CHAPTER 3: WHY IS IT NECESSARY TO EVALUATE QUALITY OF LIFE?

3.1 INTRODUCTION

One of the motivations for the assessment of quality of life is the increased attention to cancer control research at the National Cancer Institute (NCI) of America and at many, if not all of the cooperative research groups.

Quality of life is an emerging science of particular relevance to clinical cancer research. The availability of reliable quality of life measures may profoundly alter the clinical trials process. However, lack of rigor in the evaluation of such indices and uncritical interpretation of results may seriously compromise the credibility of the concept (Schipper 1985). In addition the assessment of quality of life is a complex issue.

Over the years, much research has been done in the field of quality of life, but its impact on the handling and treatment of cancer patients has been either non-existent or minimal. This is patently clear when scanning reports of clinical research in the medical literature (Stjernswärd 1986). But the diagnosis and management of cancer can have a major impact on every aspect of patients' quality of life (Ozyilkan 1998).

Cancer is frequently treated as a chronic disease, necessitating numerous periods of treatment and continual surveillance. Side–effects of chemotherapy and radiotherapy may require additional medical interventions, as will the symptoms of progressive disease such as pain and debilitation. Every factor that is fundamental to overall quality of life is at significant risk of compromise (Garfinkel 1991).

Anticancer treatments used to be evaluated mainly in terms of length of survival, with a disregard for the quality of survival. Now, partially because some chemotherapy regimens have such unpleasant side-effects, systemic measures of quality of life are being introduced, in clinical trials and in everyday clinical practice (Fallowfield 1990). Coates (1992) states that a balance must be found between the good and the harm that a given treatment is likely

to achieve. Breast cancer is a common cancer for which chemotherapy is effective but toxic and which causes controversy that might be lessened by more frequent use of appropriate quality of life assessment. With the current emphasis on "quality of life", new treatment techniques should try to minimize side effects as well as achieving better rates of cancer cure (Barraclough 1994).

The need to measure quality of life in the clinical setting is especially important in studies where survival advantages on various treatment arms may be minimal. Performance status and measures of pain provide important information, but an additional valuable dimension is measured by the patient's assessment of their functional and psychological status (Finkelstein 1987).

The true potential of a quality of life assessment is in its capacity to contribute to the design of a treatment regimen or to monitor clinical practice (Barofsky 1986).

3.2 THE METAMORPHOSIS IN MEDICAL CARE

A dichotomy has developed in the last fifty years: treatments have become much more powerful and life support systems have been developed that enable far more toxic treatments to be given, than could previously be considered. Thus the situation of "better " scientific medicine capable of replacing neoplastic bone marrow versus humanistic medicine, more in tune with patients' feelings and aspirations has developed. The validity of quality of life studies is intensified, because they represent a measure closer to the ultimate outcome measure in clinical medicine: the ability of a patient with an illness to carry on living a life of functional and philosophic meaning (Schipper 1986).

3.3 PROBLEMS AND ISSUES FOR FURTHER INVESTIGATION

3.3.1 GENERAL PROBLEMS

According to Bergner 1989 four broad problems arise from examination of the clinical research that assesses quality of life or health:

1. Conceptualization of the construct. The terms quality of life, health status and functional status are often used interchangeably and without specific definition. Each investigator must think about his or her own study, the study population, and the intervention and decide what should be assessed.
2. The need for and value of a "gold standard" for measuring health status. There is however, no gold standard. Health status, like intelligence, is a complex attribute that requires a multidimensional measure at the very least. The choice of an intelligence test for a particular situation is based on that situation.
3. The clinical significance and sensitivity of the measures. Intelligence tests do have an important advantage over measures of health status or quality of life. They have been used often enough, so that the meaning of a particular score is understood. The clinical importance of score differences in health status are still unclear, and the meaning of any particular score on a health status measure does not produce a mental picture of a real patient. There is also considerable uncertainty about the sensitivity of the measures to changes within the same person or sensitivity to differences between people.
4. Practical problems of administration.
    - Questionnaires can be self-administered or conducted as an interview. We do not know much about the equivalence of these methods, nor about the effect of the place in which the questionnaire is completed.
    - Questionnaires may be inappropriate for some segments of the population, such as illiterate people, people who are not proficient in the English language or people of different cultures to the cultural group that the questionnaire was developed and tested on.

3.3.2 NON-COMPLIANCE

Hopwood and coworkers (1998) conducted a survey to find out how quality of life questionnaires were being administered, with the aim of standardizing procedures and improving compliance. Logistical problems included unavailability of staff or lack of questionnaires (organizational) and patient-related problems (patient was too ill, or had difficulty reading or left before completing the form). Patient refusals were an uncommon reason for non-compliance and patients were considered to be generally in favour of quality of life assessment. Measures to improve these problems include publishing guidelines for

quality of life administration and information leaflets for patients together with staff training.

Seidman et al. (1995) studied quality of life in patients with metastatic breast cancer receiving paclitaxel and granulocyte colony stimulating factor (G-CSF) in a phase II trial. They found that the difficulties encountered with longitudinal data collection in a medically ill population further complicated efforts to obtain comprehensive information and introduced a dropout bias. Although methods may be employed to enhance patient compliance, difficulties unique to patients with metastatic breast cancer, such as removal from study because of disease progression and noncompliance as a result of high levels of symptom distress, may be unavoidable.

3.4 ASPECTS OF IMPORTANCE TO THE PATIENT

Studies have shown that patients are primarily concerned with non-physical matters, whereas studies designed by clinicians and most quality of life measures consider mostly physical signs (Schipper 1986, Coates 1983).

In addition to their role in clinical trials, there is a need to identify, on an individual basis, issues that may adversely affect the patient's quality of life. Ideally an instrument could be used effectively in both situations and allow reassessment of any intervention designed to improve quality of life. One reason for attempting to understand and measure quality of life is to provide for the increasing demand for informed choice for patients. (Jenney 1998).

Physicians are often unaware of important changes in their patient's physical and emotional functioning. A physician may easily spend years writing "doing well" in the notes of a patient who has become progressively more crippled before his eyes. Thus standardized information on functional ability may be useful in clinical care as well as in research. The value of such information has been shown for geriatric inpatient evaluation units, but has been harder to show for other kinds of care (Deyo 1991).

3.5 UNWANTED EFFECTS OF TREATMENT

"I knew I had cancer. They advised an operation and I declined, not because of heroism but because it did not agree with my view on life and death. I had no alternative. They should have taken out my bladder, irradiated me, and the whole incident would give me a 35% chance of survival, mutilated and for a limited time. We are all going to die. Some of us very soon, others much later. My experience is: we live a better life as it is, namely, for a limited time. Then it hardly matters how long the life prolongation lasts, when all is lost in eternity" (Stjernswärd 1986).

Unfortunately the majority of medical treatments and interventions do not only have purported beneficial effects, but also have unwanted and unpleasant side effects. The therapy may affect aspects of a person's life that are not strictly medical. It may not be pleasant to become bald and nauseous. The consequences of treatment and treatment-related side-effects may affect all of the patient's life. Therefore, a quality of life assessment should be performed (Bergner 1989).

3.6 BENEFICIAL EFFECTS OF TREATMENT

Researchers are not only interested in the unintended adverse effects of treatment but also the unintended beneficial effects (Bergner 1989).

Cancer is feared as a life-threatening disease that conveys a threat of intractable pain, hopelessness and wasting away before death occurs (Klagsbrum, 1983). Although advanced and successful forms of cancer treatment such as chemotherapy are available many adverse and unrelenting side effects must be endured. Precious little is known about the coping strategies of those undergoing chemotherapy. Understanding these experiences would provide health professionals with valuable insights into ways families cope, thus enhancing their quality of life (Wilson & Morse, 1991).

Drug companies and manufacturers of medical devices are also consumers of quality of life and health status assessments. One reason is that proof of benefits of new drugs must be

established, especially when they may be more costly. If a new drug is shown to have quality of life benefits, this is also a very useful marketing advantage (Bergner 1989).

Unfortunately, most of the drug company studies are not published or are published long after they are completed because they deal with new products or new uses for old products. Two examples can be instructive. One is the auranofin trial sponsored by Smith, Kline and French (Bomardier 1981) and the other is the trial of captopril sponsored by Squibb (Croog 1986). Both trials were designed with a primary focus on variables that are neither medical nor physiologic. The auranofin trial's objectives were to study the costs and benefits of auranofin and uses existing multidimensional measures of health status and illness-related symptoms. The captopril trial examined specific aspects of quality of life with specific and independent measures that assessed depression, distress, fatigue, impotence, cognition, etc. The measures were a mixture of existing measures, modifications of existing measures and new measures developed specifically for this trial. Outcomes of therapy were presented for each measure with no attempt at integration or aggregation (Bergner 1989).

3.7 QUALITY OF LIFE EVALUATION AS AN INTEGRAL PART OF CLINICAL TRIALS

It is now generally agreed that quality of life should be measured as an integral component of most cancer clinical trials, particularly where treatments are given with palliative intent. However, this is easier said than done. Time is short in busy cancer clinics and with increasing emphasis on trials including large numbers of patients carried out mainly in district general hospitals the logistics are formidable (Slevin 1992). There has been an increasing recognition of the need to incorporate assessment of quality of life into clinical trials. A joint working group of the Food and Drug Administration and the National Cancer Institute has recommended that end points in clinical trials should include an assessment of quality of life (Jenney 1998). The clinical usefulness of comparative (randomized) trials would be greatly enhanced if results were also expressed in terms of quality of life (Bernheim 1987).

Quality of life studies have been used to describe follow-up to a single treatment modality, such as bone marrow transplantation or in randomized clinical trials. Depending on the

goals of the study and the suitability of the instruments selected, comparisons can be made within the study population by clinically relevant sub-groupings or can be made with normative data from the general population to describe deviations in global or domain-specific assessments (Parsons 1998).

One of the most important objectives of all clinical research in oncology is to improve care of patients with malignant disease. The benefits of a cancer treatment regimen should outweigh its cost in patient suffering. By adding quality of life end points to the traditional end points of overall survival, disease-free survival and tumor response, medical researchers can make more informed decisions about risk-benefit trade-offs (Moinpour 1989).

Classic examples of how quality of life measurement can inform physicians and improve medical practice are found in the trials by Sugarbaker et al. (1982) and Hicks and coworkers (1985). The reporting of unexpected treatment impacts on quality of life variables led to changes in procedures for radiotherapy and surgical and physical therapy for patients with soft tissue sarcoma. These changes were associated with improved patient functioning.

Improved quality of life as a result of cancer treatment is highly valued by patients and physicians and is deemed an important criterion for approval of new agents and by extension, new combinations of agents – by the Food and Drug Administration (Dreicher 1998).

A study by Glimelius et al. (1989) provides valuable insight into the relation between disease control and quality of life. Chemotherapy for patients with advanced colorectal cancer is given with palliative intent. In a study of less toxic single agent 5-fluorouracil versus a more toxic combination arm of 5-fluorouracil plus methotrexate and leucovorin rescue, the patients on the combination arm had a greater response rate. Despite the increased toxicity, 55% of the patients given combination chemotherapy rated themselves as having an improved quality of life compared with only 9% of the single agent group. This suggests that the intensive chemotherapy was superior as a palliative treatment in this patient population.

A study by Kaasa and coworkers (1988) again suggests that side effects were not the major determinants of quality of life. The overall improvement in quality of life in both groups (radiotherapy or chemotherapy for non-small cell lung cancer), despite a response in only a minority, suggests that the benefits may be related to the optimism and support provided by close medical supervision.

The key policies recommended by the South Western Oncology Group (SWOG) for inclusion of quality of life endpoints in certain trials are:

- Begin assessment of quality of life in specific types of phase III protocols.
- Always measure physical functioning, emotional functioning, symptoms (general and protocol specific) and global quality of life separately.
- Include measures of social functioning and additional protocol specific measures if resources permit.
- Use patients-based questionnaires with psychometric properties that have been documented in published studies (McMillen 1989).

A most important aspect of a phase III study is the quality of the patient's survival. It seems nonsensical to apply a therapy which detracts from the quality of survival while causing objective tumor response. The patient only appreciates the toxicity of the therapy, if he is deriving a significant improvement in function as a result of the treatment. In this respect the evaluation of the quality of survival and subjective improvements is important during these studies, but as yet they (these factors) cannot be used as objective response criteria (Jones 1988).

3.7.1 THE ADJUVANT SETTING

In adjuvant therapy and even more in preventative interventions, the woman who undertakes more or less toxic treatment does so in the hope of future gain. In neither case does the patient have discernable disease at the time that therapy is used; thus any morbidity incurred can be compensated only by delay of disease or death. Where alternative strategies for the pursuit of such benefits are being compared, it is important to measure the impact of each on quality of life (Coates 1993).

In order to improve assessment of the cost-benefit balance in a trial comparing adjuvant therapies of differing intensity and duration, it was considered as important to measure quality of life related aspects prospectively. Serial quality of life assessments were obtained every three months for 2 years from patients with operable breast cancer in two ongoing International Breast Cancer Study Group (IBCSG) randomized clinical trials of adjuvant treatment. The quality of life assessments included patient-derived perceived coping (PACIS, personal adjustment to chronic illness scale), well being (Bf-S, Befindlichkeitsskala von Zerrssen), mood, physical well being and appetite (LASA, linear analogue self assessments). The analysis of serial assessments for 265 patients with each of the first four assessments completed showed that all measures improved with increasing time from study entry; that the degrees of improvement for the four major language groups were similar; and that measures were sensitive to treatment difference. Hürny et al. (1992) concluded that the measurement of quality of life related aspects in a multicultural clinical trial are feasible and possibly relevant for the evaluation of treatment results.

The research efforts to evaluate quality of life and improve survival with breast cancer adjuvant therapy have proceeded largely independently of one another. Patients rely heavily on their physician to weigh the potential benefits and risks of therapy alternatives and provide clear treatment recommendations. Since physicians play the central role in the evaluation of adjuvant therapy, quality of life must assess a concept relevant to physicians if it is to be clinically useful (Fetting 1988).

An important next step in quality of life research is what Levine et al (1988) call the "responsiveness" of quality of life measures. One aspect of this effort is to determine how well quality of life measures distinguishes among regimens in an adjuvant trial. The researchers demonstrated that their measure distinguished between patients who had completed and patients who were still receiving adjuvant therapy. But physicians do not need a test to tell them that quality of life is reduced in patients on adjuvant chemotherapy compared to those who have completed treatment. A litmus test for these measures will be how well they discriminate among regimens not so obviously different (Fetting 1988).

The first and most important finding is that adjuvant therapy improves disease-free survival in patients with stage I breast cancer. This is promising but the majority of stage I patients never develop a recurrence. Until better methods predicting recurrence or diagnosing micro metastatic disease are developed, the majority of stage I patients will be treated needlessly. The impact on these patients is of major concern (Fetting 1988).

Secondly, one real possibility is that the more intense regimens being developed for future adjuvant therapy may prove only marginally better than current therapies. Regimens with such modest survival benefits will be more compelling if it can be documented that the impact of therapy on patients is not significantly more detrimental than that with standard regimens. To date the impact of treatment has been inferred from survival and toxicity data. Survival data says nothing about the quality of survival. Toxicity evaluations describe the type, frequency, severity and duration of toxicity but do not describe personal and/or social consequences (Fetting 1988).

An intergroup trial was conducted to compare an investigational 16-week regimen with a standard CAF-regimen (cyclophosphamide, doxorubicin and fluorouracil). The 16-week regimen features greater doxorubicin and fluorouracil dose-intensity than CAF and improved scheduling of anti-metabolites with sequential methotrexate and fluorouracil, as well as infusional fluorouracil. This trial was given as adjuvant therapy for node-positive, receptor-negative breast cancer patients in the adjuvant setting.

