

# **The M. D. Anderson Symptom Inventory**

User Guide ▪ Version 1



Charles S. Cleeland, PhD

The **M. D. Anderson Symptom Inventory (MDASI)** is a multisymptom patient-reported outcome measure for clinical and research use. The MDASI's thirteen core items include symptoms found to have the highest frequency and/or severity in patients with various cancers and treatment types. The MDASI has several advantages over other symptom-assessment scales in that it applies broadly across cancer types and treatments, includes items related to symptom interference with daily life, is easy for patients to complete, and is easily translated into other languages.

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Department of Symptom Research  
Attn: Assessment Tools  
The University of Texas MD Anderson Cancer Center  
1515 Holcombe Boulevard, Unit 1450  
Houston, Texas 77030

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## Chapter 1

# Development of the M. D. Anderson Symptom Inventory

A symptom is a sensation or perception of change related to one's health.

*Webster's Third New International Dictionary* defines a symptom as “the subjective evidence of disease or physical disturbance observed by a patient.”

A *subjective* symptom is a report of health disturbance from a patient. In contrast, a measurable symptom, or “sign,” such as elevated blood pressure, is *objective* evidence of a disease or disorder. Symptoms may be classified by severity and impact on function.

As healthcare professionals have begun to appreciate the value of symptom reporting, it has become necessary to design tools, or instruments, that can quantify symptoms. Such instruments rely on patient self-report of single-symptom or multisymptom severity and, in some cases, symptom impact. Symptom reports are part of a larger group of measures designated as patient-reported outcomes (PROs). As with any measure used to make clinical or research decisions, PRO instruments—including symptom reports—must be shown to be valid (measure the construct they represent), reliable (stable when no change is expected), and sensitive (responsive to expected changes due to treatment or clinical condition).

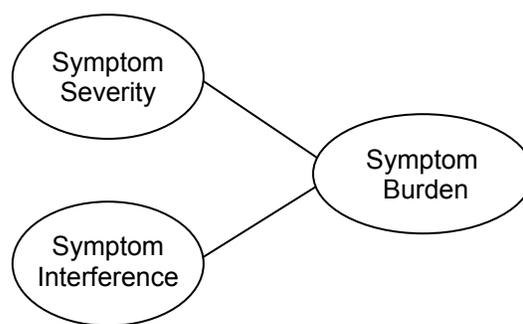
Beyond their clinical utility, symptom scales are increasingly being used to monitor symptom severity and treatment impact in clinical trials, to make regulatory and policy decisions, and to satisfy an increased need for documentation from regulatory agencies such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA). Clinical trials in cancer often focus on changes in symptoms as an indicator of either treatment benefit or toxicity. For example, a reduction of symptoms might be a primary or secondary endpoint of a trial in which comparison of treatments with similar anticancer activity might indicate that one of the agents was

associated with fewer treatment-related symptoms, or in which time to worsening of symptoms might be considered a point of treatment failure.

## Background

Our three primary symptom measures—the Brief Pain Inventory (BPI), the Brief Fatigue Inventory (BFI), and the M. D. Anderson Symptom Inventory (MDASI; Appendix A)—represent the current status of an approach to symptom measurement that was started more than two decades ago. In the 1980s, the Pain Research Group at the University of Wisconsin – Madison, led by Charles S. Cleeland, PhD, began developing cancer symptom assessment tools in response to national and international needs to better portray the severity of pain (and later other symptoms) and the impact of symptoms on function, for use in the clinic as well as for clinical trials and epidemiologic studies. Now the Department of Symptom Research at The University of Texas MD Anderson Cancer Center, Dr. Cleeland’s group continues to develop symptom assessment instruments and to work toward the standardization of symptom measurement.

The BPI, BFI, and MDASI have played a crucial role in pain and symptom-management clinical trials, including trials testing the effectiveness of new analgesics and other agents for pain and symptom control. The BPI has also been used in large-scale descriptive studies conducted by cooperative groups such as the Eastern Cooperative Oncology Groups (ECOG). The BPI and BFI were each designed to measure a single symptom; the MDASI was designed to measure multiple symptoms related to cancer and its treatment. As depicted in **Figure 1**, all of the instruments include items that report the “sensory” dimension of symptoms (intensity, or severity) and the “reactive” dimension of symptoms (interference with daily function) (Beecher, 1959; Cleeland, 1989).



**Figure 1. Symptom Assessment Constructs for the BPI, BFI, and MDASI**

## **The Brief Pain Inventory**

Employed in hundreds of studies, the Brief Pain Inventory is one of the most widely used measurement tools for assessing pain in clinical research. Although it was initially developed to assess pain related to cancer, the BPI has been shown to be an appropriate measure for pain caused by a wide range of clinical conditions. The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) recently recommended that the two domains measured by the BPI—pain intensity (severity) and the impact of pain on functioning (interference)—be included as outcomes in all chronic-pain clinical trials (Turk et al., 2003) and specifically recommended that the BPI interference items be used for assessment of pain-related functional impairment (Dworkin et al., 2005). The BPI is also recommended by the European Association for Palliative Care (EAPC) as the principal tool for assessment of pain in palliative care (Caraceni et al., 2002).

As the first instrument developed by the Pain Research Group, the BPI was the predecessor of the Brief Fatigue Inventory and the M. D. Anderson Symptom Inventory; the evolution of its measurement characteristics set the standard for the development and design of the later instruments.

The first version of the Brief Pain Inventory was the **Wisconsin Brief Pain Questionnaire** (BPQ). In the initial phase of scale development, 667 patients with breast, prostate, colorectal, or gynecological cancer, 32 patients with rheumatoid arthritis, 30 terminally ill cancer patients, and 57 patients with chronic nonmalignant pain were administered a three-page questionnaire and interviewed about the basic parameters of their pain in the past month (Daut & Cleeland, 1982). The questionnaire from this study was augmented with items from existing pain scales to form the provisional BPQ (Daut et al., 1983). The provisional BPQ asked patients to rate the severity of their pain using 0–10 numeric rating scales (NRS) with various descriptors, including their pain “at its worst” in the past month, “on the average,” and “right now” (at the time the questionnaire was administered). Anchors for the 0–10 scales were “no pain” and “pain as bad as you can imagine.” Using categorical rating scales (none, mild, moderate, severe) patients also rated how much their pain interfered with various functions or domains, such as general activity, mood, walking ability, work, relations

with others, and enjoyment of life. The BPQ also asked patients to shade a body diagram to represent the location(s) of their pain and to estimate the degree of relief they were receiving from current pain treatments or medications.

