unchanged
[ ] 1 = participation reduced slightly
[ ] 2 = participation reduced significantly
[ ] 3 = little or no participation at present

(3) FAMILY LEISURE INTEREST

Are you as interested in leisure time activities with your family (i.e. playing cards and games, taking trips, going swimming, etc.) as you were prior to your illness?

[ ] 0 = same level of interest as previously
[ ] 1 = slightly less interest than before
[ ] 2 = significantly less interest than before
[ ] 3 = little or no interest remaining

ADDENDUM 14: SOME ITEMS OF THE SICKNESS IMPACT PROFILE (BERGNER, 1976)

Dimension	**Category Items Describing Behavior Related to:**	**Selected Items**
Independent categories	Sleep and rest	I sit during much of the day I sleep or nap during the day
	Eating	I am eating no food at all, nutrition is taken through tubes or intravenous fluids I am eating special or different food
I. Physical	Ambulation	I walk shorter distances or stop to rest often I do not walk at all
II. Psychosocial	Body care and movement	I do not bathe myself at all, but am bathed by someone else I am very clumsy in body movements
	Social interaction	I am doing fewer social activities with groups of people I isolate myself as much as I can from the rest of the family
	Emotional behavior	I laugh or cry suddenly I act irritable and impatient with myself for example, talk badly about myself swear at myself, blame myself for things that happen

ADDENDUM 15: PART OF THE PROFILE OF MOOD STATES (POMS) (McNAIR, 1981)

Below is a list of words that describe feelings people have. Please read each one carefully. Then fill in ONE circle under the answer to the right which best describes HOW YOU HAVE BEEN FEELING DURING THE PAST WEEK INCLUDING TODAY.

	Not at all	A little	Moderately	Quite a bit	Extremely		Not at all	A little	Moderately	Quite a bit	Extremely
1. Friendly	(0)	(1)	(2)	(3)	(4)	21. Hopeless............	(0)	(1)	(2)	(3)	(4)
2. Tense	(0)	(1)	(2)	(3)	(4)	22. Relaxed...............	(0)	(1)	(2)	(3)	(4)
3. Angry	(0)	(1)	(2)	(3)	(4)	23. Unworthy............	(0)	(1)	(2)	(3)	(4)
4. Worn out	(0)	(1)	(3)	(3)	(4)	24. Spiteful..........	(0)	(1)	(2)	(3)	(4)
5. Unhappy	(0)	(1)	(2)	(3)	(4)	25. Sympathetic.........	(0)	(1)	(2)	(3)	(4)
6. Clear-headed ...	(0)	(1)	(2)	(3)	(4)	26. Uneasy...............	(0)	(1)	(2)	(3)	(4)
7. Lively	(0)	(1)	(2)	(3)	(4)	27. Restless...............	(0)	(1)	(2)	(3)	(4)
8. Confused	(0)	(1)	(2)	(3)	(4)	28. Unable to concentrate	(0)	(1)	(2)	(3)	(4)
9. Sorry for things done	(0)	(1)	(2)	(3)	(4)	29. Fatigued...............	(0)	(1)	(2)	(3)	(4)
10. Shaky	(0)	(1)	(2)	(3)	(4)	30. Helpful	(0)	(1)	(2)	(3)	(4)
11. Listless	(0)	(1)	(2)	(3)	(4)	31. Annoyed	(0)	(1)	(2)	(3)	(4)
12. Peeved	(0)	(1)	(2)	(3)	(4)	32. Discouraged	(0)	(1)	(2)	(3)	(4)
13. Considerate	(0)	(1)	(2)	(3)	(4)	33. Resentful	(0)	(1)	(2)	(3)	(4)
14. Sad	(0)	(1)	(2)	(3)	(4)	34. Nervous	(0)	(1)	(2)	(3)	(4)
15. Active	(0)	(1)	(2)	(3)	(4)	35. Lonely	(0)	(1)	(2)	(3)	(4)
16. On edge	(0)	(1)	(2)	(3)	(4)	36. Miserable	(0)	(1)	(2)	(3)	(4)
17. Grouchy	(0)	(1)	(2)	(3)	(4)	37. Muddled	(0)	(1)	(2)	(3)	(4)
18. Blue	(0)	(1)	(2)	(3)	(4)	38. Cheerful	(0)	(1)	(2)	(3)	(4)
19. Energetic	(0)	(1)	(2)	(3)	(4)	39. Bitter	(0)	(1)	(2)	(3)	(4)
20. Panicky	(0)	(1)	(2)	(3)	(4)	40. Exhausted	(0)	(1)	(2)	(3)	(4)

ADDENDUM 16: THE HOSPITAL ANXIETY AND DEPRESSION SCALE (HAD SCALE) ZIGMOND, 1983

Doctors are aware that emotions play an important part in most illnesses. If your doctor knows about these feelings he will be able to help you more. This questionnaire is designed to help your doctor to know how you feel. Read each item and place a firm tick in the box opposite the reply which comes closest to how you have been feeling in the past week. Don't take too long over your replies: your immediate reaction to each item will probably be more accurate than a long thought-out response.