Breast cancer outcomes included recurrence as well as disease-free overall survival. Toxicity was evaluated by the Common Toxicity Criteria. Treatment related quality of life was assessed by the Breast Chemotherapy Questionnaire (BCQ) before, during and 4 months after treatment in 163 patients. During treatment, quality of life declined significantly more with the 16-week regimen than CAF, but by 4 months post-treatment, there was no difference.

The 16-week regimen produced marginally better breast cancer outcomes than CAF with similar toxicity but a greater reduction in during-treatment quality of life. It was concluded that the 16-week regimen should not be used instead of a standard-dose regimen without careful consideration of its pros and cons (Fetting 1998).

Late effects of adjuvant treatment on perceived health and quality of life were assessed through a questionnaire mailed to 448 premenopausal and postmenopausal breast cancer patients, free from recurrence 2-10 years after primary therapy. The patients had been randomized to postoperative radiotherapy or adjuvant chemotherapy as adjuncts to primary surgery. The differences between the two treatments were generally small. However, the radiotherapy patients had significantly greater problems with decreased stamina, symptoms related to the operation scar and anxiety. The chemotherapy patients had significantly more problems with smell aversion. Activity level inside and outside the home, anxiousness and depressive symptoms were similar in both groups. The chemotherapy group scored their overall quality of life higher than the radiotherapy patients (Berglund 1991).

Gelber et al. (1991) looked at a large randomized trial comparing a single cycle of preoperative adjuvant chemotherapy with six cycles of conventionally timed chemotherapy. The quality of life would be expected to be significantly worse with the longer, more intensive chemotherapy but at five year follow up the patients who had received the longer therapy had better five year survival than those who received a single preoperative cycle. The quality of life was evaluated by using Q-twist, which looks at the quality adjusted time without symptoms. Despite the greater initial toxicity with the more intensive and longer chemotherapy these patients had a longer freedom from disease and less time with the problems of recurrent disease and its treatment. There was thus an improvement in both quantity and quality of life for patients who received the more intensive therapy.

3.7.2 THE METASTATIC SETTING

End points related to quality of life have only recently been incorporated into clinical trials. Their use in randomized, controlled (phase III) studies is increasing and is providing valuable comparative data. The potential utility of such measurements in single-arm efficacy (phase II) trials has received less attention but possibly provides the means to explore the interactions among quality of life, tumor response and treatment toxicity. Additionally, a baseline quality of life assessment often is a predictor of survival in patients with advanced breast cancer (Seidman 1995).

Seidman (1995) studied quality of life in a phase II trial of paclitaxel and G-CSF (granulocyte-colony stimulating factor) for the treatment of metastatic breast cancer. They found the information provided by quality of life measures to be quite useful, but caution that it must be recognized that interpretation of subjective data in a single-arm, open-label trial is inherently problematic. The sample size available for evaluation in most phase II trials is small, and results may not be generalizable. Furthermore, patients eligible to receive a promising new agent may experience feelings of optimism and well being not related to the treatment itself.

In the Seidman (1995) study favorable response was associated with improved quality of life. The improved symptoms and other quality of life parameters in patients with partial tumor response suggest an acceptable balance between the antitumor effect and drug-related morbidity. For patients with progression of disease it is difficult to ascertain the relative contribution of drug-related toxicity and disease progression to the decline in quality of life scores.

Priestman and Baum carried out one of the earliest studies looking at the effect of treatment on quality of life in advanced breast cancer in the mid-1970s. This study used linear analogue self-assessment scales to compare subjective responses in a trial of patients with advanced breast cancer randomized to endocrine or cytotoxic treatment. The higher response rate in patients receiving cytotoxic chemotherapy correlated with a better overall quality of life than that found in patients receiving endocrine therapy despite the higher incidence of side effects with cytotoxic chemotherapy (Slevin 1992).

Another trial in advanced breast cancer was conducted by the Australian/New Zealand breast cancer trial group, which randomized patients to receive either continuous or intermittent combination chemotherapy. In patients receiving intermittent therapy, treatment was stopped after three cycles if the disease did not progress. If the disease later progressed the treatment was given for a further three cycles (Coates 1987).

The other arm of the study received continuous chemotherapy. The results of this study were counterintuitive. Overall quality of life, response to treatment and time to ultimate treatment failure all favored continuous therapy. Patients receiving intermittent therapy

possibly had increased anxiety when they were not having treatment. However, the changes in quality of life were also found to be significant independent predictors of survival. This suggested that the quality of life reflected the state of the metastatic disease and that the increased side effects of chemotherapy were outweighed by the benefit the patients received from having better disease control (Coates 1987).

Metastatic breast cancer is rarely curable with standard chemotherapy. Since a significant portion of patients with operable breast cancer are candidates for adjuvant chemotherapy with cyclophosphamide/methotrexate/fluorouracil (CMF) or cyclophosphamide/doxorubicin/fluorouracil (CAF) or similar regimens, many patients with advanced breast cancer will have already been exposed to the drugs most commonly used to treat advanced disease, rendering them less likely to respond to such treatment a second time. The identification of active new drugs or drug combinations, therefore, is urgently needed (Perez 1996).

The optimal dose for megestrol acetate could be determined with additional support from quality of life date. Patients with stage IV breast cancer were randomly selected to receive either 160, 800 or 1600 mg of megestrol acetate daily. This medication is used as second-line hormonal therapy for advanced breast cancer. Quality of life was assessed at trial entry and at 1 and 3 months during treatment. At 3 months, women treated with 160 mg per day reported less severe side effects, better physical functioning, less psychologic distress and improvements in quality of life compared with those treated with 1600 mg daily. Patients who received 800 mg daily fell between the low- and high-dose arms in intensity of drug side effects, but responded similarly to those in the 160 mg group in terms of physical functioning, psychologic distress and overall quality of life. Thus the 160 mg daily dose may be optimal, achieving maximal treatment effects with fewer side effects and better quality of life (Stefaneck 1994).

A phase II trial evaluating the efficacy of the paclitaxel/carboplatin combination, along with an evaluation of thrombopoietin levels and quality of life (using the FACT-B instrument), was initiated in 1996. Results from this trial will help document the role of the paxlitaxel/carboplatin combination in the treatment of women with breast cancer (Perez 1996).

The result of the analysis of QOL for metastatic lung cancer patients EST 4983 showed that the variables which are highly correlated with a higher quality of life are good performance status and being male (Finkelstein 1987). Pain, race, education, marital status and living arrangements did not show any association with the QOL score after accounting for performance status and sex. The type of therapy and whether it was single agent or combination therapy also did not show any association with the QOL score. This is also true for treatment complications.

Measurements of functional status are important for the assessment of lung cancer therapies, and minimally, this can be achieved by assessment of changes in pain, performance status, and weight, which are made at each cycle of therapy. Patient-reported assessment of quality of life may also be important. However, the results of EST 4983 did not conclusively show the value of the QOL instrument, because of poor patient compliance.

Results of a phase II study for the treatment of ovarian cancer show that quality of life as measured, based on the score from the FACT-O, improved over time with a statistical significant difference from baseline detected during therapy and at the end of therapy ($p<0.01$). The purpose of the study was to evaluate an outpatient Taxol and Carboplatin regimen for patients with suboptimally debulked ovarian cancer. The specific objectives of the study were to evaluate the objective response rate and toxicity, to evaluate the progression-free interval and overall survival, and to describe changes in quality of life over time, in patients receiving Taxol plus Carboplatin. The minimal toxicity of the regimen is reflected in the high percentage of patients that completed therapy. The objective response rate was 72 %, the median duration of response was 11 months and the median overall survival was 30 months for patients with measurable disease. The favorable outcome of this trial is further supported by the improvement of quality of life that was demonstrated (Weller 1998).

The use of megestrol acetate in the treatment of weight loss in gastrointestinal cancer patients has been disappointing. The aim of the study by McMillan et al. (1999) was to compare the combination of megestrol acetate and placebo with megestrol acetate and ibuprofen in the treatment of weight loss in such patients. Quality of life was assessed with

the European Organization for Research and Treatment of Cancer's EuroQol-EQ-5D and EORTC QLQ-C30. It was found that the combination of megestrol acetate and ibuprofen appeared to reverse weight loss and appeared to improve quality of life in this patient group.

Many of the published results on palliative treatments demonstrate effects on remission or time to progression but no effects on the function of the tumour which result in decreased survival and impairs quality of life. If there are only marginal effects on duration of survival, which is in fact true for most palliative treatments, it is essential to demonstrate that our clinical interventions improve the quality of the patients' remaining life (Porzsolt 1993).

TABLE 1: CHEMOTHERAPY AND QUALITY OF LIFE (SLEVIN 1992)

- More effective therapy is usually associated with better quality of life.
- More intensive therapy is therefore not always associated with lower quality of life.
- Side effects may be less important than control of disease.
- Patients may report improved quality of life despite showing no objective response. This could be related to
  - minimal tumor shrinkage giving relief of symptoms
  - increased medical attention
  - provision of hope
  -

3.8 QUALITY OF LIFE AS A PROGNOSTIC FACTOR

Baseline quality of life assessment may provide prognostic information distinct from that obtained through standard prognostic indicators alone. Seidman et al. (1995) found that the combination of two factors – extent of disease and baseline quality of life assessment – predicted survival more accurately than either used separately.

During quality of life (QOL) validation studies, it was noted that changes in some QOL scores were significantly associated with prognosis (Coates 1987, Coates 1988). Quality of life data can be analyzed to investigate the relationships between measured aspects of QOL

and survival duration (Coates 1992). Baseline QOL scores recorded at the time of randomization were used as predictors of survival starting from that time. All baseline QOL scores except those for pain were significant predictors of overall survival. In a multivariate model, simultaneous allowances were made for significant non-QOL prognostic factors (performance status, liver metastases, brain metastases and node metastases).

Additionally Coates (1992) found that the tumor response category was clearly related to change in QOL scores, during the first three cycles of chemotherapy. Scores for physical well-being, mood, appetite, and the uniscale and QOL index all improved significantly in the group as a whole and in patients achieving a response, but there was no significant change among non-responders.

The association that Coates (1992) observed in his study between survival and scores in simple, practical measures of QOL (5 linear analog self-assessment scales for patients and the Spitzer scale completed by the physician) provides an additional powerful argument for including such measures in clinical trials and routine practice of oncology.

The prognostic value for survival of the Quality of Life Core Questionnaire of the International Breast Cancer Study Group was demonstrated in various cancer sites. Among the scales previously described as predictive were single item linear analogue self-assessment (LASA) scales for physical well being and overall quality of life. The independent prognostic information carried by such measures was again shown in patients with advanced malignancy who filled in the European Organization for Research and Treatment of Cancer (EORTC) questionnaire QLQ-C30. Single-item scores for global health status and QOL remained independently prognostic after controlling for performance status and age, and, among solid tumor patients, metastatic site. This association was also present for the social functioning scale but not for the other functional and symptom measures (Bernhard 1997).

Several studies have recently reported on the importance of quality of life in predicting the survival of patients with lung carcinoma. To confirm these reports, the relationship between survival and quality of life, as measured by the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire and Duke-UNC Social

Support Scale, was examined within a group of patients with advanced non-small cell lung carcinoma treated in a randomized clinical trial. Patients completed the questionnaires at baseline. The Cox proportional hazards model was used to determine the incremental contribution quality of life provided in predicting survival beyond the effect of known clinical prognostic variables. It was found that this study did not confirm the prognostic importance of overall quality of life. Rather, after adjustments for significant clinical factors, a patient-provided pain report had the greatest prognostic importance (Herndon 1999).

3.9 TO IMPROVE STANDARDS OF CARE

In clinical experience, quality of life assessment in cancer patients may be a supportive intervention by itself, increasing awareness of quality of life issues in both patients and staff (Bernhard 1995).

Because a large part of medical care is directed at managing chronic diseases, wider availability of quality of life information would enhance our ability to assess quality of care and to compare alternative management strategies (Deyo 1991).

3.9.1 SURGERY

For breast cancer

The approach with regard to surgery of breast cancer has undergone a metamorphosis in the last thirty years. The view that breast cancer can be treated as a regional disease solely by aggressive surgical techniques has been proven incorrect. A shift has taken place from the routine performance of a radical mastectomy, to modified radical mastectomy, to segmental mastectomy or lumpectomy. Now even the routine practice of axillary dissections, is being challenged by the concept of sentinel node biopsies (Ganz 1999).

Mastectomy still prevails as the key treatment for early breast cancer, so little is as yet known of the psychological effects of conservative surgery. There is controversy in the literature over the beneficial effects on quality of life that lumpectomy patients experience

versus those experienced by mastectomy patients. Some researchers claim that there is a benefit for lumpectomy patients and others find that there is no benefit. It is imperative that clinical trials focusing on the outcomes of different procedures on survival should include rigorous measures of psychological outcome alongside other variables. It has to be borne in mind that lumpectomy patients require radiotherapy and this can also cause psychological problems.

The body image of women is clearly more affected by mastectomy than by breast conserving treatment even several years after treatment. Sneeuw et al. (1992) examined the relationship between cosmetic and functional results of breast conserving therapy and psychosocial functioning in a sample of 76 patients with early stage breast cancer. Psychological functioning was measured with the 28-item version of the General Health Questionnaire (GHQ see chapter 2 Addendum 11). High levels of psychological distress, disturbance of body image (concerns about disfigurement and loss of femininity) and decreased sexual functioning were noted in approximately one-quarter of the study sample. About half the patients expressed concerns with disease recurrence and their future health. Psychosocial problems were only modestly associated with treatment-related cosmetic and functional outcomes, as determined by clinical ratings and objective assessments. The patient's own ratings of breast cosmesis and arm functioning exhibited somewhat higher correlations with self-reported psychosocial functioning. In particular, a significant association was noted between the patient's ratings of overall cosmesis and arm edema and their body image. The association between cosmetic and functional results and self-reported psychosocial health was strongest among those patients younger in age and treated longer ago. The patient's own assessments of cosmetic and functional outcomes should therefore be used as the primary source of information.

Dr. Maguire cites a number of articles that indicate fewer body image problems with lumpectomy than with mastectomy. Some of these lumpectomy patients however, experienced increased anxiety due to excessive fear of recurrence of their cancer (this anxiety may have been due to inadequate preoperative counseling). The foregoing seems to be the main evidence supporting Dr. Maguire's thesis that "breast conservation does not reduce psychological morbidity." In our own patients we found that the lumpectomy patients had significantly less loss of feelings of attractiveness and femininity than the

mastectomy patients. Additionally, lumpectomy patients rated their husbands' sexual behavior as having been enhanced after surgery whereas the mastectomy patients felt that their husbands' sexual behavior showed a decline. We also compared the two treatment groups with regard to the frequency of severe sexual dysfunction; this was almost three times as common in the mastectomy group as in the lumpectomy group (Wise 1994).

Axillary lymph node dissection (ALND) has been a standard procedure in the management of breast cancer. In a patient with a clinically negative axilla, ALND is performed primarily for staging purposes, to guide adjuvant treatment. Recently, the routine use of ALND has been questioned because the results of the procedure may not change the choice of adjuvant systemic therapy and/or the survival benefit of a change in adjuvant therapy would be small. Parmigiani and coworkers (1999) constructed a decision model to quantify the benefits of ALND for patients eligible for breast-conserving therapy. The largest benefits from ALND are seen in estrogen receptor (ER) positive women with small primary tumors who might not be candidates for adjuvant chemotherapy if their lymph nodes test negative. Virtually no benefit is found in ER negative women, almost all of whom would receive adjuvant chemotherapy. When adjusted for quality of life, ALND may have an overall negative impact. In general the benefits of ALND increase with the expected severity of adjuvant therapy on quality of life. This model quantifies the benefits of ALND and assists decision making by patients and physicians.