This version of the BPQ was tested and refined in a group of more than 1200 patients with breast, prostate, colorectal, or gynecological cancer and 34 patients with rheumatoid arthritis (Daut et al., 1983). In that study, researchers administered the BPQ to some of the patients via interview to identify any differences in results that might be attributable to mode of presentation. The remaining subjects completed the scale by themselves. Results showed little difference in ratings due to mode of administration. To test the BPQ's test-retest reliability, the questionnaire was given a second time (either by interview or self-administration) to two subgroups of patients, one of which completed the BPQ within a week of initial assessment; and a second of which were retested at a follow-up visit 2–32 weeks later. Test-retest reliability for the pain items was higher when the interval was short than when it was long, as expected, as pain would be expected to fluctuate over time. Overall, study results supported the reliability and validity of the BPQ for use in research.

The next iteration of our pain measure was the **Brief Pain Inventory** (Cleeland, 1989; Cleeland, 1990; Cleeland, 1991; Cleeland & Ryan, 1994). In this new instrument, the item “least pain” was added to the severity items. The four pain severity items (worst, average, now, and least) continued to be rated on 0–10 NRS, where 0 = no pain and 10 = pain as bad as you can imagine. The recall period was changed to one week in response to patient input. In addition, on the basis of patient interviews, we chose seven items that measured how much pain interfered with various daily activities: general activity, walking, work, mood, enjoyment of life, relations with others, and sleep.

Because patients expressed a preference for the numeric rating scale, and because the NRS is easily translated into other languages, we dropped the categorical rating scale for the interference items. The BPI interference items are rated on a 0–10 NRS, where 0 = no interference and 10 = interferes completely. In addition to rating pain severity and interference, patients are asked to mark the regions of their pain on front/back body diagrams and are asked to report the percentage of pain relief they have received from pain treatments and medications.

## Recall Periods in the Brief Pain Inventory

Study subjects completing symptom assessments may be asked to rate the severity of a symptom at the time of the assessment, or within a specific recall period that requires them to summarize their report over a given interval. The BPI can be used with two different recall periods (past week or past 24 hours). We have suggested that the recall period should be determined by the intent of the study. For example, if pain or other symptoms are to be rated frequently, the past-week recall period is too long.

Shi et al (2008) examined the use of a recall period in combination with the various severity descriptors (worst, least, average, now/current) in a sample of cancer patients with persistent pain. In this patient sample, ratings of worst pain in the past week, rather than ratings of current pain, least pain, or average pain, appeared to better reflect the overall experience of pain and its impact on function. Current pain ratings were closest to past-week least pain ratings. In other situations, such as breakthrough pain or acute procedural or postoperative pain, repeat assessments of current pain may better represent the patient's pain experience. Careful consideration of the recall period and severity descriptors may help investigators select appropriate symptom assessment items in clinical trials where symptoms are an outcome of interest.

## Dimensions of the Brief Pain Inventory

There is strong psychometric support for the independent measurement of pain severity and interference in the BPI. In addition, there is provisional evidence that the interference items independently measure activity and affective interference.

**Two-Factor Structure.** One of the first studies of the dimensions of the BPI compared the factor structure of four language versions of the BPI used to assess cancer pain in the United States, Mexico, the Philippines, and Vietnam (Cleeland, 1990). Factor analysis was applied to the matrix of intercorrelations of the item scores of each sample. For each language version, the same two factors emerged with an eigenvalue greater than 1: the first factor comprised the pain interference items and the second factor comprised the pain severity items. The similarity of the factor loading among the language versions indicated that patients experiencing cancer and pain, living in various countries and speaking various languages, responded to the items in a similar fashion.

This two-factor structure was confirmed in a large national study conducted in the U.S. by the Eastern Cooperative Oncology Group. More than 1200 outpatients with recurrent or metastatic cancer from 80 centers were enrolled in the study (Cleeland et al., 1994). Factor analysis verified the two separate factors, pain severity and interference, found in the previous study. Internal stability (Cronbach alpha) was also examined in this study. Alphas showed good internal consistency, ranging from 0.80 to 0.87 for the four pain severity items and from 0.89 to 0.92 for the seven interference items. Subsequent data from studies of cancer patients in many countries and many languages have demonstrated high internal consistency and the robust nature of these two dimensions of the BPI (Caraceni et al., 1996; Cleeland et al., 1988; Ger et al., 1999; Klepstad et al., 2002; Larue et al., 1995; Laudico et al., 2002; Mystakidou et al., 2001; Radbruch et al., 1999; Saxena et al., 1999; Uki et al., 1998; Wang et al., 1996; Yun et al., 2004).

**Multidimensional Scaling of Interference.** When we designed the Brief Pain Inventory, two subdimensions of pain interference were proposed for six of the seven interference items: an affective subdimension (REM: relations with others, enjoyment of life, and mood) and an activity subdimension (WAW: walking, general activity, and work). The appropriate categorization of interference with sleep within these two subdimensions was unclear. REM and WAW can be scored as separate component scores, or combined with sleep to form an interference component score.

We used multidimensional scaling to examine the dimensions of the BPI in a four-country sample of patients with cancer and pain (Cleeland et al., 1996). In this analysis, we focused on only the interference items of the survey. Our purpose was to explore potential linguistic and cultural differences in the report of pain interference.

As we had hypothesized, two dimensions of the interference scale were demonstrated. The first dimension consisted of patients' ratings of pain's interference with enjoyment of life, mood, and relations with others (REM, the affective cluster of interference items). A second dimension of interference ratings consisted of patients' ratings of pain's interference with walking, general activity, work, and sleep (WAW, the activity cluster of interference items). Subsequent studies of additional language versions (Norwegian in Klepstad et al., 2002; Hindi in Saxena et al., 1999) have shown

a similar decomposition of the interference items into the affective (REM) and activity (WAW) interference subscales.

