



Quality of Life and Patient-Reported Outcomes in Cancer: A GUIDE FOR ADVOCATES

Research Advocacy Network

Advancing Patient-Focused Research

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Chapter 1: Introduction to Quality of Life and Its Measurement

What is Quality of Life?

We all have an intuitive idea of what is meant by the phrase “quality of life.” We know that being free is better than being imprisoned, being healthy is better than being sick, and being relaxed is better than being stressed. Some people choose to live in the city because they value access to cultural and social offerings. Others choose to live in rural areas because they value the slower pace, lack of traffic, and access to nature. These features affect the inherent goodness of our lives, or our well-being, referred to in the medical and scientific arenas as quality of life.

As can be inferred from the preceding examples, quality of life is influenced by many factors, including health, emotion, employment, and the environment in which we live. In medicine, we are often interested in how disease or its treatment affects quality of life, which is generally considered health-related quality of life. Health-related quality of life, sometimes abbreviated HRQOL or HRQL, has evolved over the past few decades into a broad, multidimensional concept that includes both physical and mental health, and even social factors.

In clinical research studies, health-related quality of life measures are often included to examine the effects of treatment on patients’ well-being. These measures are referred to as patient-reported outcomes because it is the patients themselves who are doing the rating. Patient-reported outcomes are complementary to clinical outcomes such as tumor size, progression free survival, or other clinical measures in cancer.

This tutorial considers quality of life and patient-reported outcomes in cancer, with a focus on how these issues are relevant for advocates. In this first chapter, we consider some of the different uses for quality of life information. In Chapter 2, we discuss how quality of life is measured, and in Chapter 3, we delve into the effects of cancer and its treatment on quality of life based on information from clinical research. Measuring quality of life is not without its challenges, and we consider some of these in Chapter 4. In Chapter 5, we explore the related concept of patient-reported outcomes and how quality of life measures fall under this broader heading. We also outline some of the uses and initiatives related to patient-reported outcomes that are ongoing today. Finally, in Chapter 6, we discuss some of the ways that advocates can use this information to help encourage the use of outcomes that are meaningful to patients.

Uses of Health-Related Quality of Life Information

Information about a person’s health-related quality of life is of interest in medical practice and research, and to society in developing national and international policy. Let’s consider each of these uses.

Medical Practice

Quality of life information can be used several different ways in medical practice. Treatment decision making is one of the major areas in which quality of life considerations are applied in cancer. For instance, a patient and his or her physician may be attempting to decide between two treatments that show virtually no differences in survival or other disease-related outcomes. Quality of life variables may be the deciding factor in selecting one treatment over another. Alternatively, patients may choose between two different types of cancer treatment based on the expected toxicity, convenience, or other factors that impact quality of life.

Health-related quality of life has been defined many different ways, but one of the most common definitions is as follows: The extent to which one’s usual or expected physical, emotional, and social well-being are affected by a medical condition or its treatment (Cella, 1995).

Quality of life information may also help patients prepare for and interpret the treatment experience. Knowing in advance what to expect from treatment can help patients to better manage their expectations and possibly to better cope with the long-term impact of therapy.

In a more general way, patients and their healthcare providers may both gain from incorporating quality of life questions into medical practice because the data can be used to help facilitate communication about the disease and its treatment. Some of the possible uses for quality of life information and measures in medical practice are summarized in the following table.

Uses for Quality of Life Information/Measures in Medical Practice

Treatment decision making	Quality of life considerations can often be important in selecting between two or more treatment options.
Preparing for treatment experience	Information about how treatment affects quality of life can help patients prepare for and help them cope with the treatment experience
Identifying and prioritizing problems	If patients have multiple problems, quality of life reporting may help their providers to identify which are the most significant.
Facilitating communication	Quality of life measures may help patients communicate problems to healthcare providers and help staff focus on concerns that are most important to patients
Screening for hidden problems	Quality of life information can help identify problems such as depression or sexual dysfunction that may otherwise be overlooked.
Facilitating shared clinical decision making	Quality of life measures can help identify patient goals, outcomes, and expectations; healthcare providers can address whether treatment is likely to meet patient expectations and discuss discrepancies between probable outcomes and patient expectations
Monitoring changes or responses to treatment	Quality of life information can help determine whether treatment is leading to improvements that are relevant to patients.

Adapted from Higginson IJ, Carr AJ. Using quality of life measures in the clinical setting. *British Medical Journal*. 2001;322:1297.

Research

Quality of life measures also have important uses in research. They may be used to evaluate the impact of a disease or to answer the questions of whether and in what ways treatment improves or worsens quality of life. Such measures are increasingly recognized as important determinants of treatment outcome. Quality of life information gleaned from research can be used in clinical practice in all of the ways we considered in the last section. For example, clinical research studies may tell us that two treatments are comparable in reducing the size of a tumor, but one may be associated with better quality of life overall or for specific elements that may be important to individual patients. This may help physicians and patients in deciding which treatment to select.

Let's consider an example of how quality of life measures may be used in research. For the purposes of this example, let's assume that research has uncovered a new treatment for macular degeneration, a condition in which vision is gradually lost and may eventually result in blindness. In a clinical trial of the new medication, eyesight improved by an average of 3 points on a visual scale. Statistical analysis showed that this 3-point improvement was significantly better than the 0.5 point improvement

experienced by patients receiving no treatment at all, and therefore, the researchers considered the new medication a success.

However, in our hypothetical trial, participants reported that they did not experience any overall improvement in their physical or mental health. That is, the treatment didn't make any difference in how positively they viewed their lives or how well they could perform their daily activities such as brushing their teeth, cooking, or going for a walk. Was the treatment a success? What if patients experienced an improvement in reading but not in their overall physical or mental health? Would you then call the treatment a success? These types of questions are not always easy to answer but are important to ask. A growing recognition that these questions are important has increased the number of clinical trials that include quality of life questions as outcome measures.

Quality of life outcome measures in clinical research trials have increasingly been considered by the United States Food and Drug Administration (FDA) in their approval of medications. In 2009, the FDA issued guidance for industry (such as drug manufacturers) on the inclusion of these outcomes in clinical trials designed to support product approval. This guidance is available at: <http://www.fda.gov/downloads/Drugs/Guidances/UCM193282.pdf>. In the area of cancer research, one area in which quality of life outcomes are being increasingly used is in the validation of new biomarkers. In this context, they are also sometimes referred to as predictive markers. Many experts believe that the use of quality of life outcomes in research will continue to grow in the coming decade.

Societal Uses

In addition to the research and medical uses, quality of life measures can be used in evaluating progress toward health goals for larger societal groups including communities, nations, and even the world. Quality of life data can be further used to compare health disparities across segments of the population and to measure the success of initiatives designed to reduce those disparities. One example of a society-wide quality of life initiative is America's Health Rankings® published by The United Health Foundation and the American Public Health Association and Partnership for Prevention. This program uses the Healthy Days measure developed by the Centers for Disease Control and Prevention (CDC), in which Americans are asked how many days over the last month they were limited in their activities due to physical health difficulties. The same question is asked about mental health difficulties. The results are compiled each year and compared to those over the past decade as an overall indication of whether we, as a society, are getting more or less healthy over time. The results are also broken down by state so that disparities in health can be identified and addressed. More about this program is available at the Centers for Disease Control Web site: <http://www.cdc.gov/hrqol/featured-items/healthy-days.htm>.

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Chapter 2: Measuring Health-Related Quality of Life

Health-related quality of life is a subjective state and therefore must be reported or rated by individuals themselves. This rating is usually done using a questionnaire. Individuals are asked to answer one or more questions in a variety of areas that usually include physical, emotional, and social health. For instance, questions in the physical health category may relate to how well we are able to engage in everyday activities such as walking or grocery shopping. Questions in the emotional health category may explore how our health affects mood and feelings, such as the amount of anxiety we feel about our next physician's visit, whether we will ever be able to do the things we used to, or how long we will live. Social aspects may include whether our health interferes with interactions with others, such as attending religious services, participating in family gatherings, or talking with friends.

Some investigators conceptualize health-related quality of life as an overarching framework that encompasses health-related quality of life domains including physical, social, and emotional well-being, as well as specific symptoms such as pain and fatigue. An alternative perspective utilizes patient-reported outcomes as a more general term to encompass health-related quality of life domains (eg, physical, emotional, social well-being) and symptoms as distinct domains.