Velanovich and Szymanski (1999) attempted to define the incidence and effect of postoperative lymphedema on quality of life in breast cancer patients. They used the SF-36, a generic instrument, measuring eight domains of quality of life (see chapter 2 and addendum 2). Patients were divided into three groups: breast surgery without axillary lymph node dissection (ALND), breast surgery with ALND but no lymphedema and breast surgery with ALND and lymphedema. Patients in the "without ALND" and "no lymphedema" groups had similar scores in all domains of the SF-36. However, patients in the "positive lymphedema" group had significantly lower scores in the domains of role-emotional and bodily pain. Although lymphedema occurred in only 8.3% of patients, it produced demonstrable diminutions in quality of life. Therefore, efforts to reduce the incidence of lymphedema, such as sentinel lymph node biopsy or selective ALND, are to the benefit of breast cancer patients.

One of the most vexing late effects of axillary-node dissection is lymphedema of the arm. Though rarely life threatening, it is one of the most troublesome and feared consequences of breast-cancer surgery. Among women who have undergone radical mastectomy, up to 60 percent have lymphedema. The frequency is about 30 percent in women treated with modified radical mastectomy or breast-conserving surgery. For women who also receive radiation to the axillary area, the rate of lymphedema is higher (Loprinzi 1999).

Lymphedema is an important problem for women who survive breast cancer because it is unsightly, painful, restricts arm movement, increases the risk of infection and the swelling can be psychologically distressing. The management of lymphedema is also difficult.

Loprinzi (1999) used a prospective, double blind, randomised, and crossover design study, to see whether coumarin was effective in reducing lymphedema. The outcome of treatment was evaluated by detailed measurements of arm volume and a questionnaire completed by each patient. A lack of efficacy was demonstrated and we are also alerted to the potentially serious hepatotoxic effects of the drug.

For other kinds of cancer

Quality of life evaluation is one of the parameters used by surgeons to evaluate new surgical approaches in gastric cancer. Considering quality of life, endoscopic mucosal resection or laparoscopic wedge resection is the best front-line therapy for several mucosal cancers. It was found that evaluation of all information concerning tumor stage, location, histologic type, expected survival and quality of life after resection, is of paramount importance for the surgeons planning future approaches (Roukos 1999).

An assessment of the long-term results of surgery for temporal bone paragangliomas, with special consideration of the patients' ability to cope with the functional deficits was performed by Briner et al. (1999). The otologic extradural approach allowed complete tumor removal in 83% of patients, with minimal perioperative morbidity. Seventy-five percent of the patients regained their preoperative quality of life and 97% returned to their previous occupation in 1 to 2 years.

The ileoanal pull-through procedure is gaining increasing favor and use in surgical treatment of children with ulcerative colitis and familial adenomatous polyposis. Participants completed the standardized Medical Outcome Study Short Form-36 (SF-36), which has well-established normative values (see chapter 2 and addendum 2). The study group was not statistically different from age-appropriate population normal values on all assessable scales of physical and mental health in the SF-36 survey including physical functioning, role limitations-physical, bodily pain, general health, vitality, social functioning, role limitations-emotional and mental health. The surgical scar was the sole negative factor of significance. It was concluded that the ileoanal pull-through procedure is an excellent surgical option for children with ulcerative colitis or familial adenomatous polyposis and it produced minimal, if any, adverse effects on their long-term quality of life (Shamberger 1999).

During recent years considerable interest has been focused on quality of life as an additional therapeutic outcome measure in the surgical treatment of gastric carcinoma. However, the long-term consequences of gastrectomy and the impact of quality of life of different reconstructive techniques are still a matter of controversy. To broaden the criteria for choice of treatment, Svedlund and co-workers (1999) conducted a prospective randomized clinical trial to determine the impact of various gastrectomy procedures on quality of life during a 5-year follow-up period. Consecutive patients eligible for curative gastric cancer surgery were randomized to have either total or subtotal gastrectomy or a jejunal S-shaped pouch as a gastric substitute after total gastrectomy. Assessments of quality of life were made on seven occasions during a 5-year period. Survival rates were similar in all treatment groups. Patients who had a total gastrectomy continued to suffer from alimentary symptoms, during the entire follow-up period. However, patients who underwent subtotal gastrectomy had a significantly better outcome. Patients given a gastric substitute after gastrectomy improved with the passage of time and had an even better outcome in the long run. It was concluded that patients' quality of life must be taken into consideration in order to optimize the rehabilitation after gastrectomy.

Esper and coworkers (1999) conducted a descriptive comparative study to evaluate the quality of life experience in patients who are receiving treatment for advanced prostate cancer. The relationship between response to the treatment and quality of life was

investigated. Patients, who demonstrated response to therapy based on declining prostate specific antigen levels, demonstrated a significant increase in their quality of life scores compared to those patients who were not responding to treatment. Although significant differences in survival at this stage of prostate cancer, in patients who receive therapeutic treatment versus those who do not, have yet to be demonstrated, there appears to be a benefit in quality of life for those patients who respond to therapy. This data supports the use of quality of life measurements in patients undergoing treatment for advanced prostate cancer. This information can be used in discussions with patients who are facing treatment decisions and who are concerned about the impact of treatment on their overall quality of life.

Hillmann and coworkers (1999) performed a study to determine whether there is a difference, with regard to functional outcome and quality of life, between endoproshetic replacement and rotationplasty for the treatment of malignant tumors of the distal past of the femur or the proximal part of the tibia. Quality of life was measured with the European Organization for Research and Treatment questionnaire (see chapter 2 and addendum 17). A scale developed by the Muscoloskeletal Tumor Society was used to evaluate functional results. There was no statistical difference in functional scores between the two methods of treatment. Quality of life was significantly higher for hobbies and other daily activities for patients who had had a rotationplasty, who also experienced less pain restricting their daily activities. Despite good functional and quality of life results, the cosmetic appearance may be the most serious disadvantage of rotationplasty.

The quality of life of elderly patients (performance status 0 to 2) with advanced non-small cell lung cancer was explored in a randomized trial that compared vinorelbine treatment with supportive care alone. Quality of life was evaluated with the European Organization for Research and Treatment of Cancer questionnaires QLQ-C30 (see chapter 2 and addendum 17) and QLQ-LC13. Vinorelbine-treated patients scored better than control patients on quality of life functioning scales, and they reported fewer lung cancer-related symptoms but reported worse toxicity-related symptoms. It was concluded that vinorelbine improves survival of elderly (70 years and older) patients with advanced non-small cell lung cancer and possibly improves overall quality of life (Anonymous 1999).

Cruickshanks et al. (1999) attempted to determine whether quality of life differs between patients with choroidal melanoma treated with enucleation and those treated with radiation therapy. Quality of life was assessed using the Medical Outcome Study Short Form 36 (see chapter 2 and addendum 2) and the National Eye Institute Visual Function Questionnaire and by the Time-Tradeoff interview method. After adjusting for factors that could exhibit an influence, there were few differences in any of the quality of life measures by treatment status. It was concluded that choice of treatment for choroidal melanoma does not seem to be associated with large differences in quality of life during long-term follow up.

In a prospective multicenter trial, patients with metastatic colorectal cancer who had failed 5-fluorouracil therapy were randomized to receive either best supportive care plus treatment with irinotecan or best supportive care alone. Overall survival, the primary end point of the study, was significantly improved in patients receiving the irinotecan treatment. Appreciable deterioration in global quality of life (50% from baseline) occurred significantly later in the irinotecan-treated patients than in the controls. Additionally, for quality of life analyses of all symptoms, except diarrhea, mean scores were significantly in favor of patients assigned to the irinotecan treatment than for those assigned to best supportive care alone. This is the first time that the benefit of second-line chemotherapy has been demonstrated by a randomized controlled trial in advanced colorectal cancer (Cunningham 1999).

In a study by Van Cutsem (1999) patients with non-bulky metastatic colorectal cancer who had failed first-line 5-flurouracil therapy were randomized to receive second-line treatment with either irinotecan or a high-dose infusional 5-fluorouracil regimen. Patients treated with irinotecan survived significantly longer than those treated with infusional 5-fluorouracil. Overall, mean global quality of life scores were similar in the two arms of the study throughout the period of treatment and follow-up, demonstrating that the more effective disease control achieved by irinotecan at least maintains quality of life. Indeed, deterioration of quality of life (defined as > 50% decrease from baseline score) occurred significantly later in irinotecan-treated patients. In light of these data, irinotecan should be considered the reference treatment for patients with 5-fluorouracil refractory advanced colorectal cancer.

Considered during the past as a terminal condition, peritoneal carcinomatosis was approached during the last two decades as a curable disease. The introduction of cytoreductive surgery or peritonectomy in the treatment of peritoneal neoplastic diseases drastically changed the natural history of peritoneal carcinomatosis. Another technique that showed an important impact on disease control is intraperitoneal hyperthermic perfusion, one of the most fascinating treatments of peritoneal carcinomatosis, that results in an impressive increase in overall survival and quality of life in treated patients. In addition, the morbidity of intraperitoneal hyperthermic perfusion is low (Deraco 1999).

Chronic low-frequency electrical stimulation can safely transform fatiguing muscle into fatigue-resistant muscle. This fundamental discovery was used to reconstruct the anal sphincter after abdominoperineal resection for cancer. Rouanet and coworkers (1999) investigated the oncologic, functional and quality of life results of a cohort of patients who underwent the procedure. It was found to be an oncologically safe procedure and functional results improved with time. Technical progress is necessary to improve the quality of life of patients.

3.9.2 RADIOTHERAPY

Marks and coworkers (1999) assessed the cost-effectiveness of postmastectomy local-regional radiation therapy for patients with breast cancer with regard to local-regional relapse and Quality Adjusted Life Years (QALYs). Radiotherapy reduces the risk of local-regional relapse by 67%. Absolute improvements in 10-year overall survival due to radiotherapy are assumed to vary between 1 and 12%. The cost per Quality Adjusted Life Years gained at 10 years is $10 000 to $110 000 for survival benefits ≥ 3%, which compares favorably to that of other accepted medical procedures.

3.9.3 CHEMOTHERAPY

A treatment arena with potential for quality of life assessment is experimentation with granulocyte macrophage colony stimulating factors (GM-CSF) or granulocyte colony stimulating factors (G-CSF). This therapy stimulates the bone marrow to accelerate its production of granulocyte progenitors, thereby permitting high-dose cytotoxic therapy.

Neutropenia and life-threatening sepsis can be treated with the colony stimulating factors. Evaluation of the trade-off between a greater potential for cure with a higher dose of the primary drug versus the impact of the toxic effects of GM-CSF and G-CSF on patient quality of life requires feedback from the patients regarding effects of all aspects of treatment (McMillen 1989).

Advanced metastatic non-small lung cancer that has progressed on initial cisplatin-based therapy has a poor prognosis. For these patients twenty-four hour infusions of paclitaxel as second-line therapy have shown minimal activity. Prolonged infusions of paclitaxel have shown activity in breast cancer patients who have failed short infusions of paclitaxel. In this study patients with refractory non-small cell lung cancer were treated with 96-hour paclitaxel infusions. Quality of life assessments using the Factual Assessment of Cancer Therapy – Lung questionnaire were performed at baseline and with each treatment cycle. In conclusion, although no objective responses were seen, disease stabilization occurred in 31% of patients. Overall toxicity was tolerable with no major negative impact on quality of life in those patients receiving two or more cycles of treatment (Socinski 1999).

Surgical resection offers the best chance for cure for early stage non-small cell lung cancer, but the 5-year survival rates are only moderate, with systemic relapse being the major cause of death. Pre-operative chemotherapy has shown promise. A feasibility study was performed in patients with early stage (IB, II, IIIA) resectable non-small cell lung cancer; randomized either to three cycles of chemotherapy (mitomycin-C, vinblastine & cisplatin = MVP) followed by surgery or to surgery alone. Fifty-five percent achieved objective tumor response and a further 27% minor tumor shrinkage; no patients had progressive disease. No severe (WHO grade III-IV) toxicities occurred. No significant deterioration in quality of life was detected during chemotherapy. It was thus found that pre-operative MVP chemotherapy is feasible in early stage non-small cell lung cancer (de Boer 1999).

Lilleby et al. (1999) assessed morbidity, side effects and quality of life in patients treated for localized prostate cancer with curative aim. 154 Patients had undergone definitive radiotherapy and 108 patients had had a radical prostatectomy. At least 1 year after treatment the patients completed several questionnaires assessing quality of life: The European Organization for Research and Treatment of Cancer Questionnaire

(EORTC QLQ-C30), selected questions from the Psychosocial Adjustment to Illness Scale PAIS (to assess sexuality) and certain disease specific questionnaires. Despite malignancy and/or treatment-related morbidity, quality of life was comparable in both groups with respectively 9% radiation and 6% prostatectomy patients reporting moderately or severely impaired quality of life. In the mutivariate analysis physical function, emotional function and fatigue were significantly correlated with quality of life. It was found that in spite of considerable malignancy and/treatment-related morbidity, quality of life was good or only slightly impaired in the majority of patients who presented with stable disease >1 year after definitive radiotherapy or radical prostatectomy with no difference as compared to the age-matched normal population.

3.10 AS AN AID IN CLINICAL DESCISION MAKING

If survival statistics do not seem to be significantly different for several treatment procedures then one must seriously consider issues related to self-esteem and quality of life as major determinants in decisions about choice of treatment; bearing in mind a desire to conserve body integrity and sexual prowess without compromising chances for cancer cure (Schain 1980).

In the area of primary prevention it is important that quality of life investigations in cancer not only focus on the relatively small differences in quality of life between therapeutic approaches, but also consider differences in quality of life between cancer patients and individuals free of disease. Cost effectiveness is becoming increasingly important as resources are diminishing. Many countries are considering cost-effectiveness in developing national strategies to control cancer. Comparisons are being made between the extent of cancer control that can be purchased with fixed resources: prevention versus early detection versus therapy (Stjernswärd 1986). In post-apartheid South Africa, where the emphasis has shifted to favor primary medical care and resources are limited, cost-effectiveness is also at a premium in the health services.

Stjernswärd (1986) asks: "What is the difference in quality of life for patients whose cancer is detected early and easily excised as opposed to patients who present themselves at health

centers with disease in an advanced stage, where there is high morbidity with treatment, and in many cases, where only palliative therapy can be offered?"

Physicians often bear the responsibility to choose which management strategy is in the patient's best interest and must be informed about the impact of all different options on quality of life (Bernheim 1987). Incorporation of quality of life criteria has become increasingly accepted in clinical trials that test the efficacy of experimental cancer therapies. With this information, physicians and patients can approach decision-making about various treatments with a fuller understanding of their ramifications (Priestman 1976).

A landmark study, where the results of quality of life data were used to improve the quality of life of patients, is the study of Sugarbaker (1982). The study found that radiotherapy for soft-tissue sarcoma was impairing the mobility and sexual functioning of the patients. The patients' quality of life responses led to their treatment being optimized. As a result of this, a great improvement has occurred in the functional outcome of the patients. These results have provoked changes in radiotherapy, surgical procedures and physical therapy for soft-tissue sarcoma patients.

Quality of life assessments can therefore improve medical outcomes and lead to improvements in medical care (Barofsky 1986).

Quality of life information is of crucial importance in optimizing cost-benefit balances in clinical decision making (Coates 1992).

Metastatic breast cancer is not curable, but it is perhaps the most common cancer situation in which reasonable effective systemic therapy is available. Endocrine treatment is generally preferred initially, if the patient does not have dire disease, because of significantly less toxicity. Coates (1992) found that at least in some situations, the use of cytotoxic chemotherapy results in a net improvement in quality of life and that more therapy may be better than less. A similar conclusion was reached in a Canadian trial in metastatic breast cancer, one in which a reduced dosage of chemotherapy was associated with inferior objective and subjective outcomes (Tannock 1988).

Decision making in health care depends on accurate and appropriate assessment of the current status of the patient and of the impact of available therapeutic options on both the progress of the disease and the wellbeing of the patient. The net effect on the patient depends on the balance between the good the treatment may do in controlling the disease and the harm it may do by way of side effects. This balance is struck explicitly or implicitly whenever a decision is made to give or withhold a treatment. Tumor response can be categorized by means of the standard tools for tumor response. Assessment of the effect of a treatment on the tumor, in terms of response, is thus made routinely, although these tumor measurement tools are far from perfect (Coates 1992a).