### **Test-Retest Reliability of the Brief Pain Inventory**

Values from any measure should not differ significantly between assessments when no changes in the construct to be measured would be expected. This psychometric principle applies to patient-report instruments and is examined by test-retest reliability, or the stability of ratings between two administrations.

The test-retest reliability of the Brief Pain Inventory has been studied in cancer patients and other patients with pain. Initial short-term (1 day to 1 week) reliability for ratings of pain “worst” (0.93) and “usual” or “average” pain (0.78) in patients with cancer was high, which signals acceptable reliability. As expected, test-retest reliability for pain “now” severity ratings were lower (0.59), because pain intensity often changes over time (Daut et al., 1983).

Subsequent studies found similar test-retest coefficients for these items. For example, Radbruch et al. (1999) examined BPI test-retest coefficients in 109 outpatients in a German pain clinic, with the retest occurring 30 to 60 minutes after the first administration. Test-retest values were 0.98 for pain severity and 0.97 for pain interference. The individual item with the lowest value, 0.78, was pain “least.”

Reliabilities have also been examined with daily administration of the BPI. In patients with osteoarthritis (Mendoza et al., 2006), test-retest reliabilities of pain severity (worst, average, and current pain) between consecutive daily administration for a week showed correlations ranging from 0.83 to 0.88. The test-retest reliabilities for pain interference ranged from 0.83 to 0.93, beginning at day 1 for the week.

In another study of patients who underwent coronary artery bypass graft, the test-retest reliability coefficients for pain severity ranged from 0.72 to 0.95 during assessment periods where postsurgical pain declined in an expected direction (Mendoza et al., 2004). Similarly, the test-retest reliability coefficients for pain interference ranged from 0.81 to 0.93 during the same assessment period.

Finally, one study combined an examination of both test-retest reliability and alternate-forms reliability of the BPI (Saxena et al., 1999). In this study, 100 patients

with cancer who spoke both English and Hindi completed both language versions of the BPI on different days in a counterbalanced design. In addition to reporting reliability based on internal consistency, the study design allowed calculation of the alternate-forms reliability of the BPI. Treating the Hindi and English versions of the BPI as alternate test forms, the alternate-form reliabilities of the interference and severity subscales were 0.88 and 0.95, respectively. These reliabilities demonstrated that the Hindi and English versions could be substituted for one another in assessing the severity of pain and its impact in bilingual patients. These data also provided support for the high test-retest reliability of the BPI.

### **The Brief Fatigue Inventory**

The BPI's validity, ease of administration, and ease of translation for international studies made it an ideal model instrument for the development of the Brief Fatigue Inventory (BFI), an assessment tool used for the rapid assessment of fatigue severity in clinical screening and in clinical trials (Mendoza et al., 1999). Fatigue is endemic during cancer treatment and in advanced disease. We developed the BFI along the lines of the BPI and examined its psychometric properties in 305 inpatients and outpatients with cancer and a comparison sample of 290 community-dwelling adults.

Like the Brief Pain Inventory, the BFI demonstrated concurrent and discriminant validity (Mendoza et al., 1999). Internal consistency measures (Cronbach alpha) were high at 0.8 or more. The BFI has been translated into more than 30 languages, seven of which—Chinese (simplified (Wang XS, 2004) and traditional (Lin et al., 2006), German (Radbruch et al., 2003), Japanese (Okuyama et al., 2003b), Korean (Yun et al., 2005), Filipino (unpublished data), and Russian (Fedorenko et al., 2004)—are psychometrically validated.

The BFI has been used in studies in patients with obstructive sleep apnea (Roth et al., 2008), cancer (Bar-Sela et al., 2007; Chang et al., 2007; Lee et al., 2007), stroke (Mead et al., 2007), hepatitis C (Constant et al., 2005; Kramer et al., 2005), major depressive disorder (Papakostas et al., 2006), HIV (Simmonds et al., 2005), and narcolepsy (Harsh et al., 2006), among others.

## Rationale for the M. D. Anderson Symptom Inventory

Our success in assessing pain with the BPI and fatigue with the BFI led us to develop a multiple symptom assessment measure, the M. D. Anderson Symptom Inventory (MDASI) using the same approach to self-report measures. The development or worsening of multiple symptoms in patients with cancer is a serious problem that can adversely affect quality of life and, ultimately, survivorship; conversely, the reduction of symptoms is a major benefit for a treatment (Cleeland, 2007).

At the time we developed the MDASI, studies of symptoms and their measurement had almost exclusively examined a single symptom at a time (eg, studies of pain, or nausea and vomiting, or fatigue). Those who treat patients with cancer, however, are well aware that some symptoms—particularly pain, fatigue, sleep disturbance, emotional distress, and poor appetite—seem to be universal across various types of cancer and that multiple symptoms have a cumulative effect on one another and on patient functioning (Cleeland et al., 2003; Cleeland, 2007; Dodd et al., 2001; Kurzrock, 2001; Valentine & Meyers, 2001).

Many cancer-related symptoms are the result of disease. Others, such as neuropathy, fatigue, sleep disturbance, cognitive dysfunction, and affective symptoms, can also be caused by cancer treatment (Cleeland et al., 2003). These symptoms can persist for years and may even worsen despite improvement in disease prognosis. Persistent residual treatment-related symptoms are becoming more prevalent and are a barrier to the return to normal functioning. These symptoms can even affect survival by imposing treatment delays (Borden & Parkinson, 1998) or causing treatment termination.

Symptoms produced by the cancer itself or the disease treatment (referred to as side-effects or toxicities), collectively impose a **symptom burden** upon the patient that is a subjective counterpart of summary expressions of disease such as tumor or treatment burden (Cleeland, 2007). Symptom burden is the sum of the severity and impact of symptoms reported by a significant proportion of patients with a given disease or treatment.

The need to assess multiple symptoms simultaneously is necessary for reduction of patient distress and increased treatment effectiveness. Further, because clinicians

and patients must often choose among several treatments that are similarly effective, potential differences in symptom burden among treatments have become critical variables in making final treatment choices and in developing new therapies (Cleeland, 2007).