In contrast to measuring blood pressure or body weight, there is no single standard way to measure quality of life. In fact, there are hundreds, perhaps even thousands, of different quality of life measures that vary on important characteristics such as whether they contain single or multiple questions, whether they measure multiple aspects of quality of life or just one, and whether they are general or specific to a given condition or disease state. Ideally, the health-related quality of life measure selected is grounded in the investigator's theoretical model of health-related quality of life. When choosing quality of life measures to include in research studies, investigators must take into account the research objectives and setting. Similarly, healthcare professionals using quality of life measures in clinical settings must select based on their clinical objectives.

Single Versus Multiple Item Measures

Quality of life questionnaires may be classified as single or multiple item measures. A single item is one question intended to measure overall quality of life or one particular characteristic of quality of life. As we saw in the previous chapter, an example of a single item measure is the Healthy Days question posed by the Centers for Disease Control and Prevention, in which Americans are asked how many days over the last month they were limited in their activities due to physical health difficulties. In contrast, a multiple item questionnaire has more than one question focusing on a single aspect of quality of life.

In quality of life measurement, questions are often referred to as items and questionnaires are often referred to as instruments or measurement tools. Different aspects or areas of quality of life, such as mental health, social functioning, and physical health, are referred to as domains

Single and multiple item questionnaires each have advantages and disadvantages. Single items are simple and quick but lack detail. Multiple items can give a more comprehensive picture but are more expensive, time consuming, and may contain irrelevant questions. The two types of measures can be effectively used together. For example, you could ask someone how their physical health has been over the last 30 days and provide check boxes with optional answers. You could also ask a series of more detailed questions about whether their health has caused them to be limited in a variety of activities such as climbing stairs, walking, shopping, or driving.

General Health-Related Quality of Life Measures

Another important distinction between quality of life measures is whether they assess general health-related quality of life or whether they are specific to a given disease. The most well-known, standardized health-related quality of life measures are general scales that are not limited to any one particular disease. One of the most commonly used general health-related quality of life instruments used today is based on the Medical Outcomes Study (MOS). This was a 2-year study of patients with chronic conditions that used a questionnaire containing more than 100 items measuring the physical, mental, and general health components of quality of life. The study resulted in a “core” survey of 119 items organized into physical health, mental health, and general health components, as shown in the following table.

General Conceptual Components of the Medical Outcomes Survey (MOS)

Physical Health	Physical functioning, satisfaction with physical ability, mobility, pain effects, pain severity, role limitations due to physical health
Mental Health	Psychological distress (anxiety and depression), psychological well-being (positive affect and feelings of belonging), cognitive functioning, role limitations due to emotional problems
General Health	Energy/fatigue, sleep problems, psychophysiologic symptoms, social functioning, role functioning (eg, unable to work), current health perceptions, and health distress

Several shorter versions of the MOS known as short forms are extremely popular in research settings. These tools are referred to by the initials SF for short form followed by the number of questions they contain, such as the SF-36 and SF-12. The SF-36 includes 36 questions that are grouped into 8 subscales: vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health. The following are examples of several questions on the SF-36. These examples were selected because they demonstrate the different types of ratings that are used on the SF-36 (eg, a rating of how much someone is affected by the concern or limitation vs. true or false). These sample questions were also selected because they can be readily understood even when taken out of the context of the questionnaire.

- Does your health now limit you in these activities? If so, how much?
(Yes, limited a lot; Yes, limited a little; No, not limited at all)
 - Climbing one flight of stairs
 - Walking one block
- How much of the time during the past 4 weeks did you feel full of pep
(rated between all of the time to none of the time)?
- I expect my health to get worse. True or false.

Disease Specific Health-Related Quality of Life Measures

Sometimes general health-related quality of life questionnaires are not optimal for use in clinical research because they are too broad. For example, some conditions such as stroke can result in numerous health problems. A drug used to treat swallowing problems following stroke may actually improve a person’s ability to eat and drink, but would not necessarily be expected to help a person walk or sleep better. If the person is asked to consider how the drug improves overall health, he or she may say that it does not because walking and sleeping are such important components of overall health. Thus, the overall measure may show that the drug does not improve quality of life. In such cases, it may be better to ask the person whether the drug helps them eat or drink, which is where more specific health-related quality of life questionnaires can be useful.

Disease specific quality of life measures focus on a particular disease or condition. Some of these questionnaires are designed for use in only one type of disease such as cancer and would not be useful for people with another disease like arthritis. Other conditions such as depression can be associated with many different diseases. For instance, depression can be seen in cancer, Parkinson disease, and multiple sclerosis, and its measurement can provide important quality of life information for people with any of these diseases. Other examples include questionnaires designed to evaluate sexual functioning, anxiety, and activities of daily living. Each of these questionnaires has a specific name such as the Hamilton Depression Inventory and the Katz Index of Independence in Activities of Daily Living. It is not uncommon for clinical trials of treatment effectiveness to include multiple quality of life rating instruments (questionnaires) in order to determine whether a given treatment improves various aspects of quality of life related to a specific disease or condition. An example of a questionnaire that is specifically used for cancer patients is described in a later section.

The Science of Health-Related Quality of Life and Patient-Reported Outcome Measure Development

Well-designed health-related quality of life and patient-reported outcome measures have face validity, meaning that it is clearly evident what they intend to measure. As a result, investigators often hold the mistaken belief that health-related quality of life measures can be quickly and easily created by simply writing out questions they want to ask. However, there is a significant body of research on the development and validation of health-related quality of life measures for clinical and research purposes. The International Society for Quality of Life Research (ISOQOL) is a professional organization focused on this science. As an example of the complexity with health-related quality of life measures, researchers have found that asking the same questions worded negatively (eg, “I have trouble concentrating”) versus positively (“I am able to concentrate”) produce different results. Given these complexities and nuances, it is important for advocates to have a general awareness of this area of research and the importance of the evidence for health-related quality of life clinical and research projects.

Quality of Life Measures in an Actual Clinical Cancer Trial: E5103

This section explains the quality of life measures used in an actual clinical research trial for breast cancer known as E5103. This study was conducted by the Eastern Cooperative Oncology Group (ECOG) and is entitled: *A Double-Blind Phase III Trial of Doxorubicin and Cyclophosphamide followed by Paclitaxel with Bevacizumab or Placebo in Patients with Lymph Node Positive and High Risk Lymph Node Negative Breast Cancer.*

This study was designed to determine the effects of adding a monoclonal antibody drug known as bevacizumab to a standard chemotherapy regimen (doxorubicin/ cyclophosphamide/ paclitaxel) in patients with breast cancer who were at a high risk of relapse. All patients were treated with chemotherapy, but some also received treatment with bevacizumab, whereas others received additional treatment with placebo, depending on the group to which they were randomized. The quality of life objectives in this study were to compare breast cancer patients treated with doxorubicin/cyclophosphamide/paclitaxel and bevacizumab or placebo. Effects on quality of life were measured in terms of physical symptoms, physical functioning, psychological state and social functioning in a subset of patients. The specific measures selected to evaluate these aspects of quality of life were as follows: FACT-Breast, the Memorial Symptom Assessment Scale, the EQ-5D, the Kornblith Fear of Recurrence Scale, and a decision-making survey designed for E5103. Let’s take a closer look at each of these.

The Functional Assessment of Cancer Therapy (FACT) scale for breast cancer (FACT-B)

The FACT-B is an overall measure of quality of life that includes two different scales. The first is a more general scale, known as the FACT-general or FACT-G, which is a scale in its own right. This 27-item scale measures physical well-being, social/family well-being, emotional well-being, and functional well-being. Nearly all items are rated on a 5-point scale ranging from 0 (not at all) to 4 (very much). The second part of the FACT-B is a breast cancer specific scale that contains 9 items related to breast cancer, primarily addressing physical symptoms, body image, and sexual issues.

Memorial Symptom Assessment Scale (MSAS)

The MSAS contains 32 items that provide an overall measure of the physical and psychological symptoms commonly described by cancer patients. For most of the items, patients rate their symptoms in terms of frequency, severity, and distress, although 8 of the items are rated only in terms of severity and distress. For the E5103 study, additional items were added to the original MSAS to reflect symptoms or problems that were anticipated to possibly occur because of the new study drug.

European Quality of Life-5D (EQ-5D)

The EQ-5D is a general measure of health outcomes that is not specific to cancer. The EQ-5D comprises five dimensions: mobility, self-care, usual activity, pain/discomfort, and anxiety/depression. Patients rate each of these dimensions as “no problem,” “some problem,” or “extreme problem.” This scale has been standardized for the United States population and can be used for economic analyses.