The responsiveness of quality of life instruments becomes important in this context. One aspect of this effort is to determine how well quality of life measures distinguish between different regimens. A litmus test for quality of life measures will be how well they discriminate among regimens not so obviously different (Levine 1988).

QOL tools now available for assessing the impact of therapy on patients are solidly established and robust. The latest QOL instruments are arguably more directly relevant to the evaluation of the ultimate goals of therapy and demonstrably more valuable than either response or performance status in assessing prognosis. Now that simple practical scales are available, there is a strong case for their introduction into routine clinical practice. This would ensure that the level of treatment chosen is in the best interests of the patient (Coates 1992a).

In patients with ovarian cancer, quality of life is defined by the severity of the disease. In early stage disease, patients focus on the long-term effects of therapy, whereas in late-stage disease, symptom management is paramount. The chemotherapeutic agents used to combat ovarian cancer have a wide range of adverse effects, the management of which is key to ensuring a patient's quality of life. The Functional Assessment of Cancer Therapy questionnaire for ovarian cancer (FACT-O) is a short questionnaire grouped by logical categories that can be completed by most patients without assistance within 5 minutes. Furthermore, the FACT-O allows patients to weigh each category of questions based on the categories' perceived importance to the quality of the patients' lives. These two factors

allow the FACT-O to be used to institute management decisions on the level of both the individual patients and the institution (Fish 1999).

3.11 TO HELP FORMULATE HEALTH POLICY

3.11.1 GENERAL

The availability of reliable quality of life assessment methods would be very important as a tool to help convince health policy makers to set the right priorities in cancer care and to establish proper resource allocation. Results from valid quality of life measures could lead to important changes in cancer control policy in several situations: from primary prevention, early diagnosis, screening and therapy, to pain relief and care of the dying (Stjernsward 1986).

The overwhelming majority of resources for cancer are allocated to finding a cure. For most cancer patients, however, no curative treatment exists. The quality of life in these patients would be better if they had access to palliative care from the start. The WHO global cancer control program is based on the concept that enough knowledge exists today about cancer to take effective action that will significantly reduce cancer morbidity and mortality worldwide, if properly implemented. There is an urgent need for rethinking. Global resources are limited as well as unequally distributed and it is not realistic to expect them to increase in the near future. Setting the right priorities and strategies in a systematic way to gain maximum benefit from available resources, preferably through well-conceived cancer control programs, has become mandatory. Without doing so, there can be little impact on cancer, especially in the less developed countries (Stjernswärd 1991).

A number of countries are now beginning to consider cost-effectiveness in developing national strategies to control cancer. Comparisons are being made between the extent of cancer control that can be purchased with fixed resources: prevention vs. early detection vs. therapy vs. palliative care. Quality of life comparisons should be made between people without cancer and those with it and early-stage versus advanced-stage cancer patients. Unfortunately, the majority of the world's cancer patients fall into the large group where no effective therapy exists and only palliative treatments can be offered. There is a need for

quality of life studies to investigate the appropriateness of palliative care, rather than the administration of therapies that are known to be ineffective and are often given simply because the physician feels that he must provide some therapy for every patient. Such studies could provide the physicians and the patients with a suitable basis for making the most appropriate treatment decisions (Stjernswärd 1991).

Results from reliable and valid quality of life measures could lead to important changes in cancer control policy (Stjernswärd 1991).

Health status measures may be used to formulate health policy by providing information about the health status of populations, to evaluate innovations in health service delivery (e.g. shortened length of hospital stay) and in clinical research to evaluate new therapies. Ultimately the measures are intended to help improve the care and health of individuals (Bergner 1989).

Intensive care (ICU) is increasingly being used in the management of cancer patients. It is important that a disproportionate share of special care resources is not expended on the futile care of terminally ill patients. A requirement for mechanical ventilation has been stated to affect survival in cancer patients. In a study by Kongsgaard and Meidell (1999) the ICU mortality in oncologic patients was 63%. Their results indicate that this treatment modality should not generally be restricted in critically ill cancer patients. The quality of life of the patients who survived should be of interest to those involved in further medical and ethical decisions concerning the level of care in the ICU.

Women with HIV infection have a higher risk for cervical squamous intaepithelial lesions than do women without HIV infection and the optimal regimen for cervical cancer screening in these women is uncertain. Goldie and co-workers (1999) assessed the net health consequences, costs and cost-effectiveness of various screening strategies for cervical neoplasia and cancer in HIV-infected women. They measured quality-adjusted life years (QALYs), lifetime costs and incremental cost-effectiveness. They found that in HIV-infected women, cervical cancer screening with annual PAP smears after two negative smears obtained 6 months apart offers quality-adjusted life expectancy benefits at a cost comparable to that of other clinical preventive interventions.

3.11.2 QUALITY ADJUSTED LIFE YEAR (QALY)

Although quality of life is often measured, interpretation of these outcomes in relation to mortality is difficult. Survival analysis places each individual in one of two categories: alive or dead. Among those alive, all individuals are considered equivalent. Thus, a patient confined to bed with severe symptoms is scored the same as someone who is active and asymptomatic. A General Health Policy Model is proposed as a solution to this problem. The model adjusts life expectancy for diminished quality of life, which is measures using a standardized instrument known as the Quality of Well-Being (QWB) scale. The model expresses the effect of treatment in a unit known as a Well-Year or Quality Adjusted Life Year (QALY). These units integrate side effects and benefits of treatment by combining into a single number, mortality, morbidity and duration of each health state. Similar methods, such as Q-TWiST, have been proposed for use in cancer clinical trials. However Q-TwiST is a subset of the more general model and carries limitations for cross-disease comparisons. The general health outcome model can be of considerable value for analyzing the costs, risks and benefits of cancer therapies (Kaplan 1993).

3.11.2 QUALITY-ADJUSTED TIME WITHOUT SYMPTOMS AND TOXICITY (Q-TwiST)

The effectiveness of cancer treatments is often expressed in terms of disease-free survival or overall survival, relative risk reduction or odds ratios and the quality of life effects are often assessed separately from survival. Such end points and summary measures may be inadequate, however, for comparing two treatments in terms of their palliative effects because there is a trade-off between treatment toxicity and increased disease-free interval. Furthermore, this trade-off may depend on individual patient preferences and prognostic situations. Gelber (1993) describes a method for evaluating the effectiveness of cancer treatments in terms of palliation by simultaneously considering both quality and quantity of time following treatment so that therapeutic choice may be determined according to patient preferences on quality of life and prognostic situation. Gelber's method is an extension of the Quality-adjusted Time Without Symptoms and Toxicity (Q-TwiST) method for comparing treatment effectiveness in clinical trials of adjuvant therapies.

3.12 SCREENING

Screening has been shown to reduce cancer mortality. The possible negative effect on quality of life for screening approaches is overruled by the positive effect on survival. The negative effects on quality of life caused by screening methods not proven to be effective are a matter of concern (Stjernswärd 1986). Again cost-effectiveness within the framework of limited resources must be considered and quality of life studies can provide additional, valuable information as an aid to decision making about screening procedures.

3.13 QUALITY OF LIFE IN THE ADJUVANT SETTING

Adjuvant treatment for breast cancer may be associated with considerable early toxic side effects, while treatment benefits may accrue only after long follow-up periods. In order to improve assessment of the cost-benefit balance, the International Breast Cancer Study Group (IBCSG) is developing a model of treatment evaluation which incorporates the traditional endpoints (disease-free and overall survival), the toxicity and disease variables rated by physicians, but also "subjective" aspects of quality of life rated by patients (Bernhard 1997).

Because the survival benefit of adjuvant treatment so far achieved is modest, it can best be studied in large-scale randomized clinical trials. To assess the impact of adjuvant therapy in this particular setting, a quality of life measurement approach must meet the following criteria (Bernhard 1997):

1. It has to be applicable within clinical routine, taking into account the complex logistics of large-scale and especially international trials. This means that the measures must be simple, focussing on the specific trial endpoints.
2. The measures need to meet the standard psychometric criteria of reliability and validity. The measures need to be especially responsive to differences among a variety of adjuvant treatment regimens and to changes in the course of the disease.
3. In many cases these trials involve multiple cultures and countries. The measures therefore need to be cross-culturally equivalent.

In comparative clinical trials, the *difference* in quality of life between treatments is of primary interest.

3.14 PALLIATIVE CARE

In the palliative care setting a precise definition of the goals of treatment is likely to result in clinical interventions which are economical, more tailored to the patients' needs, and which could lead to an improvement of the relationship between patients and physicians and may even influence the validation of medical services (Porzsolt 1993). The development of strategies requires the definition of goals. Weak strategy leads to poor adherence to protocols and poor compliance. Both non-adherence and non-compliance are significant problems in oncology (Schleifer 1991).

Definitive curative therapy certainly overrides most quality of life questions. However, quality of life becomes important if there is more than one curative therapeutic strategy or if the therapy is not always curative. A major problem in global cancer control is that the majority of patients are found with an advanced stage of disease at the time of diagnosis. Most clinical trials today compare the quantity of survival, not the quality of survival. Mostly the only aspects of quality of life that are reported by investigators, are toxicities and complications (Stjernswäard 1986).

In the palliative care setting, quality of life and health status are the primary outcomes of the treatment. The interventions mostly have substantial impact on everyday functioning and sense of well being.

Even when the cancer is too advanced to be cured, palliative treatment can often achieve worthwhile results. The following aims may be attained by palliative treatment:

- Symptom relief.
- Preventing future symptoms, which may develop.
- The prolongation of life.

Palliative treatments should not be worse than the symptoms they are intended to control. Doses should be kept at the lowest effective level, to minimize side-effects, and regimes kept simple to avoid repeated treatment sessions (Barraclough, 1994).

3.15 SYMPTOM PALLIATION

The assessment of symptom palliation is an essential component of many treatment comparisons in clinical trials, but Stephens et al. (1999) found no consensus as to its precise definition. They attempted to define and analyze symptom palliation in cancer clinical trials. Their findings emphasize the need for caution in interpreting results and the importance of working towards a standard definition of symptom palliation. The current lack of specified criteria makes analysis and interpretation of trial results difficult and comparison across trials impossible. A standard definition for use in the analysis of clinical trials is proposed, which takes into account aspects of onset, duration and degree of palliation, and symptom improvement, control and prevention.

3.16 ACTIVE SUPPORTIVE CARE

In the palliative setting, the very important question arises of whether to treat with aggressive therapy, or not. This is an area where quality of life studies can play a crucial role. Studies where treatment versus best supportive care are examined, must investigate the quality of life of the patients intensively, as might supply the supporting evidence in favor of a specific approach (Stjernswärd 1986).

How are a few months of life prolongation with therapy at high cost and side-effects to be evaluated, if during this time the patient has no enjoyment of life and may suffer pain, despair and isolation from her family? Given reliable documented information on what can be expected, either choosing aggressive treatment or active supportive care, physicians and patients could make this difficult decision on a more rational basis (Stjernswärd 1986).

3.17 QUALITY OF LIFE ON DIFFERENT TREATMENT REGIMENS

3.17.1 INTRODUCTION

QOL measures have been used mostly to compare treatments.

Multitudes of clinical trials are undertaken where the aim is to prove the superiority of one treatment regimen (or single agent) to another. Trials of this nature can only be interpreted meaningfully if quality of life evaluations are included in the primary study design.

Coates (1992) has used QOL measures to compare treatment strategies.

A study was designed to investigate the personal experience of patients with nonmetastatic breast cancer, who were treated with the concurrent administration of radiotherapy and chemotherapy (mitoxantrone and cyclophosphamide) in terms of side effects and quality of life. Quality of life was measures by the European Organisation for Research and Treatment of Cancer QLQ-C30 and pain was measures by a visual analogue scale (VAS). Multidimensional quality of life assessment showed that treatment mainly affects physical functioning and global quality of life. Multivariate analysis showed that the main determinants of quality of life at the end of treatment were fatigue, pain and loss of appetite experienced during treatment. The concurrent administration of chemotherapy and radiotherapy deteriorates patients' quality of life but in a proportion similar to sequential administration while presenting the advantage of a shorter duration of treatment (Macquart-Moulin, 1999). The incorporation of quality of life measures enables the people involved to undertake a more informed therapeutic decision-making analysis.

3.17.2 RADIOTHERAPY

Bone is a common site for metastatic carcinoma. Bone metastases occur in about half of advanced breast cancer patients. Pain is the usual presenting symptom, for which radiotherapy is undoubtedly an effective treatment. Although the value of palliative irradiation for bone pain has been recognised for over half a century, the optimum dose and fractionation schedules remain controversial. Gaze (1997) compared the efficacy, side effects and effect on

quality of life of two commonly used radiotherapy schedules in the management of painful bone metastases. In a prospective trial patients were randomised to receive either a single 10 Gray treatment or a course of 22.5 Gray in five daily fractions for the relief of localised metastatic bone pain. There were no statistically significant differences in response rates or median duration of pain control. There were no differences between the groups in the effect of treatment on a variety of quality of life parameters.

3.17.3 CHEMORADIOTHERAPY

List and co-workers (1999) prospectively evaluated performance and quality of life in advanced stage head and neck cancer patients on a curative-intent, concomitant chemo-radiotherapy regimen aimed at improving loco-regional control, survival and quality of life. The regimen consisted of twice-daily radiation, fluorouracil, hydroxyurea and cisplatin. Patients were assessed before, during and at 3-month intervals after treatment with the Functional Assessment of Cancer Therapy – Head and Neck (FACT-HN) and patient-reported symptoms (McMaster University Head and Neck Radiotherapy Questionnaire). The data supports the feasibility of intense chemo-radiation as primary treatment for advanced head and neck cancer. Results confirm acute toxicity but indicate that many of the treatment-related performance and quality of life declines resolve by 12 months.

3.17.4 HORMONAL MANIPULATION

Sex hormone manipulation is commonly used in the treatment of breast cancer. Removal of ovaries, medication to block sex hormone function, or administration of hormones of the opposite sex, is among the procedures used. The psychological consequences of amenorrhoea, growth of body hair, and deepening of the voice in women are naturally distressing. Fortunately tamoxifen which is now the standard frontline treatment for hormone-dependant breast cancer is relatively free of such effects (Barraclough 1994).

Simons (1996) investigated the effects of medroxyprogesterone acetate on appetite, weight and quality of life in patients with advanced-stage, incurable, non-hormone-sensitive cancer. Patients were randomised between double-blind medroxyprogesterone acetate 500 mg twice daily or placebo. A beneficial effect of medroxyprogesterone acetate on appetite was

observed. A mean weight gain was seen in the medroxyprogesterone group, versus an ongoing mean weight loss in the placebo group. This difference was statistically significant. During the study, several areas of quality of life (measured with the EORTC QLQ-C30) deteriorated in the total group of patients. With the exception of an improvement in appetite and possibly also a reduction in nausea and vomiting, no measurable beneficial effects of medroxyprogesterone acetate on quality of life could be demonstrated. It must be remembered that these are patients with end-stage cancer, where the cancer has already induced metabolic wasting of the patient and the opportunity for improving quality of life is very small. The side effect profile of medroxyprogesterone acetate was favourable: only a trend toward an increase in (usually mild) peripheral edema was observed.

In breast cancer patients, once the disease spreads, 70% of these patients will eventually develop clinically manifest bone metastases. Therefore, breast cancer patients with extraskeletal metastatic disease and patients with locally advanced disease are at high risk of suffering during their limited survival time, from impairment of their quality of life due to events of skeletal morbidity such as bone pain, pathological fractures and hypercalcaemia (van Holten-Verzantvoort 1996). In previous studies van Holten-Verzantvoort and others have shown that long-term supportive bisphosphonate treatment significantly reduces skeletal morbidity in patients with breast cancer and established bone disease (Elomaa 1983; Paterson 1993; van Holten-Verzantvoort 1987), and improves selective aspects of quality of life (van Holten-Verzantvoort 1991). Koeberle and co-workers (1999) demonstrated that bone pain could be effectively reduced by repeated pamidronate infusions in patients with advanced osteolytic bone disease.