## Developing the M. D. Anderson Symptom Inventory

### Measurement Model and Items

The design of the BPI and BFI influenced the design of the more complex MDASI (Cleeland et al., 2000). We wished to find a critical set of symptoms that needed to be rated by most patients most efficiently, with least expenditure of patient time. For instance, having to rate too many symptoms would be overwhelming for very ill patients, yet boring for patients who had little current symptom distress but who nonetheless needed symptom monitoring. We sought to answer the questions: Is there a minimum critical set of symptoms common to most cancers, a “core,” that need to be rated by all patients? How can this core set of symptoms be rated most efficiently with the least expenditure of patient time?

The assessment instrument needed to include a basis for judging the burden of symptoms for all patients—the core symptom items—but be flexible enough to incorporate symptoms of potential importance that might be specific to various cancers or treatments. To characterize specific cancers or treatments, we expected that we would need to add a small number of disease-specific symptoms. Thus, the core items plus the disease-specific items might be thought of as a “module” for a specific assessment need. Retention of the core items in all modules and applications of the MDASI would allow for incremental validation of the scale, as well as for making comparisons of symptom burden across different cancers, stages, and treatments. It was expected that additional symptom items in each new module or version of the MDASI would be selected based on relevance and would have to demonstrate prevalence, ease of comprehension, and sensitivity in the targeted patient population.

## Common Elements

We retained many of the features of the Brief Pain Inventory in developing the M. D. Anderson Symptom Inventory, due in large part to our long-standing experience with the BPI, its use in hundreds of studies, and its translation into multiple languages. For example, we chose to have patients rate the severity of each symptom “at its worst” using 0–10 numerical rating scales with 0 = “not present” and 10 = “as bad as you can imagine.” We retained the dimensions of symptom severity and symptom interference, but now asked how much *all* symptoms, rather than only one symptom, interferes with such domains as walking, work, general activity, mood, relations with others, and enjoyment of life.

Finally, as we considered the design of the MDASI, we wished to take advantage of technological advances in symptom reporting and communication of information from patients to health care professionals, particularly electronic links that make use of the Internet, tablet PCs, and computer-telephone based interactive voice response (IVR) systems. The simple stem symptom items and the 0–10 rating scales made this approach attractive.

## Test Construction Standards

When we developed the predecessor instruments, we used then-current psychometric standards found in the *Standards for Educational and Psychological Tests* published by the American Psychological Association, American Educational Research Association, and the National Council on Measurement in Education (American Educational Research Association et al., 1999) as a guide to scale construction. These standards included common elements of test validity (content, criterion, and construct) and reliability (internal consistency and test-retest). These standards are very similar to those proposed by the FDA’s *Draft Guidance for Industry, Patient-reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims* (Food and Drug Administration, 2006). We continued this approach in developing the MDASI. The conceptual approach to measurement for the MDASI (symptom severity and interference), is the same as used for the Brief Pain Inventory (see *Dimensions of the Brief Pain Inventory*, p. 5).

The FDA draft guidance also highlights the importance of patient input in the selection of items and of post-test-construction cognitive debriefing of patients in targeted study populations to determine how intuitive, understandable, and relevant the items of the instruments are to patients. We have added patient cognitive debriefing to the instrument development process. While not a part of test development when the MDASI was first created, debriefing of the core items in the subsequent development of disease-specific or treatment-specific modules has allowed us to confirm the relevance and ease of understanding of the core items, as well as the ease of use of the severity and interference rating scales.

## **Generation of Items**

### **Development of the Initial Item Set**

One of our primary goals for the M. D. Anderson Symptom Inventory was that the list of symptoms had to be short enough to allow repeated use. We started with an item pool of more than 50 symptoms that were represented in several existing multisymptom assessment scales, including the Symptom Distress Scale (McCorkle & Young, 1978), the Memorial Symptom Assessment Scale (Portenoy et al., 1994), the Rotterdam Symptom Checklist (de Haes et al., 1990), and the Edmonton Symptom Assessment System (Bruera et al., 1991). On the basis of input from focus groups of medical and radiation oncologists, oncology nurses, and symptom management specialists, additional items were added and the entire list was reduced to 26 items: *fatigue, inability to get things done, weakness, worrying, distress, disturbed sleep, drowsiness, lack of appetite, dry mouth, nervousness, irritableness, sadness, pain, feeling sick, constipation, difficulty remembering, numbness or tingling, shortness of breath, difficulty paying attention, bloat, nausea, cough, diarrhea, mouth sores, vomiting, and bleeding*. The eliminated items were those that were thought to occur infrequently, were more of a sign (observable) than a symptom (self report), such as hair loss, or were felt to be difficult for the patient to interpret.

Along with the 26 symptom items, we also included six interference items from the BPI: *general activity, mood, walking ability, normal work, relations with other people,*

and *enjoyment of life*. The seventh BPI interference item, *sleep*, was already included in the list of 26 symptom items.

These 26 symptom items and six interference items were administered to three samples of patients: (1) a validation sample of 527 clinic outpatients, (2) an inpatient sample of 30 transplantation patients expected to have moderate to severe symptoms, and (3) a cross-validation sample of 113 clinic outpatients (Cleeland et al., 2000).

### Elimination of Redundant Symptom Items

Eliminating items that produce redundant information decreases the length of an instrument and reduces patient burden in filling out the questionnaire. After the initial item reduction in response to the focus groups, we eliminated additional redundant items from the initial 26 symptoms using (1) symptom prevalence information obtained from the validation study patients, and (2) hierarchical cluster analysis, which gives an overall view of the structure of patient responses for the entire set of items. Symptoms that very few patients rated > 0 on the MDASI 0–10 scale, such as bleeding, were eliminated. Clusters were formed using the average linkage between groups, and the distances between symptoms were calculated using squared Euclidian distances. The results are presented in the dendrogram below (**Figure 2**). Items that join with others more quickly (closer to the left), such as “attention” and “remembering,” were rated by patients more similarly. Therefore, it seemed logical to choose only one of these items for inclusion in the final core item list. The six items eliminated included *difficulty paying attention, feeling sick, weakness, inability to get things done, worrying, and irritableness*. Although *nausea* and *vomiting* were highly related based on the cluster analysis, clinicians opted to keep both symptoms because of differing clinical decisions routinely made based on the presence of each of these symptoms.