I feel tense or 'wound' up:			**I feel as if I am slowed down:**		
I still enjoy the things I used to enjoy:			**I get a sort of frightened feeling like 'butterflies' in the stomach:**		
I get a sort of frightened feeling as if something awful is about to happen:			**I have lost interest in my appearance:**		
I can laugh and see the funny side of things			**I feel restless as if I have to be on the move**		
Worrying thoughts go through my mind:			**I look forward with enjoyment to things:**		
I feel cheerful:			**I get sudden feelings of panic:**		
I can sit at ease and feel relaxed:			**I can enjoy a good book, radio or TV program:**		

ADDENDUM 17: EORTC QLQ-C30 (AARONSEN, 1993) AND QLQ-BR23 (SPRANGERS, 1996)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials : ______________________
Your birthdate (day, month, year) : ______________________
Today's date (day, month, year) : ______________________

		No	**Yes**
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase ?	1	2
2.	Do you have any trouble taking a <u>long</u> walk?	1	2
3.	Do you have any trouble taking a <u>short</u> walk outside the house?	1	2
4.	Do you have to stay in a bed or a chair for most of the day?	1	2
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2
6.	Are you limited in any way in doing either you work or doing household jobs?	1	2
7.	Are you completely unable to work at a job or to do household jobs?	1	2

During the past week:

		Not at all	**A Little**	**Quite a bit**	**Very much**
8	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:

	Not at all	A Little	Quite a bit	Very much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Were you limited in doing either your work or other daily activities?	1	2	3	4
27. Were you limited in pursuing your hobbies or other daily activities?	1	2	3	4
28. Has your physical condition or medical treatment interfered with your **family** life?	1	2	3	4
29. Has your physical condition or medical treatment interfered with your **social** activities?	1	2	3	4
30. Has your physical condition or medical caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

31. How would you rate your overall **physical condition** during the past week?

1 2 3 4 5 6 7

Very poor Excellent

32. How would you rate your overall **health** during the past week?

1 2 3 4 5 6 7

Very poor Excellent

33. How would you rate your overall **quality of life** during the past week?

1 2 3 4 5 6 7

Very poor Excellent

EORTC QLQ-BR23

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week.

During the past week:

	Not at all	**A Little**	**Quite a bit**	**Very much**
34. Did you have a dry mouth?	1	2	3	4
35. Did food and drink taste different than usual?	1	2	3	4
36. Were your eyes painful, irritated or watery?	1	2	3	4
37. Have you lost any hair?	1	2	3	4
38. Answer this question only if you had any hair loss: Were you upset by the loss of you hair?	1	2	3	4
39. Did you feel ill or unwell?	1	2	3	4
40. Did you have hot flushes?	1	2	3	4
41. Did you have headaches?	1	2	3	4
42. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
43. Have you been feeling less feminine as a result of your disease or treatment?	1	2	3	4
44. Did you find it difficult to look at yourself naked?	1	2	3	4
45. Have you been dissatisfied with your body?	1	2	3	4
46. Were you worried about your health in the future?	1	2	3	4

During the past four weeks:

	Not at all	**A Little**	**Quite a bit**	**Very Much**
47. To what extent were you interested in sex?	1	2	3	4
48. To what extent were you sexually active? (with or without intercourse)	1	2	3	4
49. Answer this question only if you have been sexually active: To what extent was sex enjoyable for you?	1	2	3	4

Version 1.0

ADDENDUM 18: QUALITY OF LIFE INDEX (SPITZER 1981)

ACTIVITY	**During the last week, the patient** • Has been working or studying full time, or nearly so, in usual occupation; or managing own household; or participating in unpaid or voluntary activities, whether retired or not.........2 • Has been working or studying in usual occupation or managing own household or participating in unpaid or voluntary activities; but requiring major assistance or a significant reduction in hours worked or a sheltered situation or was on sick leave........1 • Has not been working or studying in any capacity and not managing own household.....0
DAILY LIVING	**During the last week, the patient** • Has been self-reliant in eating, washing, toiletting and dressing; using public transport or driving own car ....2 • Has been requiring assistance (another person or special equipment) for daily activities and transport but performing light tasks.........1 • Has not been managing personal care nor light tasks and/or not leaving own home or institution at all.........0
HEALTH	**During the last week, the patient** • Has been appearing to feel well or reporting feeling 'great' most of the time..............2 • Has been lacking energy or not feeling entirely 'up to par' more than just occasionally.. 1 • Has been feeling very ill or 'lousy', seeming weak and washed out most of the time or was unconscious.........0
SUPPORT	**During the last week, the patient** • The patient has been having good relationships with others and receiving strong support from **at least one** family member and/or friend.........2 • Support received or perceived has been limited from family and friends and/or by the patient's condition.........1 • Support from family and friends occurred infrequently or only when absolutely necessary or patient was unconscious.........0
OUTLOOK	**During the last week, the patient** • Has usually been appearing calm and positive in outlook, accepting and in control of personal circumstances, including surroundings.........2 • Has sometimes been troubled because not fully in control of personal circumstances or has been having periods of obvious anxiety or depression.........1 • Has been seriously confused or very frightened or consistently anxious and depressed or unconscious......... 0