Kornblith Fear of Recurrence Scale

The Kornblith Fear of Recurrence Scale evaluates beliefs and anxieties related to cancer recurrence in cancer patients or cancer survivors. This scale is made up of 5 items that are rated on a 5-point scale from “strongly agree” to “strongly disagree.” This is one of several different cancer recurrence scales available; for instance, another scale, the Assessment of Survivor Concerns, was used to measure fear of recurrence in a clinical trial known as TAILORx [Trial Assigning Individualized Options for Treatment (Rx)].

Decision-Making and Risk-Benefit Evaluation

The E5103 trial also included a novel assessment procedure to examine patient decision-making and risk-benefit evaluation. Before treatment, patients were asked about their perceptions related to cancer risk and the likelihood that the treatments would cause serious problems. Patients were also asked about how well informed they believed they were and how much confidence they had in their treatment decision. These perceptions were evaluated again after patients found out the group to which they were randomized and again 18 months after treatment. At the 18-month follow-up visit, patients were also asked about the risk versus benefits of treatment, such as how willing they were to accept the toxicities of bevacizumab and the minimum benefit they would need to obtain to deem the treatment worthwhile.

As can be seen from this list of quality of life outcome measures, a single trial may incorporate numerous questionnaires that assess different aspects of health-related quality of life. This is a common scenario: Most large, multicenter clinical trials have multiple outcome measures that often include one or more quality of life measures. In the next chapter, we will talk more about quality of life issues as measured in clinical trials.

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Chapter 3: Effects of Cancer and Its Treatment on Quality of Life — Information From Clinical Research

Studying Adverse Events or Reactions in Cancer

Many of the clinical trials in cancer research are sponsored by pharmaceutical companies seeking approval for a new treatment. In these studies, adverse reactions are regularly documented according to a standardized checklist. This documentation typically requires a physician's assessment of whether the adverse event is related to the treatment under study and whether the event is mild, moderate, severe, or serious in nature. For research sponsored by the government or private organizations in the form of grants, adverse events and safety monitoring are also required as part of the studies. Regardless of whether the study is sponsored by a pharmaceutical company, the government, or a private organization such as a foundation, adverse event reporting can be rigorous and detailed. However, documentation of whether an adverse event did or did not occur and how severe it was does not give the full picture. That is, the effects of adverse reactions on patients' daily lives, their activities, and their emotions are not part of the ratings. Quality of life information, including patient-reported symptoms, can help fill this gap.

Quality of life research related to adverse events, lingering symptoms, or new challenges following treatment are important because people do not report all adverse events as equally bothersome or detrimental to their lives, even if they are rated at the same severity level on a checklist. For example, as a group, people may be more bothered by moderate hair loss than moderate diarrhea. Additionally, individual people report differences in the extent to which they are bothered by given side effects. You may be more bothered by nausea, whereas another person may be more bothered by skin abnormalities. Variables such as age, employment, and hobbies/interests can all influence the degree to which side effects influence quality of life. Moreover, the cancer experience itself, including the desire to be successfully treated, can strongly influence how patients perceive adverse reactions and the influence that these reactions have on treatment decision making. The collection of patient-reported outcomes on symptom severity, frequency, or distress can provide insights on new treatments from the patient perspective. The collection of health-related quality of life outcomes can provide insights on the extent to which treatment-related adverse events or symptoms affect well-being and functional status.

The area of research that examines how individuals weigh information about treatment benefits and side effects is often referred to as patient preferences. Understanding patient preferences related to cancer treatment can help determine standards for the development of new therapies and biomarkers. More information about patient preferences is freely available at the following Web sites:

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Thanks to progress in research and treatment, many people are now surviving cancer to live years or even decades after the initial diagnosis. As a result, quality of life issues in cancer now extend beyond the effects of treatment on physical, mental, and social well-being. Some individuals with cancer need to take medications for many years and others finish treatment completely but live wondering whether or when their cancer will return. In some cases, the treatment causes new quality of life deficits due to surgical removal or alteration of a body part such as a breast or a portion of the colon. Thus, quality of life measures in cancer are important to consider across the entire cancer care continuum, from diagnosis through survival and eventually death.

Quality of Life Issues Associated With Breast Cancer

Quality of life measures are increasingly used in the assessment of almost all types of cancer and other health conditions, but in this section we focus on breast cancer. Breast cancer survivors are a growing population of more than 2 million in the United States. The 5-year survival rate for individuals whose disease is detected early is more than 90%, with continued improvements expected in the future. As a result of early detection and more effective treatment, breast cancer may eventually become a chronic condition for many women.

Effects of Breast Cancer and its Treatment on Quality of Life

Both breast cancer and its treatment—surgery, chemotherapy, and/or radiation therapy—can have a significant impact on quality of life. Breast cancer survivors report physical health concerns such as persistent fatigue, lymphedema (tissue swelling due to accumulation of lymph fluid) and body image changes. Younger women may have special concerns such as fertility and premature menopause. In 1998, Dr. Patty Ganz and her colleagues reported on a study that examined quality of life in more than 1000 breast cancer survivors from the Los Angeles and Washington DC areas. This research specifically looked at the effects of adjuvant therapy, or cancer treatment given after surgery to lower the risk of cancer recurrence. Women in this sample were treated with tamoxifen alone as an adjuvant therapy, chemotherapy alone, tamoxifen plus chemotherapy, or no adjuvant treatment. Results showed that breast cancer survivors generally function at a level that is similar to healthy women without cancer. However, physical functioning was slightly worse in survivors who received adjuvant therapy than in those who received no adjuvant therapy. The different adjuvant therapies had somewhat different effects on sexual functioning, vaginal symptoms, and vasomotor symptoms; for instance, sexual functioning was worse in patients receiving chemotherapy (either alone or with tamoxifen) and vasomotor symptoms such as hot flashes and night sweats were more common in those treated with tamoxifen than in the other two groups. Five years later, women who had received any adjuvant therapy showed worse physical functioning than those who did not receive adjuvant therapy. Additionally, past chemotherapy treatment predicted poorer quality of life.

Among breast cancer survivors, fear of recurrence is common and can be intrusive or even disabling for some, particularly right after treatment ends. Many women report that the anxiety eventually lessens over time. Various types of psychotherapy have been shown to be effective for anxiety, depression, and general psychosocial distress among cancer survivors. These approaches may also lead to reduced fear of recurrence.

Breast cancer and its treatment can also impact employment. A 2009 analysis found that 35.6% of breast cancer survivors were unemployed, compared with 31.7% of control subjects. Another study of 273 women found that 79.8% returned to work, about half within one year. Factors that influenced the return to work were age (<55 years of age returned more often), educational level, colleague support, chemotherapy, lymphedema, and the physical and psychological demands of the job. Factors that did not affect return to work were type of surgery, tumor resection (lumpectomy) versus mastectomy, removal of the sentinel lymph node versus removal of all the lymph nodes in the axillary (underarm) area, radiation therapy, and hormone therapy. In women treated for early-stage breast cancer, both treatment-related factors and psychosocial factors influenced return to work after

treatment. This study found that women who had not returned to work at 6 months were more likely to have had chemotherapy, more likely to have had >30 days of sick leave during the previous year, and tended to have a low satisfaction with activities of daily living. Those who had not returned to work at 10 months were more likely to have received irradiation to the breast/chest wall and regional nodes and more likely to express a low satisfaction with work.

Effects of Quality of Life Measures on Breast Cancer Prognosis

Women who survive breast cancer also report mental health concerns such as depression, fear of recurrence, anxiety, insomnia, and a need for social support—especially when treatment ends. These psychological symptoms are important to breast cancer survivors and are therefore important for healthcare providers to consider. Depression in particular is often overlooked and, if left untreated, is associated with worse physical health.

However, quality of life may be important to individuals with breast cancer for another reason besides the need for support: Some evidence suggests that depression may be related to breast cancer prognosis. Specifically, one study found that depression in women with breast cancer was associated with a higher risk of recurrence and early death. In 2011, Drs. David Spiegel, Giese-Davis, and their colleagues at Stanford University reported preliminary results suggesting that decreasing depressive symptoms over the course of 1 year may be associated with longer survival for women with metastatic breast cancer. These results will need to be confirmed in larger trials, but they may support the idea that quality of life can influence disease outcomes.

Dr. Spiegel and his colleagues have also investigated a particular mechanism by which depression could influence breast cancer progression. Depression is associated with increased levels of the stress hormone cortisol, which affects the immune system. Reduced immune function could make individuals more susceptible to infections, but also may enable tumor growth. Further research will be necessary before firm conclusions can be drawn, but these types of studies point to the importance of quality of life variables.