We further reduced the set of items by using the best-subset regression model technique to find the optimal subset of items that best predicted symptom distress, as measured by the degree of reported symptom interference. On the basis of this analysis and further clinician input, we derived a 13-item model consisting of: *pain, fatigue, nausea, disturbed sleep, distress (emotional), shortness of breath, lack of appetite, drowsiness, dry mouth, sadness, vomiting, difficulty remembering, and numbness or*

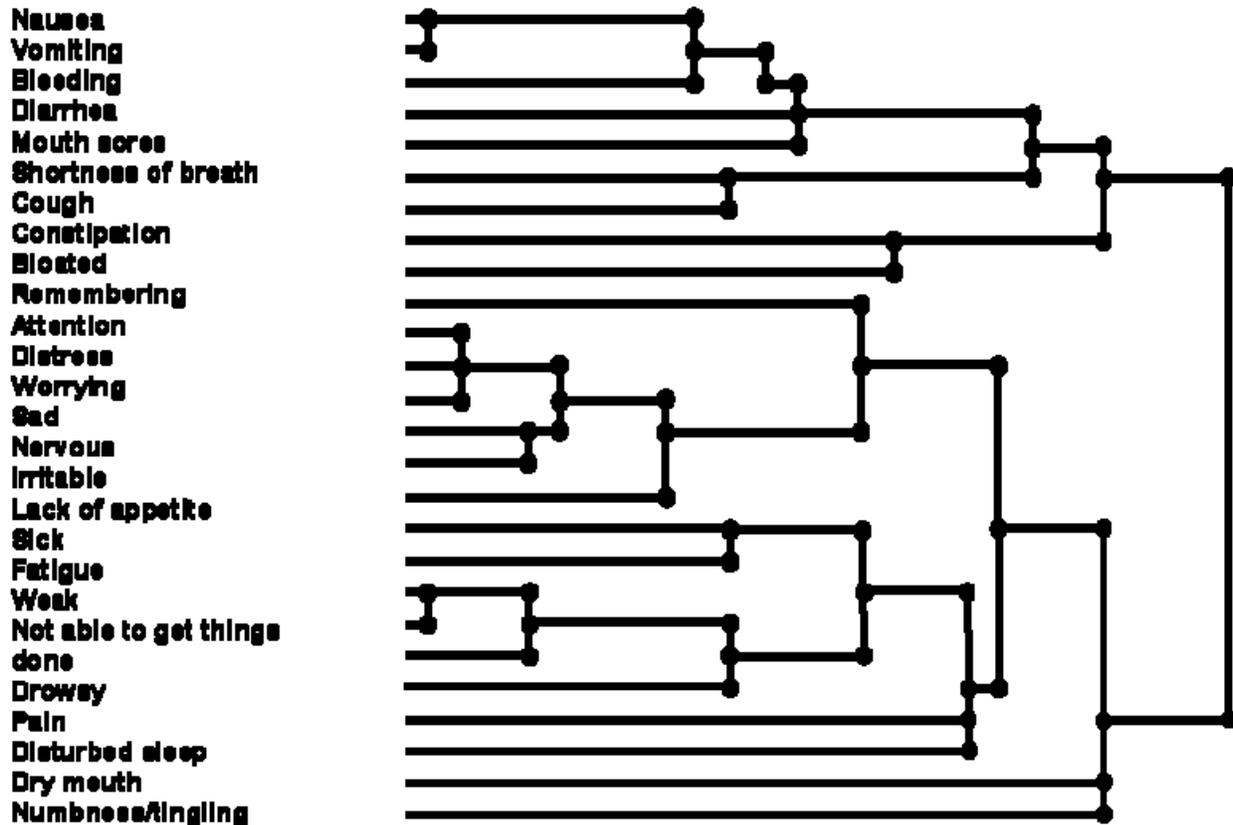


Figure 2. Relative Distance Between Symptoms (Cleeland et al 2000)

*tingling*. These items explained approximately 64% of the variability in symptom interference and were designated as the “core” list of symptom items for the MDASI, to be used for all assessments. Some of the items eliminated from the initial list of 26 symptoms were retained in an item pool to be used in specific MDASI modules (p. 41).

### **Cognitive Debriefing: Evaluating Patient Understanding**

The purpose of cognitive debriefing is to gain the patient’s perspective on understandability of items and scales used in an assessment instrument, and to seek patient input on redundancy of items or possible missing items. In structured interviews with the instrument developer, patients indicate how well they understood items of the instrument, how comfortable they were with answering the items, and how well the items reflected their concerns with their disease or treatment (Turner et al., 2007). A sample of a form used to collect cognitive debriefing information is included as Appendix B.

We have included cognitive debriefing as a routine part of the development of the M. D. Anderson Symptom Inventory modules, all of which include 13 core MDASI symptom items and six interference items. Several studies have been conducted to compile results of cognitive debriefing for the MDASI. A total of 83 patients were asked to evaluate their understanding and ease of comprehension of the symptom items to which they were being asked to respond. Almost all of the patients reported that the core MDASI severity and interference items were relevant and easy to understand, and that the 0–10 scale was intuitive and easy to use (Gning et al., 2009, and unpublished data). Patients also reported that they highly preferred the 0–10 numeric rating scale.

### **Measurement Conceptualization: The Multidimensionality of Symptoms**

The MDASI includes items that report the “sensory” dimension of symptoms (intensity, or severity) and the “reactive” dimension of symptoms (interference with daily function) (Cleeland, 1989). Severity is assessed for the 13 core MDASI symptom items (*pain, fatigue, nausea, disturbed sleep, distress (emotional), shortness of breath, lack of appetite, drowsiness, dry mouth, sadness, vomiting, difficulty remembering, and numbness or tingling*) and for the six interference items (*general activity, mood, walking ability, normal work, relations with other people, and enjoyment of life*). Subdimensions of symptom interference include an affective subdimension (REM: relations with others, enjoyment of life, and mood) and an activity subdimension (WAW: walking, general activity, and work).

A graphic representation of the conceptual framework for our measurement model is shown in **Figure 3** below. The model conforms to the FDA *Draft Guidance for Industry, Patient-reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims* (Food and Drug Administration, 2006).