Hortobagyi (1996) conducted a phase III clinical trial comparing pamidronate disodium to placebo in breast cancer patients with bone metastases. Quality of life was one of the important aspects of the trial. The Spitzer Scale (see chapter 2 and addendum 18), ECOG performance status, evaluation of bone pain and the use of analgesics were included in the analysis. Changes from baseline in these parameters were compared between groups by the Wilcoxon rank-sum test. There were no differences between the two groups in the use of analgesic drugs or quality of life scores. There was significantly less increase in bone pain and deterioration of performance status in the pamidronate group than in the placebo group. Pamidronate was well tolerated.

Toxicity of treatment is of great importance when palliation is the objective. In a study by van Holten-Verzantvoort (1996) the occurrence of nausea and vomiting, and stomatitis in one case, was attributed to pamidronate treatment resulting in withdrawal from the study. Primary gastrointestinal intolerance does occur, usually within weeks after the start of treatment. In contrast to these clinical findings, the quality of life survey did not detect a difference in the level of gastrointestinal complaints between pamidronate and control patients.

3.18 FOR OVERALL PATIENT BENEFIT

The identification of the effects of therapy on quality of life both in the short and long term may be of value. This is particularly relevant for the evaluation of long term survivors of cancer. Measurement of quality of life may also be of value even if cure is not possible. For example, the quality of life of a patient may be the most important end point in the context of palliative care (Jenney 1998).

During the development of the Life Evaluation Questionnaire (LEQ) a number of patients commented on the opportunity that it provided to express concerns that were normally unexpressed (Salmon1996).

Epstein et al. (1999) investigated quality of life and oral function following radiotherapy for head and neck cancer. They found that oral complications following radiotherapy for head and neck cancer are common and affect quality of life. Use of a general function scale such as the European Organization for the Research and Treatment of Cancer questionnaire (EORTC) with the addition of disease/site specific scales may provide useful data on outcome of therapy and upon the complications associated with therapy and impact upon the quality of life.

3.19 CONCLUSION

There are several important reasons why the quality of life of patients should be measured accurately in the medical field:

- The identification of problems that are particular to the specific field of medicine, so that these problems can be ameliorated.
- Quality of life assessments can be useful in making medical treatment decisions and it can be used as an outcome measure in clinical trials. It is important to demonstrate in cancer patients that the palliative treatment is not more harmful than the disease itself, particularly when survival rates are disappointing and the treatments are increasingly toxic.
- It can be usefully employed in the health policy field where standard units are used to compare the different impact of chronic diseases and to assess the cost-effectiveness of interventions. Reliable quality of life assessments are helpful in calculating the direct and indirect cost of illness.

Interest in the measurement of quality of life has dramatically increased over the last six years. The patients' perspective is increasingly being recognized as the most important component in medical treatment and care. However, the inadequacy of reporting quality of life data in the medical literature has been highlighted on numerous occasions recently. Problem areas that have been identified are:

- There is a lack of clarification as to what is being measured?
- Why is it being measured?
- Is the measure valid?

It is obviously desirable to have a standard approach and common measuring instruments. There are however, so many different measures to be found that it becomes almost impossible to make progress in the field. Many instruments have unknown psychometric properties and cannot usefully be compared to some of the more standard measures. Even for a well-known and often used instrument norms generally are non existent. It is therefore important not to develop new measures but to choose among the existing instruments with an eye to brevity and simplicity as well as established reliability and validity.

3.20 BIBLIOGRAPHY

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CHAPTER 4: MATERIALS AND METHODS

4.1 INTRODUCTION

Metastatic breast cancer is almost always incurable with standard chemotherapy, utilized either as a single agent or in combination. No new combination of agents has shown significantly greater activity than a variety of Adriamycin-containing combinations first used in the mid - 1970's. Variations in dose and schedule have had little impact on long-term survival in patients with metastatic breast cancer.

It must also be borne in mind that the aim of treatment in the metastatic setting is palliative rather that curative. Therefore it becomes imperative to examine the impact of treatment for metastatic breast cancer on the overall quality of life of the patient.

This study provides an opportunity to address several important quality of life issues. It allows us to examine and compare the quality of life of patients receiving therapies that differ significantly in toxicity, i.e. chemotherapy, chemo-hormonal therapy or hormonal therapy. Treatments for any line of locally advanced or metastatic disease were included, whereas the current studies on quality of life only analyze specific time-spans, mostly of front-line treatment. Salvage therapy for metastatic breast cancer has been almost exclusively studies in small Phase II trials which have not evaluated quality of life (Petru 1987). The other very important aspect is the unique opportunity to compare the quality of life of different ethnic groups in South Africa. Quality of life comparisons will be drawn between white and black patients.

The quality of life measure to be used is the **F**unctional **A**ssessment **C**ancer **T**herapy–**B**reast Cancer (FACT-B) see Addendum 3. It is a multidimensional and disease specific instrument. The FACT-B has a 29 item generic core plus10 items that are specific for breast cancer patients. Patients rate all items on a 5-point rating scale ranging from "not at all" to "very much". The FACT-B provides a total QOL score as well as information about physical well being, social/family well being, relationship with the doctor, emotional well

being, functional well being and disease-specific concerns. The FACT-B has been demonstrated to have sufficient reliability, validity and sensitivity to change over time.

The Functional Assessment of Cancer Therapy for breast cancer (FACT-B) scale was chosen as the measurement instrument for the study, because:

- The instrument has already been proven to have sound psychometric properties.
- Experience in its utilization had already been established through previous work with the FACT-B.
- FACT-B is a self-report measure that nearly all patients with a sixth grade reading level can quickly and easily complete without assistance.
- FACT-B is reliable and valid and appears responsive to changes in health status over time.
- Translations of FACT-B into Zulu, Pedi and Tswana, the three most common black languages in South Africa are available (Mullin 99).
- It is widely used worldwide in clinical research involving QOL issues.

4.2 OBJECTIVES

When a person is diagnosed with cancer, it necessarily has an impact on their quality of life. Additionally the treatment of cancer will change their quality of life. Differences in ethnicity will lead to the impact of disease and treatment to be different. This hypothesis will be tested by means of the following objectives:

1. Are there differences in quality of life at different time-points, i.e. before therapy, during therapy or after therapy?
2. Are there quality of life differences between patients receiving chemotherapy, hormonal therapy, chemo-hormonal therapy, radiotherapy or patients who are on observation?
3. Are there differences in the quality of life of different ethnic groups, with specific regard to the individual quality of life domains?

4.3 SELECTION OF PATIENTS

- Histologically confirmed Stage III B (inoperable) or Stage IV adenocarcinoma of the breast with manifestations of progressing regional or metastatic cancer (See Table 7: AJCC Staging of Breast Cancer).
- Female patients above 18 years of age.
- Within the frame of inoperable Stage III or IV disease, any patient is eligible, irrespective of treatment line, or treatment type.
- Patients with Stage III or IV disease in complete remission are eligible.
- Written informed consent obtained (See Addendum 2 for Model Informed Consent Document).

4.4 INTRODUCTION TO THE FACT SCALES

The **F**unctional **A**ssessment **C**ancer **T**herapy (FACT) scales have been under development since October 1987 (Cella 1987) and are copyrighted. Written permission for its use was obtained from:
Dr. David Cella, Rush–Presbytarian-St. Luke's Medical Center, Chicago, Illinois, USA.

The FACT scales are self-report measures of quality of life in people with cancer and HIV infection. Nearly all patients with a sixth grade reading level can easily complete them without assistance. There are currently twelve Cancer-specific scales (see table 1), eleven of which are disease-specific extensions of the 29-item general version (FACT-G) and include items relevant to that particular disease (Cella 1994). Versions of the FACT are listed below in Table 1:

TABLE 1: AVAILABILITY OF FACT CANCER-SPECIFIC SCALES

FACT-G	A General version of the scale which can be used with patients of any tumor type, and which constitutes the core of the following disease-specific scales:
FACT-B	For Breast cancer patients
FACT-BL	For BLadder cancer patients
FACT-Br	For Brain tumors
FACT-C	For Colorectal cancer patients
FACT-CNS	Cancer in the Central Nervous System
FACT-Cx	For Cervical (Cx) cancer
FACT-E	Esophageal cancer
FACT-H&N	For Head and Neck cancer patients
FACT-L	For Lung cancer patients
FACT-O	Ovarian cancer
FACT-P	Prostate cancer
FACT-Pa	Pancreatic cancer

There are 29 Likert-type items, which comprise 5 sub scales common across all seven measures (FACT-G). The number of items specific to the cancer site varies from 9 to 12 (see table 2).

One additional item at the end of each sub scale asks respondents to rate how much that particular aspect of life (e.g., physical well being, social/family well-being etc.) affects his or her quality of life. These ratings are made on a 0 - 10 scale where "0" corresponds with "not at all" and a "10" corresponds with "very much so". These items are currently experimental and may ultimately be used to weight sub-scale scores. For now, unweighted scores are used, so these particular items are nor used in either the sub-scale scores or in the overall quality of life score.

TABLE 2: THE SIX SUB-SCALES OF THE FACT QUESTIONNAIRES

1. Physical Well-being	7 items
2. Social/Family Well-being	7 items
3. Relationship with Doctor	2 items
4. Emotional Well-being	5 items (version 2) 6 items (version 3)
5. Functional Well-being	7 items
6. Additional concerns	9 items for FACT-B thus total items=37 for version 2 thus total items=38 for version 3

Format of version 3: The FACT-G is now comprised of 29 items due to the addition of one item to the Emotional Well-being subscale. However, this item is not scored in FACT version 3. All other items, including the additional 6 experimental items have been retained.

The FACT scales are designed for patient self-administration, but can also be administered as an interview. For self-administration, patients should be instructed to read the brief directions at the top of the page. After the patient's correct understanding has been confirmed, he/she should be encouraged to complete every item in order without skipping any, except where directed (e.g., item 15). For interview administration, it is helpful to have the patient hold a card on which the response options have been printed. Data is available from Dr. Cella as to the comparability of interview and written methods.

It is important that the questionnaire is administered before being influenced by any "news" that the physician may have and also before the administration of chemotherapy. The patient should also be alone in a room, or in the case of an interview, with only the interviewer present. This is because the presence of friends or family members could influence certain answers, especially on items such as "sex life".

When the FACT scale is administered as an interview, it is extremely important not to influence the patient in any way. The patient must know that there are no "right" or

"wrong" answers and that participation or response to the questionnaire, will not influence the patient's treatment or management in any negative way.

The FACT-B was available to patients in any of the following languages:

FACT-B PEDI	(see Addendum 5).
FACT-B ZULU	(see Addendum 7).
FACT-B TSWANA	(see Addendum 6).
FACT-B ENGLISH	(see Addendum 3).
FACT-B AFRIKAANS	(see Addendum 4).

4.5 TRANSLATION PROCEDURE FOR THE FACT–B INTO AFRIKAANS

- Identification of source (original document). The FACT-G and one disease-specific subscale for breast cancer was identified as the original document to be translated into Afrikaans an indigenous South African language.
- All items were checked for redundancy so that the smallest possible number of items was translated.
- A list of all items was prepared for submission to the translators.
- Identification of bilingual translators.
- All translators were required to be native speakers of the target language (i.e. the language FACT was being translated into), and to be fluent in English.
- Forward translation by two independent persons.
- Translators were instructed to consider that the items on the FACT attempt to measure physical and psychological states of health and well being and that these states can be somewhat abstract. Therefore, translators were asked to focus on capturing the essential content (meaning) of the question rather than performing an exact (literal) translation.
- Translators were also instructed to use simple, straightforward language rather than to use phrasing that might be more precise but difficult for less educated patients to comprehend.
- The result of this was the creation of two separate forward translations of the FACT-B.
- The forward translations were reconciled and discrepancies were resolved.

- The most culturally relevant way of stating the translated questions was chosen and a reconciled version, which combined input from the two forward translations, was constructed.
- After deliberation the reconciled version was back translated.
- Investigator review. An independent bilingual health professional was asked to review the following documents to ensure consistency and cultural relevance:
  1. source document (original)
  2. reconciled forward translation and
  3. back translation.
- The investigator was asked to consider simple, straightforward translations of each item.
- It was stressed that all translations should be culturally meaningful to members of that particular culture. Special emphasis was placed on creating a document that could be applied to members of all educational levels.
- The reviewer had not seen the documents before.
- All reviewer comments were sent back to Pretoria Academic Hospital's Oncology Centre.
- Reconciliation of reviewer comments and the translated documents.
- Additional input from the reviewer along with the comparison of all documents permitted us to arrive at a final translation.
- Final check.
- The FACT-G and the disease-spesific subscale (for breast cancer) items were compiled in questionnaire form.
- The Afrikaans FACT-B was given to a few independent persons for final approval.
- Validation was performed during the final statistical analysis.

PERSONS INVOLVED WITH THE TRANSLATION

IJ Ueckermann MAPhil.
Tel: (H) 043-7484255

MS Mertz MSc.PHARM
Tel: (W) 3541399 (H) 6542320

Dr. C Dicks MMed(Rad)
Tel: (W) 341 3502 (H) 329 0214

4.6 TRAINING OF INTERVIEWERS

- As the majority of the black patients attending the Oncology Unit are currently illiterate, nursing staff of Pretoria Academic Hospital Department of Medical Oncology were approached to assist with the administration of the FACB-B as interviews. These were the FACT-B translations into the most prevalent ethnic languages found in South Africa, namely Pedi, Tswana and Zulu.
- Nurses who are fluent in each of these languages were identified and trained to administer the FACT-B.
- They were introduced to the concept of quality of life and the FACT-B. The important steps in the administration of a quality of life instrument as an interview was taught to them (as described in 4.4).
- During the course of the project, two more training sessions were held.
- When problems were encountered, the interviewere had to clarify the problem with the researcher.

4.7 SCORING OF THE FACT-B

The FACT-B scale description is given in table 3. Refer to table 4 for a FACT-G scoring guide. The scoring guide identifies those items, which must be reversed before being added to obtain subscale totals. Items are reversed by subtracting the response from "4". After reversing proper items, all subscale items are summed to a total, which is the subscale score (Cella 1994). The FACT-B score is obtained by adding the Additional concerns subscale total to the FACT-G total.

4.7.1 HANDLING MISSING ITEMS

If there are missing items, subscales can be prorated. This is done by multiplying the sum of the subscale by the number of items in the subscale, then dividing by the number of items actually answered. This can be done directly on the scoring guide (Table 4).

When there are missing data, prorating by subscale in this way is acceptable as long as more than 50% of the items were answered. The total score is then calculated as the sum of the unweighted subscale scores. The FACT scale is considered to be an acceptable indicator of patient quality of life as long as overall item response rate is greater than 80% (i.e. at least 23 of 28 FACT-G items completed). This is not to be confused with individual item response rate, which allows a subscale to be prorated for missing items if greater than 50% of items are answered (Cella 1994).

4.7.2 SCORING THE SPECIFIC FACT-B SCALE

The total score for the specific FACT Scales is the sum of the FACT-G (the first 5 subscales common to all scales) plus the "Additional Concerns" subscale. Again, over 50% of the items (i.e. 5 of 9 items) must be completed in order to consider the subscale valid.

For the "Additional Concerns" subscale (i.e. disease-specific questions), a scoring guide is incorporated at the end of table 4. The procedure for scoring is the same as described above for the FACT-G. By following this scoring guide and transcribing the FACT-G score, the two totals can be summed to derive the TOTAL FACT SCORE. The translated versions can be scored in exactly the same way (Cella 1994).