In another study conducted by the North Central Cancer Trial Group (NCCTG), Drs. Angelina Tan, Jeff Sloan and colleagues found that quality of life predicts the survival of late-stage cancer patients. In their analysis, 3704 patients with a variety of cancer types who had participated in one of 24 different NCCTG trials were asked how they rated their quality of life on a scale from 0 to 100. Quality of life was found to be a strong predictor of survival duration—patients whose scores were at least 83, showed a 6.1 month increase in survival time over those with scores lower than 83. Although these findings are intriguing, it is important to remember that they indicate an association only—they do not imply that higher quality of life scores caused the increase in survival or that if you can convince yourself to be happy, you will live longer. That is, several other relationships between these variables are possible. One possibility is that the longer survival duration leads to an improved quality of life. Another possibility is that a third factor such as higher levels of a certain biochemical could cause both an increase in survival as well as higher quality of life scores. As a result, we can conclude that knowing someone's quality of life score can help predict survival duration but not that a higher quality of life causes the longer duration.

Support for an association between quality of life and cancer survival also comes from the lung cancer literature. A 2012 study found that quality of life scores 6 months after surgery for lung cancer predicted long-term survival in a population of 141 Swedish patients. This study used the SF-36 to measure quality of life. The SF-36 is made up of 8 domains, 4 of which are classified as the physical component and 4 of which are classified as the mental component. The physical component contains items related to a person's ability to carry groceries, walk, amount of pain, and general health. The mental component contains items related to a person's vitality or pep, social functioning, nervousness, and depression. In the Swedish cancer study, patients whose scores on the mental

component of quality of life were below those of the normal population had a 3 times greater risk of death than patients with higher mental component scores. These findings strongly suggest that we need to continue studying the association between quality of life scores and cancer survival, although again, we must bear in mind that an association does not mean that quality of life causes shorter or longer survival.

Quality of Life Issues Associated With Colorectal Cancer

More than 140,000 people in the United States are diagnosed with colorectal cancer each year, making it the third most common type of cancer for both men and women. Due to advances in screening protocols and novel treatments, the 5-year survival rates for colorectal cancer have doubled since the 1970s.

As with other cancers, the increase in survival rates is accompanied by quality of life challenges that may persist or emerge following completion of initial treatment. The use of adjuvant chemotherapy with 5-fluorouracil has increased survival rates by approximately 30% and the addition of the chemotherapy drug oxaliplatin in stage III colon cancer provides an additional 20% improvement. Unfortunately, peripheral neuropathy occurs in up to 92% of colorectal cancer survivors treated with oxaliplatin and adjuvant therapies. Peripheral neuropathy is a problem with sensory nerves that causes numbness and pain and can lead to difficulties with fine motor skills such as writing, holding objects, buttoning shirts, picking up coins, and walking. Dr. Stephanie Land and colleagues studied peripheral neuropathy in colorectal cancer survivors and found that most people recover their nerve function within a month after finishing treatment. However, up to 20% may experience worsening neuropathy symptoms and up to 12% may still have symptoms four years after treatment completion.

Other long-term issues for colorectal cancer survivors may include fatigue, sleep difficulty, fear of recurrence, anxiety, depression, negative body image, gastrointestinal problems, urinary incontinence, and sexual dysfunction. In two separate studies, Dr. Scott Ramsey and Dr. Eric Schneider found that health-related quality of life issues reported by colorectal cancer survivors in the short-term generally improved within three years of diagnosis, and by four years after diagnosis, approximately 66% of survivors reported having no symptoms and fewer than 10% reporting more than two symptoms. However, emotional symptoms such as fear of cancer recurrence and of future diagnostic tests persist in some patients, and approximately a quarter of individuals may require further evaluation for clinical depression.

Low income and financial worry has been associated with increased pain levels, mobility issues, and lower social and emotional well-being in colorectal cancer survivors. In 2009, Dr. Angela de Boer conducted a large meta-analysis of studies, including more than 20,000 cancer survivors, and looked at risk factors leading to disability resulting in unemployment. She determined that 49% of survivors of female reproductive cancers and gastrointestinal cancers, including colorectal cancer, were the most likely to be unemployed, further compounding the effects of low income on quality of life for these individuals.

For colorectal cancer survivors who have had a part of their colon removed, the presence of a stoma may also influence quality of life. A stoma is an opening from the digestive system or urinary system that functions as an exit point for feces or urine. The waste is typically collected in a small bag worn on the outside of the body. Having a permanent stoma can substantially impact the functioning and lifestyle of colorectal cancer survivors and has been associated with negative body image in nearly 25% of individuals. However, many people adjust over time, with one study showing that a permanent stoma did not have lasting negative effects on social functioning or activities of daily living in colorectal cancer survivors.

As shown by these findings, colorectal cancer survivors may experience post-treatment symptoms, including both physical and emotional difficulties, which can affect quality of life. Some of these, such as the presence of a stoma, are unique to the location of the cancer, whereas others like fear of recurrence are seen across all cancer types. Survivorship is increasingly recognized as a distinct phase of cancer treatment that requires attention and study, and quality of life assessments are central to these efforts.

These studies illustrate the value in collecting patient-reported outcomes to identify the most critical concerns among colorectal cancer survivors from the patient's perspective and the course of recovery following treatment.

Office of Cancer Survivorship (OCS) of the National Cancer Institute (NCI)

With the growing number of cancer survivors over the past few decades, the National Cancer Institute (NCI) recognized the need to better understand the unique concerns and issues facing individuals and their families after the diagnosis and treatment of cancer. In 1996, the NCI founded the Office of Cancer Survivorship (OCS) whose goal is to enhance the quality and length of survival of all persons diagnosed with cancer and to minimize or stabilize adverse effects experienced during cancer survivorship. Toward this end, the OCS supports research into the physical, psychological, social, and economic effects of cancer and its treatment.

In the following text, we consider some of the research projects that OCS has supported in an effort to highlight the breadth of issues considered in survivorship.

- Dr. Erin Kent and fellow researchers are exploring the unique challenges of adolescents and young adult cancer survivors. They have identified several themes of significant importance to cancer diagnosis as a young adult, including challenges with the care continuum and associated psychosocial concerns such as infertility and reproductive concerns, changing social relationships, and financial burden. Dr. Kent also stresses the importance of the young patient's voice and involvement in each stage of their care. This work has set a foundation for potential modifications to intervention development for adolescent and young adult survivors that may not be addressed by cancer clinicians and overlooked in their standard care plans.
- Dr. Catherine Alfano and colleagues are studying the effects of inflammation on feelings of fatigue in cancer survivors. These researchers evaluated the diets of 633 breast cancer survivors and examined how the findings compared to levels of fatigue as measured on a validated fatigue measurement scale. Results showed an association between higher intake of omega-3 polyunsaturated fatty acids, found in some fish and plant oils, decreased inflammation, and decreased physical aspects of fatigue commonly encountered by breast cancer survivors.
- Dr. Laura Forsythe and colleagues recently studied factors that contribute to the presence of pain in breast cancer survivors. They evaluated associations of body mass index and physical activity for up to a decade following diagnosis. Results showed that women who maintained a normal weight and met the guidelines for physical activity levels were less likely to report above-average pain following treatment.
- Dr. Karen Bowman led a team of researchers that assessed the stressfulness of the cancer experience for family members and long-term cancer survivors. They found that family members tended to appraise the cancer experience as more stressful than their surviving relatives, and beliefs about the effect of the diagnosis and treatment on family members were important correlates for both family members and survivors. The results highlight the stressful impact of the cancer experience on family members and may help guide health care interventions.

The findings of OCS-funded research have been presented at conferences around the world and appear in various high-impact academic journals, reaching other researchers and also providing guidance to clinicians within their practice and treatment strategies.

More information can be found at: <http://cancercontrol.cancer.gov/ocs/office-survivorship.html> and at <http://cancercontrol.cancer.gov/ocs/>.

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Chapter 4: Challenges With Quality of Life Measures

Most people agree that quality of life is important. However, this agreement doesn't always translate into the incorporation of quality of life measurement and information in clinical research and practice. In this chapter, we explore some of the challenges surrounding the measurement and use of quality of life data. Some of these challenges are specific to clinical research trials, whereas others apply to quality of life information across the board, whether it is used in research, clinical practice, or for societal purposes.

Deciding Which Quality of Life Measure(s) to Use

As we saw in Chapter 2, numerous different instruments exist that vary from single item questionnaires to long multiple item questionnaires that cover a variety of different health-related domains. An important consideration with quality of life measurement that applies across all situations is deciding which questionnaire to use. Unlike many other types of information obtained in clinical research and practice, there is no one standard way to measure quality of life, although several robust validated instruments exist. Selection of a quality of life measure should be based on a definition of health-related quality of life because the working definition determines which domains are important to assess in various clinical and research contexts. To conduct rigorous science, it is important that the quality of life research be driven by hypotheses.