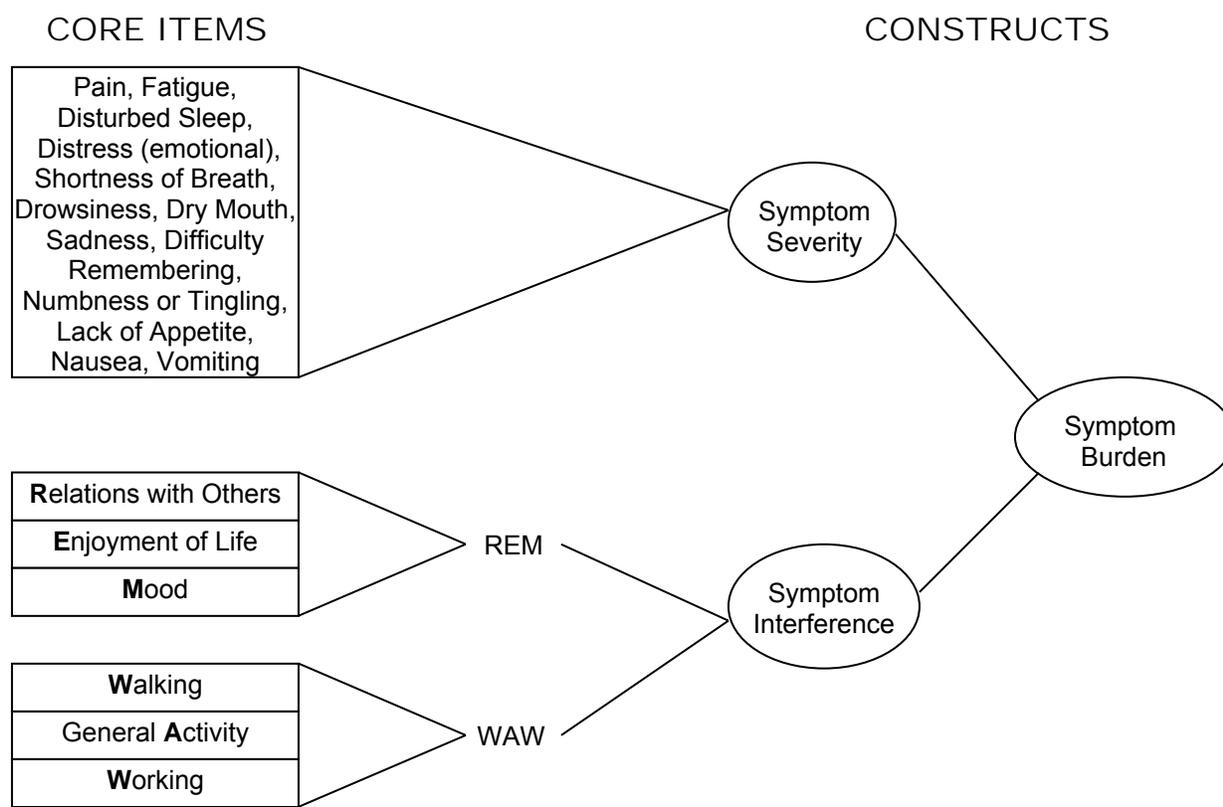


Figure 3. Conceptual model of the M. D. Anderson Symptom Inventory

## Recall Period

Use of a recall period (eg, the past week, the past 24 hours, or currently) may provide a more accurate picture of a patient's symptom status. In clinical research, choice of a suitable recall period depends on the specific purpose of the trial, the characteristics of the disease, and the treatment to be tested. As with the Brief Pain Inventory, the M. D. Anderson Symptom Inventory can be used with a 24-hour recall period or a past-week recall period. By default, the MDASI is designed for 24-hour recall; past-week recall versions are available by special request. Shi et al (unpublished data) recently compared multisymptom severity ratings with a one-week versus a 24-hour recall period in a crossover study that included patient debriefing. The severity ratings were essentially equivalent with the two recall periods. Patients found rating of symptoms with the recall period of one week to be easier.

## Response Options

### Rating Scale

Like the Brief Pain Inventory and the Brief Fatigue Inventory, the M. D. Anderson Symptom Inventory uses a 0–10 numerical rating scale (NRS) to assess the severity of symptoms and interference. We chose the NRS from among several widely used options, including verbal descriptor scales (VDS, Lasagna, 1980), which use word descriptors such as “none,” “mild,” “moderate,” “severe,” and “excruciating” to describe severity, and visual analogue scales (VAS, Wallenstein, 1984), in which the patient indicates what portion of a line anchored by “none” and “as bad as you can imagine” is equivalent to the severity of the symptom. The VDS, VAS, and NRS are highly intercorrelated and in clinical settings all three measures approach equivalency (De Conno et al., 1994; Jensen et al., 1986); therefore, ease of use becomes the primary factor in scale selection.

The NRS has a number of advantages over the VDS and VAS. It is easily adaptable to both clinical and research needs. In clinical trials, the NRS has been found to be more reliable and easier to complete than the VAS, especially with less-educated patients (Ferraz et al., 1990). Numerical scales have been shown to produce equivalent data when presented in different languages, at least for pain (Cleeland et al., 1996). As a research tool, the VDS is limited by unequal distances between descriptors and dependence on language comprehension. The 11-point rating scale maximizes the trade-off between a patient’s ease of responding and the marginal increase in reliability associated with a greater number of response choices (Nunnally & Bernstein, 1994). Finally, national pain treatment guidelines (Benedetti et al., 2000) and consensus groups such as IMMPACT (Dworkin et al., 2005) increasingly recommended the 0–10 NRS, given its ease of use with the largest proportion of patients. Several authors (Breivik et al., 2000; Hollen et al., 2005; Li et al., 2007; Sze et al., 1998) have shown that the NRS and VAS are equally sensitive to changes in pain intensity and are equally reliable. However, most patients prefer to use the NRS (Gagliese et al., 2005; Paice & Cohen, 1997).

### **Severity Descriptor**

On the basis of our experience with multiple severity ratings with the BPI, we chose to have patients rate their symptom severity “at its worst” for multisymptom assessment.

## Chapter 2

# Administering the M. D. Anderson Symptom Inventory

### Modes of Administration

The MDASI can be administered in a number of formats, including traditional “paper and pencil” format (either self-administration or research-staff interview) and electronic formats such as telephone-based interactive voice response (IVR) systems, PC tablets, and Web-based applications.