4.7.3 A NOTE ON SELECTING SCORES FOR ANALYSIS

These scoring templates allow one to obtain two different total scores in addition to each individual subscale score. The FACT-G total score provides a useful summary of overall quality of life across a diverse group of patients. The disease-specific questionnaire total scores (i.e. FACT-G plus disease-specific subscale score) may further refine the FACT-G summary score. However two alternative approaches are noteworthy: One is to seperately analyze the FACT-G total score and the disease-specific subscale score. Another is to select subscales of the FACT which are most likely to be changed by an intervention being tested. For example, the Physical, Functional and Disease-specific subscales would be most likely to change in a chemotherapy clinical trial. On the other hand, the Emotional or Social

Wellbeing subscale would be expected to change most when evaluating a psychosocial intervention (Cella 1994).

TABLE 3: FACT-B SCALE DESCRIPTION

FACT-B scale	Number of items	Highest possible score
	28 general 9 specific (6 experimental)	37 x 4 = 148

TABLE 4: FACT-G SCORING GUIDE (UNWEIGHTED) INCORPORATING THE ADDITIONAL CONCERNS OF THE FACT-B

1. Record answers in "item response" column.
2. Perform reversals as indicated to obtain "item scores".
3. Multiply the sum of the item scores by the number of items in the subscale, then divide by the number of items answered. This produces the subscale score.
4. Add subscale scores to derive total score.

Subscale	Item Number	Reverse?	Item Response		Item Score	
Physical Well Being	1	4 -		=		
	2	4 -		=		
	3	4 -		=		
	4	4 -		=		
	5	4 -		=		
	6	4 -		=		
	7	4 -		=		
Sum Item Scores → [___] x 7 ÷ [___] =[___] **Enter number of items answered** _____ ↑						
Social/ Family Well Being	9	4 -		=		
	10	0+		=		
	11	0+		=		
	12	0+		=		
	13	4 -		=		
	14	0+		=		
	15	0+		=		
Sum Item Scores → [___] x 7 ÷ [___] =[___] **Enter number of items answered** _____ ↑						
Relationship With Doctor	17	0+		=		
	18	0+		=		
Sum Item Scores → [___] _____ →[___]						

Continued on the next page

Subscale	Item Number	Reverse?	Item Response		Item Score	
Emotional Well Being	20	4 -		=		
	21	0+		=		
	22	4 -		=		
	23	4 -		=		
	24	4 -		=		
Sum Item Scores → [___] x 5 ÷ [___] =[___]						
Enter number of items answered _____ ↑						
Functional Well Being	27	0+		=		
	28	0+		=		
	29	0+		=		
	30	0+		=		
	31	0+		=		
	32	0+		=		
	33	0+		=		
Sum Item Scores → [___] x 7 ÷ [___] =[___]						
Enter number of items answered _____ ↑						

Sum of SUBSCALE Scores = FACT-G TOTAL SCORE → [___]

Subscale	Item Number	Reverse?	Item Response		Item Score	
Additional subscale	35	4 -		=		
	36	4 -		=		
	37	4 -		=		
	38	0+		=		
	39	4 -		=		
	40	4 -		=		
	41	4 -		=		
	42	4 -		=		
	43	0+		=		
Sum Item Scores → [___] x 9 ÷ [___] =[___]						
Enter number of items answered _____ ↑						

Enter FACT-G score → [___]

Add to get TOTAL FACT-B SCORE → [___]

4.8 METHOD FOR COLLECTION OF THE FACT-B

- Eligible patients were identified by screening.
- Patients were approached and the study was introduced to them.
- Informed consent was signed.
- The FACT-B was explained to the patient and the patient was given the option to either complete the questionnaire on her own or alternately the questionnaire was administered as an interview.
- The FACT-B was completed in a quiet area, before the physician had seen the patient. The patient was on her own, as family memebers of friends might have influenced her responses.
- If the Fact-B was conducted as an interview as is the case for illiterate patients, great care was taken not to influence the patient's answers in any way.
- The completed FACT-B was checked for missing items or items with more than one response and the patient was asked to clarify her answers.
- Follow-up administrations of the FACT-B were scheduled. The FACT-B was given to the patients at basline, during treatment (as close as possible to day 1 week 16 when maximum toxicity and response would be expected) and after treatment.
- The baseline database for each patient was completed with the aid of all the relevant clinical and demographic information. This included the Hospital classification, which is an indication of the patient's financial status (see Addendum 8). Baseline sociodemographic data was entered into an Exel spreadsheet.

4.9 VALIDATION OF THE FACT-B TRANSLATIONS

English speaking patients completed the original FACT-B that had previously been validated for North American breast cancer patients (Brady 1997). The validity of the FACT-B for South-African patients, where cultural differences might influence the composition of the FACT-B, was calculated. This was even more important because of the cultural diversity that was found in the sample group, namely Pedi, Zulu, Tswana,

Afrikaans and English patients. An analysis was done using the STATA Release 6 (1999) statistical package, to validate the FACT-B for the South-African breast cancer population.

Initial validations were done for the tranlations of the FACT-B (Mullin 1999) that were already available in the three most common indigenous black languages, namely Pedi, Tswana and Zulu. Chrohnbach's alpha was calculated for each separate domain and for the total FACT-B score. An alpha value of 0.7 or higher suffices and is indicative of modest reliability.The alpha values that were obtained, were compared to the validations of Mullin (1999). Mullin's validations were for a "mixed" cancer group and specifically for the FACT-G core questionnaire. Validation for the Afrikaans FACT-B was done in the same manner, but comparisons could not be made, because no other validated Afrikaans questionnaire exists currently.

The number of breast cancer patients for each validation sample were as follows:

Afrikaans	64
Zulu	63
Pedi	62
Tswana	64

For the final analysis group (N=100) alpha values were generated separately for each of the questionnaire items for the white patients, the black patients and the group as a whole. This was done for FACT-B questionnaires completed before and during treatment.

4.10 STATISTICAL CONSIDERATIONS FOR THE ANALYSIS OF THE PILOT PROJECT

During August to November 1998 an interim analysis of the data collected by means of the FACT-B instrument was performed. The rationale for the interim analysis was twofold:

1. To establish norms for the statistical procedures.
2. To ascertain if there were any gross shortcomings in the quality of the data which might still be ameliorated.

4.10.1 PRELIMINARY REMARKS ABOUT GENERAL METHODOLOGY

A two-factor analysis of variance with repeated measure was deemed to be a suitable analytical method for the objectives set out in 4.2. The Null hypothesis for the following potential effects was tested by this method:

- Main effect A (effect of the treatment method with regard to racial groups): "There are general differences in QOL score, between the distinct treatment types for individual racial groups."
- Main effect B (timing effect): "There are general differences in the QOL scores at different time points."
- Interchange between A and B: "QOL differences for distinct treatment types found between different race groups, are dependent on timing. Simultaneously, different QOL scores at distinct timings are dependent on the treatment type (while taking the effect of race into consideration)."

Besides the 2-factor analysis of variance, which took the progress information into consideration, a one-factor analysis of variance was calculated at each time point. This type of variance analysis is less powerful but it is also less restrictive on the available amount of evaluable data.

4.10.2 DEPENDENT VARIABLES AND GROUP VARIABLES

For all the analyses the dependent variable was the Quality of Life (QOL) calculated as set out in 4.7. For each questionnaire there are 7 possible scales being measured:

1. Total QOL score
2. Physical well-being
3. Social/family well-being
4. Relationship with doctor
5. Emotional well-being
6. Functional well-being and
7. Additional concerns pertaining to breast cancer

The group variable for the analysis of the complex of questions 1 and 2 is the type of treatment. The group variable for the analysis of the complex of questions 1 and 3 is racial group.

4.11 SELECTION OF CASES FOR THE FINAL ANALYSIS

Because of the reasons discussed in Chapter 6, it was decided to select only the following cases for the final analysis:

- Patients receiving chemotherapy.
- Patients receiving either frontline, secondline or thirdline treatment.
- Patients who had completed a baseline, and at least one FACT-B questionnaire during treatment. The "during" treatment FACT-B was scheduled for day one week 16.
- If there was more than one questionnaire completed during treatment, the questionnaire that co-incided, or was closest to day one week 16, was chosen.
- The number of patients in the pilot sudy was 200 and 100 of these were included in the final analysis.

4.12 STATISTICAL CONSIDERATIONS FOR THE FINAL ANALYSIS

The objectives were re-formulated as follows:

1. Are there differences in quality of life during treatment between the different races?
2. What are the reasons for the differences in quality of life as they relate to the different race groups?
3. Are there changes in quality of life before treatment versus during treatment?

Multiple regression analyses were used for both the total score as well as the individual domains:

- Baseline quality of life was the only quality of life score included in the predictors.
- Time 2 (during treatment) was the dependent variable.
- Time 1 was the baseline measure.

- Predictors were race, time 1 or 2, performance status, disease stage, actual age, educational status, marital status, time elapsed between baseline and the "during" questionnaire,
  co-morbid disease and baseline quality of life scores. Living arrangement was not included, because there was less than 25% of patients living alone in each race group.

The analyses reported are:

1. Summary statistics – total sample and by race.
2. Chronbach's alpha was calculated for each construct and for the total score the final analysis group, for each construct, both at baseline and during treatment. Alpha assesses the reliability of a summative rating scale composed of the items in the construct. Modest reliability of 0.7 or higher suffices.
3. Hotelling's T-square was employed to assess whether race groups differed with respect to the observation vector (dphys, dsoc, ddoc, demot, dfunct, dadd), and races were found not to differ (in absence of covariates).
4. Dphys is defined as the difference between the physical well being score during treatment and physical well being score at baseline. The definitions for the social well being score, the relationship with the doctor, the emotional, functional, additional concerns and total scores were similar. Comparisons of races with respect to dphys through dadd initially without a covariate (model has poor R-square), then with baseline totals i.e. phys through add as cofactor (R-square improved markedly) and then finally by adding age, performance status, stage, education, time between the two questionnaires, marital status and concomitant medication (R-square improved slightly). It was suspected that race and education will be confounded but eliminating education did not improve the results and it was therefore not deleted.
5. Kaplan-Meier survival curves were drawn for the two different race groups and the chi square was calculated.

TABLE 5: LEGEND FOR THE PREDICTORS USED IN THE REGRESSION ANALYSIS

PREDICTOR	LEGEND	N IN EACH CATEGORY
Race	0= white	50%
	1= black	50%
Disease status	Stage 3	25%
	Stage 4	75%
Educational status	0= less than grade 12	55%
	1= grade 12 or higher	45%
Marital status	0= single/married	82%
	1= divorced/widowed	18%
Co-morbid disease	0= none	72%
	1= has co-morbid disease	28%

Living arrangement was not included in the analysis because there was less than 5% of patients living alone.

4.13 GENERAL ONCOLOGY PRINCIPLES UTILIZED IN THE STUDY

A number of general oncology principles were used throughout the study:

ECOG performance status: see Table 6.

AJCC staging of breast cancer (Beahrs 1992): see Table 7.

Declaration of Helsinky: see Addendum 1.

TABLE 6: ECOG PERFORMANCE STATUS WITH CORRESPONDING KARNOFSKY SCORE

GRADE	DESCRIPTION	KARNOFSKY
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

TABLE 7: AJCC STAGING OF BREAST CANCER (Beahrs 1992)

TNM DEFINITIONS

Primary Tumor

Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ: intraductal carcinoma, lobular carcinoma in situ, or Paget's disease of the nipple with no tumor
T1	Tumor 2 cm or less in greatest dimension
T1a	0.5 cm or smaller
T1b	More than 0.5 cm, but not more than 1 cm in greatest dimension
T1c	More than 1 cm, but not more than 2 cm in greatest dimension
T2	Tumor more than 2 cm but not more than 5 cm in greatest dimension
T3	Tumor more than 5 cm in greatest dimension
T4	Tumor of any size with direct extension to chest wall or skin
T4a	Extension to chest wall
T4b	Edema (including peau d' orange), ulceration of the skin of the breast or satellite skin nodules confined to the same breast
T4c	Both (T4a and T4b)
T4d	Inflammatory carcinoma

Regional Lymph Node Involvement (Clinical)

Nx	Regional lymph nodes cannot be assessed (e.g. previously removed)
N0	No regional lymph node metastasis
N1	Metastasis to movable ipsilateral axillary node(s)
N2	Metastasis to ipsilateral axillary lymph node(s) fixed to one another or to other structures
N3	Metastases to ipsilateral internal mammary lymph node(s)

Distant metastases

Mx	Presence of distant metastases cannot be assessed
M0	No distant metastasis
M1	Distant metastasis (including metastases to ipsilateral supraclavicular node(s)

STAGE GROUPING

Stage 0	Tis, N0, M0
Stage I	T1, N0, M0
Stage IIA	T0, N1, M0
	T1, N1, M0
	T2, N0, M0
Stage IIB	T2, N1, M0
	T3, N0, M0
Stage IIIA	T0, N2, M0
	T1, N2, M0
	T2, N2, M0
	T3, N1, M0
	T3, N2, M0
Stage IIIB	T4, any N, M0
	Any T, N3, M0
Stage IV	Any T, any N, M1

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ADDENDUM 1: DECLARATION OF HELSINKI

Recommendations guiding physicians in biomedical
Research involving human subjects

Adopted by the 18th world Medical Assembly,
Helsinki, Finland, June 1964
amended by the 29th World Medical Assembly,
Tokyo, Japan, October 1975
and
The 35th World medical Assembly,
Venice, Italy, October 1983
and
The 41th World Medical Assembly, Hong-Kong, September 1989

INTRODUCTION:

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfillment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient".

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding or the etiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research that ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research that may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. BASIC PRINCIPLES

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.
2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided and this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.
3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent

medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.

4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.

6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.

8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in the Declaration should not be accepted for publication.

9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely given informed consent, preferably in writing.

10. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case a physician who is not engaged in the

investigation and who is completely independent of this official relationship should obtain the informed consent.

11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation. Whenever the minor child is in fact able to give consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.

12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. MEDICAL RESEARCH COMBINED WITH PROFESSIONAL CARE (Clinical research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgment it offers hope of saving life, re-establishing health or alleviating suffering.

2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

3. In any medical study, every patient – including those of a control group, if any – should be assured of the best-proven diagnostic and therapeutic method.

4. The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.

5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent Committee (1,2).

6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. NON-THERAPEUTIC BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS

(Non-clinical biomedical research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.
2. The subjects should be volunteers – either healthy persons or patients for whom the experimental design is not related to the patient's illness.
3. The investigator or the investigating team should discontinue the research if in his/her or their judgement it may, if continued, be harmful to the individual,

In research on man, the interest of science and society should never take precedence over considerations related to the wellbeing of the subject.

ADDENDUM 2: PROPOSED INFORMED CONSENT FOR PATIENTS EVALUATED WITH THE FACT-B

QUALITY OF LIFE IN PATIENTS WITH METASTATIC BREAST CANCER

I _____ willingly agree to participate in this study which has been explained to me by _____ . Participation in this study is voluntary. No compensation for participation will be given. I understand that I am free to withdraw my consent to participate in this program at any time without prejudice to my subsequent care. If I do not take part in or withdraw from the study, I will continue to receive the best possible care.

PURPOSE OF THE STUDY

It has been explained to me that I have locally advanced or metastatic breast cancer. Investigation into my quality of life will be done to determine which factors influence quality of life and to what extent these factors influence quality of life.

DESCRIPTION OF PROCEDURES

A socio demographic form inquiring about facts such as marital status and income will be filled in at the start. Thereafter the Functional Assessment of Cancer Therapy (FACT) for Breast cancer (FACT-B) will be explained to me. It takes about 10 minutes to fill in the form. The FACT-B will be completed at certain clinic visits. If I cannot read, the questionnaire will be administered as an interview.

RISKS AND DISCOMFORTS

I will be reminded of unpleasant aspects of my disease or life. Additionally some of the questions are of a personal nature. I may choose to refuse to answer certain questions.

Continued on the next page

BENEFITS

There is no clearcut benefit at this time. The knowledge gained from the study may however be used directly to improve the quality of life of patients with breast cancer.

I have read all of the above, asked questions, received answers concerning aspects that I did not understand, and I willingly give my consent to participate in this program. Upon signing this form, I will receive a copy.