When selecting among the various different measures or questionnaires available, it is essential to take into account the objective or purpose for obtaining the information. If your research question involves a specific disease state such as cancer, it may be useful to select an instrument developed for the cancer population such as the Functional Assessment of Cancer Therapy (FACT) questionnaire. If you are specifically interested in depression or pain, you may want to include questionnaires that are specific to those symptoms. However, if you are interested in how the quality of life of cancer patients differs from that of the general population, you may want to select a more general scale. Another important consideration in deciding which quality of life measure to use is the setting. Is the questionnaire to be given in a hospital? Over the internet? At a physician's visit? Are the patients well enough to answer the questions? Are multiple language versions needed? The setting will help determine which measure or measures are most appropriate. An important consideration related to the setting is how much time individuals will have to fill out the questionnaire. For instance, will the questionnaire be given after multiple other assessments or before? Will the questionnaire be one of many or is it the only one? Are people likely to be in a hurry in the setting you have selected? All of these questions can help in matching the questionnaire to the setting.

Regardless of the objectives or setting, it is important to ensure that the quality of life instrument is reliable, valid, and sensitive enough to detect changes. Some of the commonly used quality of life instruments have been rigorously designed and validated. These include the general measures known as short form 36 (SF-36) and the Functional Assessment of Chronic Illness Therapy (FACIT), and the cancer-specific instruments European Organization for Research and Treatment of Cancer (EORTC) QLQ-C3013 with tumor-specific modules and the FACT scale with its tumor and treatment-specific subscales. A useful Web site has been developed by Information Resources Centre of the Mapi Research Institute in France and Dr. Tamburini of the Institute Nazionale Tumori in Italy (<http://www.proqolid.org/>). This site, known as the Patient-Reported Outcomes and Quality of Life Instruments Database (PRO-QOLID) contains information on numerous quality of life questionnaires that can be helpful in determining their validation status. This database requires a subscription to access.

Meaningful Differences in Quality of Life Ratings

Another important consideration with quality of life measures is the amount of change on the rating scale that is clinically important or clinically meaningful. This consideration is not unique to quality of life ratings; the question actually applies to many different types of measures. Examples include how much improvement in walking speed is meaningful in people with nerve damage and how much pain relief is needed to be considered a meaningful reduction from the patient's perspective. It is generally agreed that a change perceived by patients as beneficial or detrimental is clinically important. For instance, if your score on a depression question decreases by 2 points but you don't notice any change in your mood, that decrease may not be clinically important. It may just be day-to-day variation or may represent a change so slight that you don't even notice it. On the other hand, if your score decreases by 2 points and you feel noticeably better, then a 2-point reduction is clinically meaningful.

Another potential metric is the amount of decline in quality of life scores that leads a person to seek healthcare for the problem (eg, adverse reaction) or request changes in treatment. From the clinician's standpoint, the smallest change in quality of life scores that leads them to recommend a treatment or therapy to their patients is often considered clinically important. This approach is referred to as an anchor-based method for determining a clinically significant change score because it is established using known, clinically significant events such as treatment change.

Another approach is called a distribution-based method, which involves using a statistical measure to calculate the clinical significance of quality of life scores. The basis of this recommendation was an analysis of 38 quality of life studies that used a variety of different rating instruments, all of which evaluated the minimally important difference in quality of life as the amount of change that people noticed or perceived as a change. This paper was published in the journal *Medical Care* in 2003 by Dr. Norman and colleagues at McMaster University in Ontario, Canada. In looking at the minimally important difference reported in these studies, the authors noted that most were about one half of a standard deviation away from the mean. Other studies have also examined minimally important differences in quality of life measures. For example, minimally important differences on the National Institutes of Health (NIH) project known as Patient-Reported Outcome Measurement Information System (PROMIS®) were published in a 2011 paper by Yost and colleagues. PROMIS® is more thoroughly described in Chapter 5.

In interpreting the distribution-based method, it may be helpful to know a few statistical terms. The mean is simply the average, and a standard deviation is a statistical measure of how variable the data are—higher standard deviations mean greater variability in people's scores on the questionnaire. The 0.5 standard deviation number has been criticized as being too simple; for instance, some have argued that the detectable difference in quality of life varies depending on the population (eg, the important difference to cancer patients may be different than that of spinal cord injury patients). However, the number has also been influential, at least in part because of its simplicity, in an area of research that is often bemoaned as complex.

Differences in Values and Priorities

When considering quality of life measurement, it is important to recognize that individuals place different value on various aspects of quality of life. The same person may even show a different emphasis depending on his or her stage of life. For example, a mother of young children may place less emphasis on remaining socially active during treatment than a woman whose children are grown, and the priorities of the mother with young children may change over the years. Diarrhea—a common side effect of many cancer therapies—may be more problematic for a man whose work requires him to travel frequently than for a man who works at home or who is retired. Some people may simply be more bothered by diarrhea than others. Additionally, some people may be more willing than others to put up with the toxicities of cancer treatment in order to achieve a better

“As more studies are completed, clinicians will gain greater insight into the magnitude of change that is clinically important. Eventually, a universal standard will emerge as being acceptable.” — David Osoba, 2011 in Osoba D. Health-related quality of life and cancer clinical trials. *Ther Adv Med Oncol.* 2011;3(2):57-71.

chance of treatment benefit. These value differences make it difficult to judge the significance of changes in quality of life measures for individual patients.

Barriers to Inclusion in Clinical Research and Practice

Another important challenge with quality of life information is the resistance often encountered when trying to incorporate these measures into clinical research and practice. In this section, we consider some of the common barriers or objections that are often cited as reasons not to measure quality of life.

Some Common Objections to Including Quality of Life Measures in Clinical Research and Practice

- They are too time consuming
- They are too expensive
- No good questionnaires are available; don't know which one(s) to choose
- They are difficult to analyze and interpret; doctors believe that they lack the experience to assess quality of life
- They are subjective
- Patients are too ill to fill out questionnaires or they place too much of a burden on patients
- Asking patients questions about their symptoms, distress, or personal matters will be too upsetting to the patient
- Some patients don't speak English well
- There is too much missing data
- The lack of preclinical research to justify clinical symptom management studies

Adapted from Fallowfield L. What is quality of life? *Hayward Medical Communications*. May, 2009. Available at: <http://www.medicine.ox.ac.uk/bandolier/painres/download/whatis/WhatisQOL.pdf>. Accessed February 7, 2013.

Let's explore each of these issues in more detail.

• **Quality of life instruments are too time consuming and expensive.**

This is likely a misconception; people can fill out a 28-item quality of life questionnaire in about 5 to 10 minutes. It is true that some of the longer quality of life measures are time consuming (which can be expensive), but numerous shorter questionnaires are available and widely used.

• **No good quality of life questionnaires are available; don't know which one(s) to choose.**

It is simply untrue that no good questionnaires are available. Hundreds of questionnaires have been developed and many are well designed, widely used, and validated. A consideration of the research or clinical practice objectives and setting can help determine which scale to use and several Web sites are available that can assist in selection of a questionnaire: www.nihpromis.org/ and <http://www.proqolid.org/>.

- **Quality of life instruments are difficult to analyze and interpret; no one is available who has the experience needed to assess quality of life.**

In both clinical practice and clinical trials, physicians must learn to interpret quality of life data through education and experience. In this regard, it is not different from any other type of measure. Moreover, in clinical trials, quality of life data is typically entered into the database and sent to a central location, where it is analyzed and interpreted by experienced researchers. Physicians who are interested in learning about quality of life measures in their practices can read published articles on the topic, such as the following:

- Guyatt GH, Ferrans CE, Halyard MY, Revicki DA, Symonds TL, Varricchio CG, Kotzeva A, Valderas JM, Alonso J; Clinical Significance Consensus Meeting Group. Exploration of the value of health-related quality-of-life information from clinical research and into clinical practice. *Mayo Clin Proc.* 2007 Oct;82(10):1229-39.
- Higginson IJ, Carr AJ. Using quality of life measures in the clinical setting. *Br Med J.* 2001;322:1297.
- Halyard MY, Frost MH, Dueck A, Sloan JA. Is the use of QOL data really any different than other medical testing? *Curr Probl Cancer.* 2006;30(6):261-271.