### Pencil-and-Paper Forms

The traditional method for MDASI administration is for the patient (or, if necessary, the research staff assigned to gather patient data) to fill in a paper form. The 0–10 scale is presented as circles that are filled in, circled, or checked by the patient or staff member. Staff members filling in the form for a patient, whether in person or over the phone, are not allowed to direct the patient’s response in any way or to add to or attempt to define the meaning of the item. See Instructions for Administration by Field Staff below (p. 21) and Appendix C for examples of administration scripts.

### IVR Systems

Analyzing symptom data in a longitudinal study is a challenging undertaking because of the complexities arising from missing data. Missing data due to illness or mortality are major factors in study design and outcome analysis that can seriously hinder evaluation of treatment efficacy (Du Pen et al., 1999). Traditional telephone communication between research staff and patient may ensure little-to-no missing data, but requires considerable staff time and is not feasible for assessing symptoms on a regular basis.

An interactive voice response (IVR) system is an effective way to collect patient data. In combination with the MDASI, the IVR can track outpatients with symptoms like pain that need to be monitored closely while away from the hospital. The system automatically calls patients at times they

select and has them rate their symptoms on a 0–10 scale by pressing numbers on the telephone keypad. Missed calls or hang-ups are repeated three times at preset intervals. Symptom assessment via IVR is easy and takes less than five minutes.

Besides the likelihood of eliminating missing data, the IVR has several other advantages. IVR systems are especially helpful for assessing symptoms that patients may be reluctant to report. IVR data is transmitted directly from the patient to the study database, greatly improving data accuracy and enhancing data security and patient privacy. Further, IVR-based symptom ratings can generate real-time alerts to clinicians when the ratings exceed a certain threshold. An IVR system can be configured to alert providers to severe symptoms that need immediate attention. Accurate and regular symptom assessment, when provided to physicians and advanced practice nurses, may facilitate effective symptom management.

### **Tablet PCs**

Tablet PCs have been successfully used to collect patient self-reported symptom data in clinical trials (Uronis et al., 2008). Abernethy et al (2008) compared paper-and-pencil and tablet PC methods of collecting PRO data and found that the electronic responses validly reflected responses provided by standard paper data collection on nearly all of the subscales tested, and that the tablets were a valid, feasible, acceptable method for collecting research-quality PRO data in outpatient academic oncology. Our own pilot studies are underway to test the administration of the MDASI in the clinic using tablet PCs. Research staff and patients will make responses using an electronic version of the MDASI displayed on a tablet PC. Data collected in this manner will be uploaded directly into study databases, eliminating the possibility of human data-entry error.

### **Web-Based Applications**

As the World Wide Web becomes accessible to more and more people, using it to collect patient data is becoming more possible. Web-based applications allow the patient to respond to the MDASI from anywhere, so long as Internet access is available. As with the IVR and tablet PC, data collected in this manner may be uploaded directly into study and/or patient databases.

## Instructions for Administration by Field Staff

Administering the M. D. Anderson Symptom Inventory involves more than just asking research participants to fill out a form. It is important that MDASI data be collected in a uniform manner so that research participants' responses to items on the questionnaire are not influenced by the actions or words of the data collector. Adhering to the following rubrics should allow the data collector to remain as neutral as possible:

- Listen attentively to whatever the patient says, but do not respond with statements of sympathy, concern, or other indications of how severe you think the symptoms are. Expressions of sympathy can influence patient responses.
- Do not give specific answers to questions patients ask while completing questionnaire items, and do not offer additional information or clarification about the questionnaire items. Giving patients additional information may cause them to respond to the items differently than patients who do not have that information. Instead, simply ask the patient to answer the questions to the best of their ability. Make a note that the patient did not understand an item and let the person in charge of the research study know this information.
- Do not offer advice on how to prevent, treat, or control symptoms or other disease-related aspects. Refer patients' questions about their disease or treatment to direct health care providers.
- If a patient reports serious symptoms that represent a significant threat to safety, instruct the patient to report these symptoms their direct health care provider. If the patient resists, inform him or her in a very simple and direct manner that you will need to report the symptoms to direct health care providers.
- If at all possible, arrange for patients to answer questions in private. Having other people within earshot when a patient is verbally answering research questions can influence the patient's answers. Patients may report that symptoms are less severe than they would report if no one but the data collector could hear the answers. Family caregivers may also interject their opinions of how severe symptoms are.

- If a research questionnaire is to be completed on the phone, have a copy of the questionnaire available to read along with the patient.
- When the questionnaire is to be completed multiple times by phone, give the patient a laminated copy of the questionnaire to keep by the phone. The laminated copy is much more substantial than a paper copy, is less likely to be lost or accidentally discarded, and gives patients a sense of how important it is to have the questionnaire readily available when the call to answer the questionnaire comes.

Using a script to administer a questionnaire can help to ensure that patient interactions with a data collector are as uniform as possible. Examples of instructions and scripts for research administration are included in Appendix C. A sample of a patient IVR instruction pamphlet is included in Appendix D.

### **Assessment of Respondent and Administrator Burden**

Completion of the M. D. Anderson Symptom Inventory and its modules in paper and pencil format takes approximately 2–5 minutes. Presented in IVR format, only 1–2 minutes are needed.

## Chapter 3

# Scoring the M. D. Anderson Symptom Inventory as an Outcome Measure

### Scoring Symptom Severity

The MDASI assesses the severity of symptoms at their worst in the last 24 hours on a 0–10 NRS, with 0 being “not present” and 10 being “as bad as you can imagine.” The ratings in the MDASI can be averaged into several subscale scores: mean core symptom severity (13 core symptom items), mean module symptom severity (additional module symptom items if using a module), mean total symptom severity (13 core symptom items plus additional module symptom items if using a module), and mean interference (6 interference items only). The interference items can further be broken down into mean activity interference (work, general activities, and walking ability) and mean affective interference (relations with others, enjoyment of life, and mood). Symptom items may be presented individually.

When calculating any subscale score (arithmetic mean of items in the subscale), a majority of the subscale’s items must have been responded to (ie, 7 of the 13 core symptom severity items or 4 of the 6 interference items would represent the majority of the items for the subscale). If the patient responded to fewer than half of the subscale’s items, consider the subscale “missing.”