_____

PATIENT SIGNATURE DATE

_____

WITNESS DATE

_____

PHYSICIAN OR DATA MANAGER DATE

ADDENDUM 3: FACT-B (VERSION 3) ENGLISH

Below is a list of statements that other people with your illness have said are important.
By circling one number per line, please indicate how true each statement has been for you during the past 7 days.

PHYSICAL WELL-BEING

	not at all	a little bit	somewhat	quite a bit	very much
1. I have a lack of energy	0	1	2	3	4
2. I have nausea	0	1	2	3	4
3. Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
4. I have pain	0	1	2	3	4
5. I am bothered by side-effects of treatment	0	1	2	3	4
6. I feel sick	0	1	2	3	4
7. I am forced to spend time in bed	0	1	2	3	4
8. Looking at the above 7 questions, how much would you say your **PHYSICAL WELL-BEING** affects your quality of life?	(circle one number) **0 1 2 3 4 5 6 7 8 9 10** **not at all** **very much so**				

SOCIAL/FAMILY WELL-BEING

	not at all	a little bit	somewhat	quite a bit	very much
9. I feel distant from my friends	0	1	2	3	4
10. I get emotional support from my family	0	1	2	3	4
11. I get support from my friends and neighbors	0	1	2	3	4
12. My family has accepted my illness	0	1	2	3	4
13. Family communication about my illness is poor	0	1	2	3	4
14. I feel close to my partner (or the person who is my main support)	0	1	2	3	4
15. Have you been sexually active during the past year? No_____ Yes_____ If yes: I am satisfied with my sex life	0	1	2	3	4
16. Looking at the above 7 questions, how much would you say your **SOCIAL/FAMILY WELL-BEING** affects your quality of life?	(circle one number) **0 1 2 3 4 5 6 7 8 9 10** **not at all** **very much so**				

RELATIONSHIP WITH DOCTOR

	not at all	a little bit	Somewhat	quite a bit	very much
17. I have confidence in my doctor(s)	0	1	2	3	4
18. My doctor is available to answer my questions	0	1	2	3	4
19. Looking at the above 2 questions, how much would you say your **RELATIONSHIP WITH THE DOCTOR** affects your quality of life?	(circle one number) **0 1 2 3 4 5 6 7 8 9 10** **not at all** **very much so**				

EMOTIONAL WELL-BEING

	not at all	a little bit	Somewhat	quite a bit	very much
20. I feel sad	0	1	2	3	4
21. I am proud of how I'm coping with my illness	0	1	2	3	4
22. I am losing hope in the fight against my illness	0	1	2	3	4
23. I feel nervous	0	1	2	3	4
24. I worry about dying	0	1	2	3	4
25. I worry that my condition will get worse	0	1	2	3	4
26. Looking at the above 6 questions, how much would you say your **EMOTIONAL WELL-BEING** affects your quality of life?	(circle one number) **0 1 2 3 4 5 6 7 8 9 10** **not at all** **very much so**				

FUNCTIONAL WELL-BEING

	not at all	a little bit	somewhat	quite a bit	very much
27. I am able to work (include work in the home)	0	1	2	3	4
28. My work (include work in home) is fulfilling	0	1	2	3	4
29. I am able to enjoy life	0	1	2	3	4
30. I have accepted my illness	0	1	2	3	4
31. I am sleeping well	0	1	2	3	4
32. I am enjoying the things I usually do for fun	0	1	2	3	4
33. I am content with the quality of my life right now	0	1	2	3	4
34. Looking at the above 7 questions, how much would you say your **FUNCTIONAL WELL-BEING** affects your quality of life?	(circle one number) **0 1 2 3 4 5 6 7 8 9 10** **not at all** **very much so**				

ADDITIONAL CONCERNS

	not at all	a little bit	somewhat	quite a bit	very much
35. I have been short of breath	0	1	2	3	4
36. I am self-conscious about the way I dress	0	1	2	3	4
37. My arms are swollen and tender	0	1	2	3	4
38. I feel sexually attractive	0	1	2	3	4
39. I have been bothered by hair loss	0	1	2	3	4
40. I worry about the risk of cancer in other family members	0	1	2	3	4
41. I worry about the effect of stress on my illness	0	1	2	3	4
42. I am bothered by a change in weight	0	1	2	3	4
43. I am able to feel like a woman	0	1	2	3	4
44. Looking at the above 9 questions, how much would you say your **ADDITIONAL CONCERNS** affects your quality of life?	(circle one number) **0 1 2 3 4 5 6 7 8 9 10** **not at all** **very much so**				

ADDENDUM 4: FACT-B (WEERGAWE 3) AFRIKAANS

Instruksies: Die lys stellings hieronder dui aan wat vir ander persone/pasiënte met u siekte-toestand belangrik is. **Dui asseblief aan hoe waar u elke stelling gedurende die afgelope 7 dae gevind het, deur die toepaslike nommer by elkeen van die stellings te merk.**

FISIESE WELSTAND

	glad nie	bietjie	gemiddeld	taamlik baie	geweldig
1. Ek ly aan energieverlies	0	1	2	3	4
2. Ek is naar	0	1	2	3	4
3. Weens my fisiese toestand vind ek dit moeilik om aan my gesin se behoeftes te voldoen	0	1	2	3	4
4. Ek verduur pyn	0	1	2	3	4
5. Newe-effekte van die behandeling tas my aan	0	1	2	3	4
6. Ek voel siek	0	1	2	3	4
7. Ek word gedwing om tyd in die bed deur te bring	0	1	2	3	4
8. As u die voorafgaande 7 vrae indringend beskou, in watter mate beïnvloed u **FISIESE WELSTAND** u lewenskwaliteit ?	(omkring een nommer) **0 1 2 3 4 5 6 7 8 9 10** **glad nie** **geweldig baie**				

SOSIALE WELSTAND

	glad nie	bietjie	gemiddeld	taamlik baie	geweldig
9. Ek voel afgesonder van my vriende	0	1	2	3	4
10. Ek kry emosionele ondersteuning van my familie	0	1	2	3	4
11. My vriende en bure ondersteun my	0	1	2	3	4
12. My familie het my siekte aanvaar	0	1	2	3	4
13. Gesinskommunikasie oor my siekte is swak	0	1	2	3	4
14. Ek voel na aan my lewensmaat (of die persoon wat my hoof-ondersteuner is)	0	1	2	3	4
15. Was u seksueel aktief gedurende die afgelope jaar? Nee_____ Ja_____ indien ja: Ek is tevrede met my sekslewe	0	1	2	3	4
16. As u die voorafgaande 7 vrae indringend beskou, in watter mate beïnvloed u **SOSIALE WELSTAND** u lewenskwaliteit ?	(omkring een nommer) **0 1 2 3 4 5 6 7 8 9 10** **glad nie** **geweldig baie**				

VERHOUDING MET U GENEESHEER

	glad nie	bietjie	Gemiddeld	taamlik baie	Geweldig
17. Ek het vertroue in my dokter(s)	0	1	2	3	4
18. My dokter is beskikbaar om my vrae te beantwoord	0	1	2	3	4
19. As u die voorafgaande 2 vrae indringend beskou, in watter mate beïnvloed u **VERHOUDING MET U GENEESHEER** u lewenskwaliteit ?	(omkring een nommer) **0 1 2 3 4 5 6 7 8 9 10** **glad nie** **geweldig baie**				

EMOSIONELE WELSTAND

	glad nie	bietjie	gemiddeld	taamlik baie	geweldig
20. Ek voel hartseer	0	1	2	3	4
21. Ek is trots op die wyse waarop ek my siekte baasraak	0	1	2	3	4
22. Ek voel negatief oor my kanse op herstel	0	1	2	3	4
23. Ek voel senuweeagtig	0	1	2	3	4
24. Ek bekommer my oor die dood	0	1	2	3	4
25. Ek bekommer my daaroor dat my toestand kan versleg	0	1	2	3	4
26. As u die voorafgaande 6 vrae indringend beskou, in watter mate beïnvloed u **EMOSIONELE WELSTAND** u lewenskwaliteit ?	(omkring een nommer) **0 1 2 3 4 5 6 7 8 9 10** **glad nie** **geweldig baie**				

FUNKSIONELE WELSTAND

	glad nie	bietjie	gemiddeld	taamlik baie	Geweldig
27. Ek kan werk (insluitend huiswerk)	0	1	2	3	4
28. My werk (insluitend huiswerk) is vervullend	0	1	2	3	4
29. Ek is in staat om genot uit die lewe te put	0	1	2	3	4
30. Ek aanvaar my siekte	0	1	2	3	4
31. Ek slaap goed	0	1	2	3	4
32. Ek geniet my normale ontspanningsaktiwiteite	0	1	2	3	4
33. Ek is tevrede met my huidige lewenskwaliteit	0	1	2	3	4
34. As u die voorafgaande 7 vrae indringend beskou, in watter mate beïnvloed u **FUNKSIONELE WELSTAND** u lewenskwaliteit ?	(omkring een nommer) **0 1 2 3 4 5 6 7 8 9 10** **glad nie** **geweldig baie**				

ADDISIONELE BEKOMMERNISSE

	glad nie	bietjie	gemiddeld	taamlik baie	Geweldig
35. Ek is kortasem	0	1	2	3	4
36. Ek is selfbewus oor die wyse waarop ek aantrek	0	1	2	3	4
37. My arms is geswel en seer	0	1	2	3	4
38. Ek voel seksueel aantreklik	0	1	2	3	4
39. Ek ondervind haarverlies	0	1	2	3	4
40. Ek is bekommerd oor die risiko van kanker in ander gesinslede	0	1	2	3	4
41. Ek is bekommerd oor die effek van stres op my siekte	0	1	2	3	4
42. Gewigsverlies is 'n bron van kommer	0	1	2	3	4
43. Ek voel volkome vroulik	0	1	2	3	4
44. As u die voorafgaande 9 vrae indringend beskou, in watter mate beïnvloed u **ADDISIONELE BEKOMMERNISSE** u lewenskwaliteit ?	(omkring een nommer) **0 1 2 3 4 5 6 7 8 9 10** **glad nie** **geweldig baie**				

ADDENDUM 5: FACT-B (VERSION 3) PEDI / NORTH SOTHO

Ka fase go na le lenaneo la dipego leo batho ba bangwe ba go swarwa ke bolwetši bja go swana le bja gago ba rego di bohlokwa. ka go thalela sediko nomorong e tee mothalading o tee bontšha ka fao pego ye nngwe le ye nngwe e nepagetšeng malebana le ka fao o bego o le ka gona mo lebakeng la matšatši a šupa a a fetilego

PABALELO MMELENG

	le ga-nnyane	gannyane	bokao-nenyana	bokoane	bokoan-kudu
1. Ga ke na maatla	0	1	2	3	4
2. Ke tlabatlaba dibete	0	1	2	3	4
3. Ka baka la go se phiphsine mmeleng, ke šitwa go phethagatša dinyaka kwa tša ba lapa la ka	0	1	2	3	4
4. Ke na le sehlabi	0	1	2	3	4
5. Ke tshwenywa ke ditlamorago tša ka morago ga kalafo	0	1	2	3	4
6. Ke ikwa ke lwala	0	1	2	3	4
7. Ke gapeletšega go dula lebakanyana ka malaong	0	1	2	3	4
8. Ge o lebeletše dipotšišo tša ka godimo tše 7 pabalelo mmeleng wa gago e ama bjang khwaliti ya bophelo bja gago?	(thalela sediko nomorong e tee) **0 1 2 3 4 5 6 7 8 9 10** **le gannyane** **kudukudu**				

PABALELO YA LEAGO / LAPA

	le ga-nnyane	gannyane	bokao-nenyana	bokoane	bokoan-kudu
9. Ke lewa ke boduto	0	1	2	3	4
10. Ke hwetša thekgo moyeng go tšwa go ba lapa la ka	0	1	2	3	4
11. Ke hwetša thekgo moyeng go tšwa go bagwera le go baagišani	0	1	2	3	4
12. Ba lapa ba amogetše bolwetši bja ka	0	1	2	3	4
13. Kgokagano ya ba lapa ka ga bolwetši bja ka ga e kgotsofatše	0	1	2	3	4
14. Ke ikwa ke le kgauswi le molekane wa ka (goba motho wo a nthekgilego kudu)	0	1	2	3	4
15. Tumo ya gago ya tša leratano e be e le ya mahlahla ngwageng wa go feta? Aowa ____ Ee____ Ge eba ee: Ke kgotsofatšwa ke bophelo bja ka bja leratano	0	1	2	3	4
16. Ge o lebeletše dipotšišo tša ka godimo tše 7 kamano yagago go ba lelapa le leago ya leago la lapa e ama bjang khwaliti ya bophelo bja gago?	(thalela sediko nomorong e tee) **0 1 2 3 4 5 6 7 8 9 10** **le gannyane** **kudukudu**				

TSWALANO LE NGAKA

	le ga-nnyane	Gannyane	bokao-nenyana	bokoane	bokoan-kudu
17. Ke tshepa ngaka (dingaka) ya ka	0	1	2	3	4
18. Ngaka e gona go araba dipotšišo tša ka	0	1	2	3	4
19. Ge o lebeletše dipotšišo tše pedi tša ka godimo, tswalano le ngaka e ama bjang khwaliti ya bophelo bja gago?	(thalela sediko nomorong e tee) **0 1 2 3 4 5 6 7 8 9 10** **le gannyane** **kudukudu**				

PABALELO MOYENG

	le ga-nnyane	gannyane	bokao-nenyana	bokoane	bokoan-kudu
20. Ke kwa ke nyamile	0	1	2	3	4
21. Ke ikgogomoša ka mokgwa wo ke laolago bolwetši bjaka	0	1	2	3	4
22. Ke felelwa ke maatla go lwantšha bolwetši bja ka	0	1	2	3	4
23. Ke ikwa ke tšhogatšhoga	0	1	2	3	4
24. Ke ikwa ke tshweywa ke kakenyo ya lehu	0	1	2	3	4
25. Ke tšhošwa ke gore maemo a ka a tlaaba šoro go ya pele	0	1	2	3	4
26. Ge o lebeletše dipotšišo tše di tshelelago tša ka godimo, pabalelo moyeng e ama bjang khwaliti ya bophelo bja gago?	(thalela sediko nomorong e tee) **0 1 2 3 4 5 6 7 8 9 10** **le gannyane** **kudukudu**				

PABALELOTIRIšWA

	le ga-nnyane	Gannyane	bokao-nenyana	bokoane	bokoan-kudu
27. Ke kgona go šoma (go akaretšwa mošomo wa ka gae)	0	1	2	3	4
28. Mošomo wa ka (go akaretšwa mošomo wa ka gae) o a phethagatšwa	0	1	2	3	4
29. Ke ipshina ka bophelo	0	1	2	3	4
30. Ke amogetše bolwetši bja ka	0	1	2	3	4
31. Ke robala gabotse	0	1	2	3	4
32. Ke ipshina ka dilwana tšeo ke di dirago go ithabiša	0	1	2	3	4
33. Ke ikwa ke kgotsofala ka bophelo baka	0	1	2	3	4
34. Ge o lebeletše dipotšišo tše di šupago tša ka godimo, pabalelo tirišwa e ama bjang khwaliti ya bophelo bja gago?	(thalela sediko nomorong e tee) **0 1 2 3 4 5 6 7 8 9 10** **le gannyane** **kudukudu**				