- **Quality of life is subjective.**

It is true that quality of life scales are subjective, and that is the point. These scales provide information from the patient's point of view, which is complementary to information obtained from objective measures such as overall survival in cancer or blood pressure in hypertension. In addition, some symptoms such as pain and nausea are entirely subjective and can only be rated by the patient. Subjective information can be extremely valuable in determining whether a treatment's benefits outweigh its drawbacks. A classic example of how useful quality of life information can be in cancer research is in the comparison of two drug regimens that increase overall survival to a similar extent. We may learn from quality of life data that patients are able to engage in more of their usual activities when taking one treatment versus another. We may also learn that a minimal increase in survival benefit obtained with a given treatment is not worth the decrease in quality of life it causes. This type of information cannot be obtained from more objective measures.

When people object to quality of life information on the basis that it is subjective, the word subjective is often used as a pejorative to mean that it is not as good as the objective measures. However, research argues strongly against this. Quality of life has been found to be a good predictor of survival in patients with several different types of cancer, as discussed in the previous chapter. It seems possible that if we had physician-derived measures that predicted survival, people would be clamoring for their use. Thus, it is important to convince people that subjective measures can be as worthy as objective measures.

- **Patients are too ill to fill out questionnaires or they place too much of a burden on patients.**

Findings from researchers working in Ireland have demonstrated that individuals with advanced, incurable prostate cancer can complete quality of life rating instruments with good internal consistency and validity. Thus, the assumption that patients are too ill to fill out questionnaires may not be true. If patients seem fatigued by long questionnaires, shorter ones can be selected. However, patients generally like to report how they are feeling and are typically willing to answer questions about their health status.

- **Patients will become upset if asked about bothersome symptoms, distress, or personal questions**

Several studies have documented that patients do not become upset when asked to report on symptom or distress severity and in fact, view being asked about health-related quality of life and well-being as an indicator of high quality cancer care. Clinical trials that include health-related quality of life and patient-reported outcomes typically report very low refusal rates when patients are asked to complete questionnaires.

- **Some patients don't speak English well.**

Many of the most commonly used questionnaires are available in multiple language versions.

- **There is too much missing data.**

If the quality of life measures are well matched to the trial or clinical practice situation and the personnel administering the questionnaires are trained and motivated (ie, they understand and agree with the importance of collecting quality of life information), missing data can effectively be minimized. One of the most common reasons for missing quality of life data from cancer clinical trials is staff error, due to clinical research staff neglecting to administer health-related quality of life forms. When given the opportunity to complete health-related quality of life forms, patient participation rates are extremely high and generally well over 90%.

- **Lack of robust preclinical research to justify clinical palliative care or symptom management studies.**

Palliative care refers to care given to improve quality of life in patients with serious diseases like cancer. This is similar to the concept of symptom management, except that symptom management is broader. Studies examining palliative care or symptom management in cancer are not necessarily preceded by preclinical research, which can help establish the effectiveness of the drug and the need for a clinical study. For example, by the time new cancer drugs get to clinical trials, they have already shown promise in laboratory studies such as inhibiting a certain protein in cancer cells. Animal studies usually follow and, together, the effects of the drug in these preclinical studies can make a strong case that a clinical trial examining the efficacy and safety of the drug is needed and is important to conduct. In contrast, many palliative care or symptom management trials in cancer do not have preclinical studies to support them. Drugs or interventions for cancer symptom management are often tried because they work in a different disease or for a different symptom. The treatments may go directly to clinical research without the preclinical evidence base.

Although each of the common objections to quality of life information can be countered, the inclusion of quality of life measures in clinical research and practice often comes down to priorities. In situations where resources such as time and money are limited, choices must be made about what to include and what to exclude. Unfortunately, quality of life measures are often the first to be cut when resources dwindle. Physicians, already busy with current measures of health and administrative duties, may be reluctant to take on what they view as another time consuming assessment. It seems that to fully integrate quality of life measures in research and practice, it will first be necessary to change attitudes and perhaps provide education. In the next chapter, we will discuss several important initiatives aimed at increasing the acceptance and incorporation of quality of life measures into clinical research and practice.

Palliative care or symptom management:

Care given to improve the quality of life of patients who have a serious or life-threatening disease. The goal is to prevent or treat as early as possible the symptoms of a disease, side effects caused by treatment of a disease, and psychological, social, and spiritual problems related to a disease or its treatment. Also called comfort care and supportive care.

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Chapter 5: Patient-Reported Outcomes

Quality of life is often considered in conjunction with a concept known as patient-reported outcomes, or PROs, as described earlier. Patient-reported outcomes are evaluations of health as rated by the patient. The formal definition, from the United States Food and Drug Administration (FDA) is “any report of the status of a patient’s (or person’s) health condition, health behavior, or experience with healthcare that comes directly from the patient, without interpretation of the patient’s response by a clinician or anyone else.” These outcomes encompass physical, mental, and social outcomes and, in fact, all quality of life measures are patient-reported outcomes as long as they are rated by the patient. As we saw earlier, healthcare providers can ask their patients to rate outcomes such as quality of life as part of their treatment, but the phrase patient-reported outcomes is often heard in reference to clinical trials.

In clinical trials, outcomes are factors measured as part of the study to see how patients are doing and/or to evaluate treatment effectiveness. Quality of life measures are often used in this way; however, patient-reported outcomes is a broader term that encompasses but is not limited to quality of life measures. For example, during clinical trials, participants may be asked whether they are satisfied with the treatment, whether they would consider taking the treatment again once they finish the trial, or whether they prefer one treatment over another. When considering these questions, patients likely take into account how the treatment affects their quality of life; however, questions about treatment satisfaction or preference fall under the general umbrella of patient-reported outcomes and are not quality of life measures per se. This example illustrates how using quality of life and patient-reported outcomes synonymously can generate confusion. As described earlier, patient-reported outcomes can encompass many domains (eg. symptom severity, patient satisfaction)—one of which is health-related quality of life.

Historically, patient-reported outcomes in clinical trials have not been considered as important as clinical outcomes such as tumor size, progression free survival, or overall survival. This may be due to the study objectives, which have historically focused on variables related to tumor size and prolonging life. The lack of attention to patient-reported outcomes has been seen not only in cancer, but other areas of medicine as well, where established practices have historically dictated that clinical measures be used as the major outcomes. Over the past decade, attitudes have shifted somewhat, with patient-reported outcomes gaining importance and recognition, especially as treatments have improved and more options have become available. Many people now accept that patient-reported outcomes can serve as the primary measures of effectiveness for certain diseases and conditions, and can be complementary in others. For example, a new drug may not increase progression free survival compared with a current drug, but may improve quality of life. This drug would still be valuable and would represent a treatment advance, but we would only know this if the study had included quality of life measures as patient-reported outcomes.

In 2009, the United States FDA issued a document that provides guidance for drug manufacturers in the use of patient-reported outcomes in clinical trials. These FDA guidelines are not laws or absolutes, but rather are recommendations on how to select patient-reported outcomes, how to measure them, and how to document the sensitivity, reliability, and validity of the measurement tool. By following the recommendations in the FDA guidance document, manufacturers may be able to use patient-reported outcomes for approval of their drug. Indeed, some drugs have been approved for the treatment of diseases or conditions using patient-reported outcomes as the primary efficacy

measure or main outcome variable. The FDA guidance document is available on the Web at: <http://www.fda.gov/downloads/Drugs/Guidances/UCM193282.pdf>. Additional guidelines on incorporating patient-reported outcomes specifically into cancer trials have been issued by the Center for Medical Technology Policy. These guidelines are available on the Web at: <http://cmtpnnet.org/wp-content/uploads/downloads/2011/12/PRO-EGD-FINAL.pdf>.

Incorporating Patient-Reported Outcomes into Phase II Trials

One specific area in which patient-reported outcomes could be incorporated more consistently is in Phase II trials. Phase II trials are the initial stage of efficacy testing for a drug. They are smaller than Phase III trials and can be used to inform Phase III study design.

Summary of Clinical Trial Phases

Phase 0 – Exploratory Investigational New Drugs (IND)

Phase 0 trials are designed to determine whether the new drug actually affects its intended target. In these studies, people are given small doses of the drug and the drug's effects on the target are measured. These studies do not provide information about whether the drug is safe and effective.

Phase I – Safety Testing

Phase I trials involve a small number of people and are designed to determine whether the drug is safe. Often the dose of a drug is gradually increased until problematic side effects occur. Participants in Phase I trials may be cancer patients whose disease has not responded to other therapies.

Phase II – Efficacy Testing

If the drug passes Phase I trials, it is eligible for Phase II studies in which the effectiveness of the drug is examined. These studies usually involve about 100 people, usually those whose cancers have not responded to other treatments.

Phase III – Efficacy Testing in Larger Populations

Phase III trials are the primary safety and efficacy studies that determine whether a drug will be approved by the FDA to treat a given condition. In Phase III trials, hundreds or thousands of people are usually randomized to treatment with the experimental strategy/drug or the current standard treatment. Outcomes such as disease control, side effects, and quality of life are then compared between the two groups. The goal of these trials is to determine whether a drug's benefits outweigh its risks for the disease in question.

Phase IV – Studying Long-Term Effects or Safety in Larger Populations

After a drug receives FDA approval, it may be required to undergo further studies to evaluate its long-term effects and/or safety when used in actual clinical practice as opposed to a controlled clinical trial. These studies may also involve hundreds or thousands of patients.

For more information on clinical trials, you may want to read the National Cancer Institute's tutorial on targeted therapies: www.cancer.gov/cancertopics/understandingcancer/targetedtherapies/htmlcourse/page5.

When patient-reported outcomes are included in clinical trials, they are most often incorporated into phase III. However, there are important advantages to including them into phase II studies as well. Patient-reported outcomes may be useful in phase II studies for the following reasons:

- In cases where the disease is unmeasurable or when tumor response is not a surrogate for patient benefit.
- To examine the effects of a potentially toxic treatment on health-related quality of life.
- To determine whether the specific measurements are reliable, valid, acceptable, and feasible in the patient population under study.
- To help develop management strategies for identifiable quality of life issues.
- To understand health-related quality of life, symptom burden, and the most important concerns among individuals with rare cancers or rare diseases.

In a 2007 publication in the *Journal of Clinical Oncology*, Dr. Wagner and colleagues argued for the importance of including patient-reported outcomes in Phase II studies. Evidence in support of this

argument includes a Phase II Eastern Oncology Group study of ovarian cancer, which showed that the toxicity experienced was not associated with a decrease in health-related quality of life. This was an important finding that was then incorporated into the Phase III study. Another study of lung cancer patients found that a certain type of radiation therapy decreased quality of life during treatment. However, quality of life returned to normal a month after treatment ended. This finding helped establish the lack of negative long-term effects of the therapy on quality of life. Yet another study of head and neck cancer patients examined the swallowing problems caused by a treatment regimen of combined chemotherapy and radiation therapy. Objective swallowing results different from patient-rated swallowing problems, demonstrating that the physiological outcome measure does not always agree with the patient experience.

Some experts have suggested that Phase II studies are not large enough to provide strong quality of life data. It has also been suggested that missing data in Phase II studies can negate its value due to the small numbers of patients. However, as the studies described in the preceding paragraph demonstrate, these problems are surmountable with good study design and attention to quality of life outcomes. The unique data provided by patient-reported outcomes and the many examples of their successful inclusion in Phase II studies argue strongly for their inclusion and challenge the common practice of dismissing patient-reported outcomes for Phase II trials without evaluating the unique merits of each trial.

PROMIS®

In recognition of the growing importance of patient-reported outcomes, the National Institutes of Health (NIH) established the Patient-Reported Outcome Measurement Information System (PROMIS®) network as part of the NIH Roadmap Initiative. The objective of PROMIS® (without an “e” on the end) is to provide clinicians and researchers with access to efficient, precise, valid, and responsive adult and child reported measures of health and well-being.

As per the National Institutes of Health Web site, the strategic goals of PROMIS® are as follows:

- Create and promulgate a set of qualitative and quantitative methodological standards for development and validation of PROMIS® instruments.
- Launch a sustainable PROMIS® entity that is able to continue and grow the research, development, and dissemination activities for the network.
- Identify and prioritize a set of research and development opportunities for PROMIS® that include, but are not limited to, clinical applications.
- Disseminate information on PROMIS® to forge strategic alliances with key individuals and organizations that will help PROMIS® fulfill its vision and enhance its adoption in research, clinical practice, and policy.

The PROMIS® Web site lists 64 validated instruments designed to measure various aspects of physical, mental, and social well-being in adults and children, and 17 additional instruments for individuals with neurological disorders. Many more instruments are listed on the Web site as under development and the PROMIS® site is updated regularly to reflect newly published measures and supporting publications. These tools can be used to measure what patients are able to do (daily functioning) and how they feel (mental/emotional state) by asking a series of questions; examples of areas measured include pain, fatigue, depression, and sexual functioning. The measures can be used as endpoints in clinical trials for a variety of diseases and conditions. A list of these instruments can be found in the Assessment Area of the PROMIS® Web site at the following link: <http://www.assessmentcenter.net/documents/InstrumentLibrary.pdf>.

PROMIS® is an important program for several reasons, not the least of which are increased visibility of and commitment to patient-reported outcomes. PROMIS® instruments all have undergone an

unprecedented level of scientific development, including documented reliability and validity, which are prerequisites to the use of patient-reported outcome measures in clinical trials. The PROMIS® tools have also been standardized, including common domains and metrics across conditions, allowing for comparisons across domains and diseases. The instruments are also flexible—a variety of tools of varying lengths are available that can be administered in different ways. Finally, PROMIS® strives to include all people regardless of literacy, language, physical function or life course. The PROMIS® Web site is a good starting point for advocates wanting to learn more about patient-reported outcomes. Brief PROMIS® short forms and PROMIS® computer adaptive tests offer the potential to dramatically reduce the time and effort needed to include validated patient-reported outcomes into clinical research. Drawing on these tools, advocates are in an excellent position to influence the incorporation of quality of life measures into research, which has the potential to help current and future patients.

Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE)

The National Cancer Institute (NCI) is developing a system for patients to report symptomatic adverse events in cancer clinical trials. Currently, this information is reported by research staff during studies, but it has been found that many symptom adverse events like nausea or fatigue may be challenging to accurately evaluate. Starting in 2008, the NCI contracted with Memorial Sloan Kettering Cancer Center to develop the PRO-CTCAE, which consists of a library of 124 questions reflecting the many different symptom adverse events that patients may experience during cancer treatment. Patients can report their own symptom adverse events in English or in Spanish using these questions. Software has been developed for these questions to be answered via the internet or through an automated telephone system. This project is ongoing and near completion. This project is directed by Dr. Sandra Mitchell, a Research Scientist in the Outcomes Research Branch at NCI, and Dr. Ethan Basch, an oncologist and health outcomes researcher at the University of North Carolina and Memorial Sloan-Kettering Cancer Center, is the Principal Investigator. To date, the questions have been developed, translated, and tested through interviews in patients across the US from many different backgrounds. A validation study has been done to make sure that the questions are reliably detecting meaningful information, and PRO-CTCAE is currently being tested for feasibility in multiple clinical trials as well as in observational studies. For information about the PRO-CTCAE, please contact mitchlls@mail.nih.gov or visit <http://outcomes.cancer.gov/tools/pro-ctcae.html>.

Edmonton Symptom Assessment System (ESAS)

A different system for cancer patients to report symptoms has been developed and implemented in Ontario, Canada using a rating instrument known as the Edmonton Symptom Assessment System (ESAS). The idea behind this initiative is to provide greater attention to cancer patients' symptoms so that they can be treated, if necessary. The assessment includes physical symptoms such as pain, shortness of breath, appetite and fatigue, and emotional symptoms such as depression and anxiety. Over the past few years, the number of cancer patients using this reporting system has increased to approximately 23,000 per month. Nearly all of the patients (92%) surveyed strongly agreed or somewhat agreed that their ESAS scores were taken into account by a healthcare provider when planning their care. Use of this system appears to be proceeding successfully; for more information about the ESAS and Cancer Care Ontario's model for patient-reported outcomes that directly impact clinical care, you can visit the Cancer Quality Council of Canada's Web site at the following link: <http://www.csqi.on.ca/cms/One.aspx?portalId=126935&pageId=128207>.

Physician Consortium for Performance Improvement (PCPI®)

The Physician Consortium for Performance Improvement® (PCPI®) is a program initiated by the American Medical Association designed to align patient-centered care, performance measurement and quality improvement. This organization is working on standards for developing and evaluating patient-reported outcome performance measures that are expected to be available by mid-2013.

Patient-Reported Outcomes (PROs) in Performance Measurement Project — National Quality Forum

Another patient-reported outcome initiative is being pursued by the National Quality Forum. This initiative was undertaken in response to The Patient Protection and Affordable Care Act of 2010 that specifies the development of a National Quality Strategy to serve as a blueprint to improve the delivery of healthcare services, patient health outcomes, and population health in the United States. In addition to improving care, it is hoped that this program will also help address variation in healthcare and reduce healthcare costs in the United States.