TLALELETŠO YA DIPOTŠIŠO

	le ga-nnyane	gannyane	bokao-nenyana	bokoane	bokoan-kudu
35. Ke be ke hlaelela moya	0	1	2	3	4
36. Ke hlokomela ka fao ke aparago ka gona	0	1	2	3	4
37. Matsogo a ka a rurugile goba a bohloko	0	1	2	3	4
38. Ke a ratega (ge ke na le molekane waka)	0	1	2	3	4
39. Ke tshwenywa ke go loba moriri	0	1	2	3	4
40. Ke hlobaetša ke kgonagalo ya go ba gona ga bolwetši bja kankere ka lapeng	0	1	2	3	4
41. Ke hlobaetšwa ke go tshwenye ga mogopolong ka ga sephetho sa bolwetsi bjaka	0	1	2	3	4
42. Ke hlobaetšwa phetogo ya boima bja ka	0	1	2	3	4
43. Ke ikwa ke le mosadi	0	1	2	3	4
44. Ge o lebeletše dipotšišo tše senyane tša ka godimo o bona tlaleletšo ya dikamego e ama bjang khwaliti ya bophelo bja gago?	(thalela sediko nomorong e tee) **0 1 2 3 4 5 6 7 8 9 10** **le gannyane** **kudukudu**				

ADDENDUM 6: FACT-B (VERSION 3) TSWANA

Fa tlase go tlhagelela dipolelwana tse batho ba bangwe ba ba nang le bolwetse jo bo tshwanang le jwa gago ba di kaileng e le tsa botlhokwa. Sekeletsa nomoro e le nngwe mo moleng mongwe le mongwe, go supa gore polelwana nngwe le nngwe ke boammaruri jang mo go wena, mo malatsing a a supa a a fetileng

BIOTEKANELO JWA MMELE

	le goka	go le gonnye-nyane	ka mokgwa o o rileng	go le thata	thata thata
1. Ke tlhoka maatla	0	1	2	3	4
2. Ke a sellega	0	1	2	3	4
3. Ke tlholwa ke go tlamela ba lolapa lwa me ka ntlha ya bokoa ba mmele wa me	0	1	2	3	4
4. Ke na le ditlhabi	0	1	2	3	4
5. Mmele o koafatsa ke kalofo - Mmele wa ka o koa kagofetse morago ga kalafo	0	1	2	3	4
6. Ke ikutlwa ke bobola / lwala	0	1	2	3	4
7. Ke patelesega go tlhola ke robetse	0	1	2	3	4
8. Fa o lebile dipotso tse supa 7 tse di fa godimo, o bona e kete **BOITEKANELO JWA MMELE** wa gago bo ama jang boleng jwa botshelo jwa gago?	(sekeletsa nomoro e le nngwe) **0 1 2 3 4 5 6 7 8 9 10** **Le goka** **Thatathata**				

BOTSALANO / BOITEKANELO JWA LOLAPA

	le goka	go le gonnye-nyane	ka mokgwa o o rileng	go le thata	thata thata
09. Ke ikutlwa ke sa tlhole ke na le nako le ditsala tsa me	0	1	2	3	4
10. Ke bona tshegetso go tswa go ba lolapa lwame	0	1	2	3	4
11. Ke bona tshegetso go tswa go ditsala le go baagisani bame	0	1	2	3	4
12. Ba lolapa lwa me ba amogetse bolwetse jwa me	0	1	2	3	4
13. Puisano ka ga bolwetsi jwame e bokoa go ba lolapa lwame	0	1	2	3	4
14. Ke ikutlwa ke le gaufi le molekane wa me (kgotsa motho yo o ntshegeditseng e le ruri)	0	1	2	3	4
15. A o ntse o robalana ngwageng o o fetileng? Nnyaya _____ Ee _____ Fa o rile ee, re tlhalosetse o re : Ke kgotsofetse ka botshelo jwa me fa ke robalana	0	1	2	3	4
16. Fa o lebile dipotso tse supa 7 tse di fa godimo, o bona e kete **BOTSALANO / BOITEKANELO JWA LOLAPA** lwa gago bo ama jang boleng jwa botshelo jwa gago?	(sekeletsa nomoro e le nngwe) **0 1 2 3 4 5 6 7 8 9 10** **Le goka** **Thatathata**				

BOTSALANO JWA GAGO LE NGAKA YA GAGO

	le goka	go le gonnye-nyane	ka mokgwa o o rileng	go le thata	thata thata
17. Ke ikanya (di)ngaka ya me	0	1	2	3	4
18. Ngaka ya me e teng / gone go araba dipotso tsa me	0	1	2	3	4
19. Fa o leba dipotso tse pedi tse di fa godimo, a o ka kaya gore **BOTSALANO JWA GAGO LE NGAKA** ya gago bo ama botshelo jwa gago jang?	(sekeletsa nomoro e le nngwe) **0 1 2 3 4 5 6 7 8 9 10** **Le goka** **Thatathata**				

MAIKUTLO A A ITEKANETSENG

	le goka	go le gonnye-nyane	ka mokgwa o o rileng	go le thata	thata thata
20. Ke ikutlwa ke hutsafetse	0	1	2	3	4
21. Ke motlotlo ka mokgwa o ke tswelelang ka ga bolwetsi jwa me	0	1	2	3	4
22. Ke felelwa ke tshepo ya go fenya bolwetse jwa me	0	1	2	3	4
23. Ke a boifa	0	1	2	3	4
24. Ke tlhobaetswa ke go akanya ka go swa	0	1	2	3	4
25 Ke tshwenngwa ke phetogo ya seemo sa botshelo jwame	0	1	2	3	4
26. Fa o leba dipotso tse thataro 6 tse di fa godimo, o bona e kete botshelo jwa gago bo amiwa jang ke **MAIKUTLO A A ITEKANETSENG** ?	(sekeletsa nomoro e le nngwe) **0 1 2 3 4 5 6 7 8 9 10** **Le goka** **Thatathata**				

GO DIRA O ITEKANETSE

	le goka	go le gonnye-nyane	ka mokgwa o o rileng	go le thata	thata thata
27. Ke kgona go dira (ke akaretsa tiro ya kwa gae)	0	1	2	3	4
28. Tiro ya me (ke akaretsa le ya kwa gae) e a kgotsofatsa	0	1	2	3	4
29. Ke itumelela go dira dilo tse ka gale ke di dirang go itumedisa fela. Ke thabela go tshela	0	1	2	3	4
30. Ke amogetse bolwetse jwa me	0	1	2	3	4
31. Ke robala sentle	0	1	2	3	4
32. Ke thabela dilo tse ka gale de di dirang go itumedisa	0	1	2	3	4
33. Ke kgotsofadiwa ke boleng jwa botshelo jwa me mo nakong ya ga jaana	0	1	2	3	4
34. Fa o leba dipotso tse supa 7 tse di fa godimo, o bona e kete botshelo jwa gago bo amiwa ke **GO DIRA O ITEKANETSE** jang?	(sekeletsa nomoro e le nngwe) **0 1 2 3 4 5 6 7 8 9 10** **Le goka** **Thatathata**				

DILO DINGWE TSE DI NTSHWENYANG / NTLHOBAETSANG

	le goka	go le gonnye-nyane	ka mokgwa o o rileng	go le thata	thata thata
35. Ke felelwa ke mowa	0	1	2	3	4
36. Ke kelothlhoko gore ke apara jang	0	1	2	3	4
37. Matsogo a me a rurugile kgotsa a bonolo	0	1	2	3	4
38. Ke ikuthlwa ke ratwake banna	0	1	2	3	4
39. Ke tshwenngwa ke go felelwa ke moriri	0	1	2	3	4
40. Ke tshwenngwa ke tekeletso ya boletse jwa kankere mo lapeng lame	0	1	2	3	4
41. Ke tshwenngwa ke kakoretso ua bolweise jajo kankere mo lolopeng lome	0	1	2	3	4
42. Ke tshwenngwa ke moikutlo ka ntiha ya bolwetse jwa me	0	1	2	3	4
43. Ke kgona go ikutlwa jaaka mosadisadi	0	1	2	3	4
44. Fa o leba dipotso tse robongwe 9 tse di fa godimo, o bona e kete **DILO DINGWE TSE DI GO TSWHENYANG / TLHOBAETSANG** di ama jang boleng jwa botshelo jwa gago?	(sekeletsa nomoro e le nngwe) **0 1 2 3 4 5 6 7 8 9 10** **Le goka** **Thatathata**				

ADDENDUM 7: FACT-B (VERSION 3) ZULU

Ngezansi Kunohlu Iwenzinto abantu abagula njengawe abati zibalulekile, Ngokuzungeleza inombolo eyodwa emgqeni ngamunye, yisho ukuthi isitatimende ngasinye sibe yiqiniso kangakanani kuwe ezinsukwini eziyisikhombisa 7 ezedlule.

ISIMO SEMPILO

	aKwenzeki	Kuyenzeka kancane	Kuzenzeka Kwesinye Isikhathi	Kuvamile ukwenzeke	Kuyenzega kakhulu
1. Ngiphelelwa amandla	0	1	2	3	4
2. Kuthi mangibuyise	0	1	2	3	4
3. Ngenxa yesimo sempilo yami ngi nenkinga ukumelana nezidingo zomndeni wami	0	1	2	3	4
4. Nginezinhlungu	0	1	2	3	4
5. Ngikhathazwa okunye ukugula okubangwa imithi engilashwe ngayo	0	1	2	3	4
6. Ngiyagula	0	1	2	3	4
7. Ngiphoqelekile ukuchitha isikhathi sami embhedeni	0	1	2	3	4
8. Uma ubheka kulemibuzo eyisikhombisa 7 engenhla ungathi isimo sempilo yakho silithinta kanjani izinga lempilo yakho	(zungelezela inombolo eyodwa) **0 1 2 3 4 5 6 7 8 9 10** **Asilithinti Neze** **Silithinta Kakhulu**				

ISIMO SEZENHLAWAKAHLE YOMNDENI

	aKwenzeki	Kuyenzeka kancane	Kuzenzeka Kwesinye isikhathi	Kuvamile ukwenzeke	Kuyenzega Kakhulu
09. Ngizwa ngiqhelile kubangane bami	0	1	2	3	4
10. Ngithola ukwesekelwa ngokomoya ngabomndeni	0	1	2	3	4
11. Ngithola ukusekelwa ngekomoya ngabamgane nomakhelwane bami	0	1	2	3	4
12. Umndeni wami uyakwamukele ukugula kwami	0	1	2	3	4
13. Umndeni awusaxoxi kahle ngokugula kwami	0	1	2	3	4
14. Ngizizwa ngisondelene nomngane wami (noma lowomuntu ongisizayo kakhulu)	0	1	2	3	4
15. Ubuhlangane oconsini kulonyaka odlule Qha_____ Yebo_____ Uma kunjalo: Ngenelisekile Ngempilo yobulili bami	0	1	2	3	4
16. Uma ubheka lemibuzo eyisikhombisa 7 engenhla ungathi isimo sezenhlalakahle somndeni wakho silithinta kanjani izinga lempilo yakho?	(zungelezela inombolo eyodwa) **0 1 2 3 4 5 6 7 8 9 10** **Asilithinti Neze** **Silithinta Kakhulu**				

UBUDLELWANO BAKHO NODOKOTELA

	aKwenzeki	Kuyenzeka kancane	Kuzenzeka Kwesinye isikhathi	Kuvamile ukwenzeke	Kuyenzega kakhulu
17. Ngiyamethemba udokotela wami (odokotela bami)	0	1	2	3	4
18. Udoketela wami uyathembakala ukuphendula imibuzo yami	0	1	2	3	4
19. Uma ubheka lemibuzo emibili 2 engenhla ungathi uudlelwana bakho nodokotela bukuthinta kanjani izinga lempilo yakho?	(zungelezela inombolo eyodwa) **0 1 2 3 4 5 6 7 8 9 10** **Asilithinti Neze** **Silithinta Kakhulu**				

UKUPHATHEKA KAHLE EMOYENI

	aKwenzeki	Kuyenzeka kancane	Kuzenzeka Kwesinye isikhathi	Kuvamile ukwenzeke	Kuyenzega kakhulu
20. Ngikhathazekile	0	1	2	3	4
21. Ngiyaziqhenya ngendlela engikwazi ngayo ukumelana nesifo sami	0	1	2	3	4
22. Ngiphelelwa yithemba ekulweni nesifo sami	0	1	2	3	4
23. Nginovalo	0	1	2	3	4
24. Ngiyakhathazeka ngokugula kwami	0	1	2	3	4
25. Ngikhathazwa ukuthi isimo sokugula kwami singahle sibe sibi kakhulu	0	1	2	3	4
26. Uma ubheka lemibuzo eyisithupha engenhla 6 ungathi ukuphatheka kahle emoyeni kulithinta kanjani izinga lempilo yakho?	(zungelezela inombolo eyodwa) **0 1 2 3 4 5 6 7 8 9 10** **Asilithinti Neze** **Silithinta Kakhulu**				

UKUPHATHEKA KAHLE NGOKOMSEBEZI

	aKwenzeki	Kuyenzeka kancane	Kuzenzeka Kwesinye isikhathi	Kuvamile ukwenzeke	Kuyenzega kakhulu
27. Ngiyasebenza (ngisho nomsebenzi wasekhaya)	0	1	2	3	4
28. Umsebenzi wami ngisho nowasekhaya uyangenelisa	0	1	2	3	4
29. Ngiyakwazi ukuzijabulisa ngempilo yami	0	1	2	3	4
30. Sengikwamukele ukugula kwami	0	1	2	3	4
31. Ngilala kahle	0	1	2	3	4
32. Ngiyazijabulisa ngezinto engejwayele ukuzijabulisa ngazo	0	1	2	3	4
33. Ngenelisiwe yizinga lempilo yami	0	1	2	3	4
34. Uma ubheka lemibuzo eyisikhombisa 7 engenhla ungathi ukuphatheka kahle ngokomsebenzi owenza ngemihla kulithinta kanjani izinga lempilo yakho?	(zungelezela inombolo eyodwa) **0 1 2 3 4 5 6 7 8 9 10** **Asilithinti Neze** — **Silithinta Kakhulu**				

OKUNYE OKUKUKHATHAZAYO

	aKwenzeki	Kuyenzeka kancane	Kuzenzeka Kwesinye isikhathi	Kuvamile ukwenzeke	Kuyenzega Kakhulu
35. Ngiphelelwa umoya	0	1	2	3	4
36. Ngiyakhathazeka (noma giyazenyaza) ngendlela engigquoka ngayo	0	1	2	3	4
37. Izingalo zami zivuvukele	0	1	2	3	4
38. Ngiyabukeka	0	1	2	3	4
39. Ngikhathazwa ukuqothuka kwezinwele	0	1	2	3	4
40. Ngikhathazwa ukuthi abanye bomndeni bangaba sengozini yesifo somdlavuza (cancer)	0	1	2	3	4
41. Ngikhathazwa imiphumela yokukhathazeka empil weni yami	0	1	2	3	4
42. Ngikhathazwa ukushintsha kwesisindo somzimba wami	0	1	2	3	4
43. Ngisakwazi ukuzizwa ngiwumuntu wesifazane	0	1	2	3	4
44. Uma ubheka lemibuzo engu 9 engenhla ungathi okunye okukukhathazayo kulithinta kanjani izinga lempilo yakho?	(zungelezela inombolo eyodwa) **0 1 2 3 4 5 6 7 8 9 10** **Asilithinti Neze** — **Silithinta Kakhulu**				

ADDENDUM 8: HOSPITAL CLASSIFICATION

This addendum gives an indication of the patient's financial status.

CLASSIFICATION	INCOME SINGLE PERSON Annual	INCOME FOR FAMILY Annual	HAS TO PAY Per visit
02	Less than R10 000 or assets less than R50 000	Less than R18 000 or assets less than R90 000	R13
03	Less than R14 000 or assets less than R70 000	Less than R18 000 or assets less than R130 000	R26
04	Less than R21 000 or assets less than R105 000	Less than R35 000 or assets less than R175 000	R39
17	More than R21 000 or assets more than R105 000	More than R35 000 or assets more than R175 000	R55
67	Patient has a medical aid	Patient has a medical aid	R55 entrance and all tests to be paid by the medical aid
08	Patient has the military medial aid	Family has the military medical aid	All costs covered by the military medical fund
58	Pensioner has the military medial aid	Pensioner and family has the military medical aid	All costs covered by the military medical fund