This program recognizes that patient-reported outcomes are a key component to improving healthcare on multiple fronts, and an important goal is to speed their adoption in clinical practice. However, the National Quality Forum has identified several challenges that may interfere with the rapid acceptance of these measures in healthcare situations: (1) healthcare professionals may not be familiar with them and (2) methodologic challenges such as analyzing the data from a group of patients so that healthcare performance can be measured at multiple levels. In response to these challenges, the program has three main goals:

- To identify key characteristics for selecting patient-reported outcome measures (PROMs) to be used in PRO-based performance measures (PRO-PMs).
- To identify any unique considerations for evaluating PRO-PMs for National Quality Forum endorsement and use in accountability or performance improvement applications.
- To lay out the pathway to move from PROs to National Quality Forum-endorsed PRO-PMs.

For more information about this program, you may want to visit the National Quality Forum's Web site on the topic at the following address: http://www.qualityforum.org/Projects/n-r/Patient-Reported_Outcomes/Patient-Reported_Outcomes.aspx. A specific publication on this topic is available by clicking on the "Access the final report" text on this Web site.

As can be seen by the many national initiatives in this area, patient-reported outcomes are increasingly being recognized as critical measures to incorporate into both clinical practice and research. In the next chapter, we will explore some of the ways that advocates can get involved to make this happen.

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Chapter 6: How Can Advocates Use This Information?

As advocates, we tend to view quality of life and patient-reported outcomes as highly important issues in both clinical research and practice. Because many advocates have participated in the healthcare system, either as patients, caregivers or healthcare providers, we typically have first-hand experience with health-related quality of life concerns and may have a strong commitment to the use of patient-reported outcomes. Through leveraging scientific advances in quality of life and patient-reported outcomes measurement, patient advocates can bring the patient voice to the clinical or research context, using systematic and validated methods. In this chapter, we explore some of the ways that advocates can get involved to further the incorporation of quality of life and patient-reported outcomes across healthcare and research settings.

Incorporating Quality of Life and Patient-Reported Outcomes into Clinical Research

Through participation in advisory boards, study sections, the National Clinical Trials Network (ie. cooperative groups), and Specialized Programs of Research Excellence (SPOREs) sponsored by the National Cancer Institute, advocates can urge the incorporation of quality of life measures and patient-reported outcomes in clinical research studies. Some of the specific issues that may interest advocates are as follows:

- Ensuring that quality of life measures and patient-reported outcomes are supported by the objectives of the study.
- Informing researchers of symptoms and concerns that are the most relevant to survivors' quality of life and ensuring that quality of life measures selected adequately assess these concerns.
- Ensuring that the measures selected for inclusion in clinical studies are reliable, valid, and sensitive.
- Offering suggestions on specific measures such as those available on the PROMIS® Web site.
- Working for the incorporation of quality of life and patient-reported outcomes into more Phase II studies based on information in the preceding chapter.
- Organizing information seminars or meetings on the importance of quality of life measures and patient-reported outcomes.
- Generating materials outlining the benefits of quality of life research and describing the evidence showing that these measures can predict survival.
- Helping other patients and advocates understand their importance
- Disseminating the results of studies that incorporate patient-reported outcomes and quality of life measures.
- Working to include the quality of life results of clinical studies along with the clinical results of the intervention in the same publication or as companion publications in the same issue of the same journal. Currently, the clinical results of trials such as those investigating a new medicine are published separately from the quality of life results, which may be published much later.

Some of the specific vehicles through which advocates may influence the incorporation of quality of life measures and patient-reported outcomes in clinical studies are listed below. These are just a few ideas; there are many groups in which to participate. For a more thorough listing and description of these groups, you may want to consult several publications on the topic of "Roadmaps to Advocacy" available through Research Advocacy Network (www.researchadvocacy.org).

- National Cancer Institute study sections
- Patient representative or advocacy committees/working groups in cancer cooperative groups (<http://www.cancer.gov/cancertopics/factsheet/NCI/clinical-trials-cooperative-group>)
- Specialized Programs of Research Excellence (SPOREs) sponsored by the National Cancer Institute Translational Research Program (TRP) (<http://trp.cancer.gov>)
- Online forums and discussion boards

Incorporating Quality of Life and Patient-Reported Outcomes into Clinical Practice

Writing in the *Journal of Clinical Oncology*, Drs. Mark Levine and Patricia Ganz note that, although quality of life measures have been widely incorporated into clinical trials, they have not necessarily led to improved patient care. These authors conclude, “there are relatively few examples of formal quality-of-life measurement that have influenced individual patient decision-making or treatment policies.” A related question is how the measurement of quality of life in groups of patients, such as those in clinical trials, is relevant to individuals in the clinical treatment situation.

Many advocates have personal experience that may be valuable to include in discussions of how to incorporate quality of life and patient-reported outcomes into clinical practice. Specific initiatives in which advocates may want to participate include the Patient-Reported Outcomes (PROs) in Performance Measurement Project conducted by the National Quality Forum (described in the previous chapter). Additionally, the Edmonton Symptom Assessment System (ESAS) that has been implemented in Ontario, Canada may be a useful model to study and/or emulate given that their real-time assessment and feedback system has a direct impact on patient care.

Strategies designed to help facilitate the transfer of information between clinical research and practice and back again are needed, and this is an area in which advocate participation may be valuable. Initiatives through the Patient-Centered Outcomes Research Institute (PCORI) clearly acknowledge and formalize advocate participation. An example of how patient and advocate input was used to inform the development of a cancer study protocol is a trial known as TAILORx (Trial Assigning Individualized Options for Treatment [Rx]). The research team conducting this study wanted to design a trial that would be acceptable to patients. They sought recommendations from patients and advocates that were subsequently incorporated into the trial design.

Documented Information on the Importance of Quality of Life Measures

When participating in various forums related to quality of life measures, it may be helpful for advocates to have documented materials outlining the importance of quality of life measures. Topics may include the following:

- Data showing that quality of life information can predict survival

Tan AD, Novotny PJ, Kaur JS, et al. A patient-level meta-analytic investigation of the prognostic significance of baseline quality of life (QOL) for overall survival (OS) among 3,704 patients participating in 24 North Central Cancer Treatment Group (NCCTG) and Mayo Clinic Cancer Center (MC) oncology clinical trials. *J Clin Oncol* 26: 2008 (May 20 suppl; abstr 9515); abstract available at: http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=55&abstractID=33656.

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- Evidence that the inclusion of quality of life evaluation engenders a feeling of being cared for and understood by the healthcare team, which may subsequently increase treatment compliance and retention rates

Herman JM, Smith DC, Montie J et al. Prospective quality-of-life assessment in patients receiving concurrent gemcitabine and radiotherapy as a bladder preservation strategy. *Urology*. 2004; 64(1), 69–73; Abstract available at: <http://www.ncbi.nlm.nih.gov/pubmed/?term=herman+smith+montie+gemcitabine+quality>; full study publication available for purchase at: [http://www.goldjournal.net/article/S0090-4295\(04\)00282-1/abstract](http://www.goldjournal.net/article/S0090-4295(04)00282-1/abstract).

- Unmet needs are a strong predictor of quality of life among women with recurrent breast cancer

Park BW, Hwang SY. Unmet needs and their relationship with quality of life among women with recurrent breast cancer. *J Breast Cancer*. 2012 Dec;15(4):454-461.; full study publication available at: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3542855/>.

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Why Was this Guide Developed?

As advocates try to work within the system to advance research, it is important to understand the basic tenets of the science. By gaining a better understanding, advocates can identify and illustrate the issues and problem-solve to support solutions. Quality of life research and patient-reported outcomes are areas that advocates can help influence and advance the science. We hope that this information will be helpful to advocates and others interested in advancing the science and improving care for cancer patients.

About Research Advocacy Network

Research Advocacy Network is committed to improving patient care through research. Our goals are to get results of research studies for new treatments and improved methods of detection of cancer to patients more quickly, to give those touched by the disease an opportunity to give back and to help the medical community improve the design of its research to be more attractive to potential participants. Because research holds the hope for improvements in treatment, diagnostics and prevention, we are dedicated to patient focused research. We believe dissemination of research results to the medical community and patients can have a major impact on clinical practice.

The Research Advocacy Network (RAN) is a not for profit (501 c 3 tax exempt) organization that was formed in 2003 to bring together participants in the research process with the focus on educating, supporting, and connecting patient advocates with the medical research community. While there are many organizations addressing the needs of patients with specific diseases, political advocacy, cancer education and fundraising, no organization has focused on advancing research through advocacy. RAN works with advocates and organizations to effectively integrate advocates into research activities. Please learn more about us at our website at www.researchadvocacy.org or contact us about our work by e-mailing us at info@researchadvocacy.org or by phone 877-276-2187 or FAX at 888-466-8803.

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