Additionally, for a given study, the means of the symptom items can be inspected and a subset of the most prevalent or severe items can be selected to represent symptom burden in that study. For example, in a recent study of patients with non-small cell lung cancer, we calculated a composite score based on the sample’s five most highly rated symptoms—fatigue, pain, sleep disturbance, lack of appetite, and drowsiness. In another study of patients with head and neck cancer, we similarly computed a composite score on that

sample's five most highly rated symptoms—fatigue, pain, sleep disturbance, lack of appetite, and difficulty swallowing (unpublished data).

## Scoring Symptom Interference

The MDASI measures how much the symptoms have interfered with six daily activities: *general activity, mood, work, relations with others, walking, and enjoyment of life.*

Interference is rated on a 0–10 numerical rating scale, 0 being “did not interfere” and 10 being “interfered completely.”

The mean of the interference items can be used to represent overall **symptom distress**. This mean can be used if more than 50% (four of six items) are completed on a given administration: (sum of items answered) / number of items answered.

We are exploring the utility of scoring the MDASI's activity and affective dimensions described on p. 15 above (WAW and REM, see Figure 3) as arithmetic means of these sets of items. We have tested this method with the Brief Pain Inventory (Cleeland et al., 1996).

## Chapter 4

# Psychometric Properties of the M. D. Anderson Symptom Inventory

The MDASI was first validated in three samples of patients: an initial validation sample of 527 clinic outpatients from the Departments of Blood and Marrow Transplantation, Hematology, Breast Medical Oncology, Genitourinary Medical Oncology, Gastrointestinal Oncology, Radiation Oncology, and Thoracic/Head and Neck Medical Oncology at MD Anderson Cancer Center; (2) a cross-validation sample of 113 outpatients from the same departments; and (3) a sample of 30 inpatients undergoing treatment that included blood or bone marrow transplantation and who were expected to have moderate to severe symptoms. Patients were instructed to rate how severe the symptoms had been in the last 24 hours, as well as the degree of symptom interference in various functional areas in the last 24 hours.

The MDASI is continually validated with every new module and every new language translation. Because the core items from the original MDASI are part of every MDASI module and translation, assessments of validity, sensitivity, and reliability transcend the new versions themselves and indicate that the original MDASI also has these characteristics. Validation of PROs is a journey, an iterative and never-ending process that will never arrive at a perfect solution. However, along the road of validation there are measures that are "good enough," in the words of Ronald Serlin (Serlin & Lapsley, 1993), who has contributed much to this development.

## Reliability of the M. D. Anderson Symptom Inventory

Tests of reliability seek to determine whether a PRO instrument reliably measures the concepts it was designed to measure, and to establish the quality of the evidence of reliability. Appropriate reliability tests were conducted during development of the MDASI.

## **Test-Retest Reliability**

Test-retest reliability reflects the stability of scores over time when no change has occurred in the concept of interest. The MDASI's test-retest reliability has been examined in several studies.

We examined the test-retest reliability of the MDASI in a sample of 20 patients undergoing chemotherapy for lung cancer. The MDASI was administered at a clinic visit and again one day later. The test-retest reliability coefficients for the MDASI severity and interference items were 0.83 and 0.84, respectively.

We also examined the test-retest reliability of the MDASI in a sample of 33 patients with multiple myeloma, non-Hodgkin's lymphoma, or breast cancer who underwent autologous transplantations (bone marrow or peripheral blood stem cell) (unpublished data). The MDASI was administered in paper-and-pencil format at the beginning and end of the 30-day study, and via IVR in between. The number of IVR administrations per patient varied in this study, so we calculated test-retest reliabilities for the first three and the last three IVR administrations during the 30-day period. These coefficients ranged from 0.75 to 0.96, indicating that the MDASI used in conjunction with an IVR system is a very reliable and sensitive symptom assessment tool.

### **Test-Retest Reliability in an Adolescent Population**

The test-retest reliability of the MDASI was confirmed in a non-adult sample in a validation study of 108 adolescent Taiwanese cancer patients aged 11-18 years (Tseng et al., 2008). All patients completed the MDASI upon enrollment. A test-retest interview was conducted 3 days later on a subsample of 35 adolescents. Test-retest reliability over the 3-day interval, evaluated using the Pearson coefficient, was 0.73 for symptom severity composite score and 0.75 for the interference composite score.

### **Test-Retest Reliability in Foreign-Language Translations**

Test-retest reliability of the MDASI was examined in a sample of 556 Taiwanese patients with multiple diagnoses of cancer (Lin et al., 2007) Test-retest reliability over a 3-day interval was evaluated in a sample of 12 patients by calculating the Pearson product-moment correlation coefficient between pretest and posttest. The test-retest

reliability was 0.97 for the symptom severity composite score and 0.96 for the interference composite score.

A Greek translation of the MDASI was administered to patients in a palliative care unit in Athens, Greece (Mystakidou et al., 2004). The entire sample of 150 patients answered the questionnaire at study entry, and 100 of these answered it again 3 days later. The test/retest reliability of scales for the validation and cross-validation samples were evidenced by coefficients of agreement that were 0.9 or greater.

### **Internal Consistency Reliability**

Internal consistency reliability reflects whether the items in a domain are intercorrelated, as evidenced by an internal consistency statistic (eg, a Cronbach coefficient alpha > 0.7). Reliability tests determine the proportion of the observed variance in the measurements that could be attributed to real score differences among subjects and the proportion attributable to internal variability in the instrument itself.

### **Initial MDASI Validation**

The internal consistency of the M. D. Anderson Symptom Inventory was demonstrated in the initial validation sample by Cronbach coefficient alphas of 0.85 for the general symptom severity items, 0.82 for the gastrointestinal items, and 0.91 for the interference items (Cleeland et al., 2000) (see *Construct Validity*, p. 29, for a description of the MDASI's factor structure). The internal consistency of the cross-validation sample was indicated by Cronbach alphas of 0.87 for each of the general symptom severity and gastrointestinal items and 0.94 for the interference items. All items except *numbness or tingling* loaded on the same factors in the cross-validation sample as they had in the initial validation sample. These values show a high level of reliability for these sets of items.

### **Further MDASI Validation Studies**

In a sample of 201 patients with primary brain tumor (Armstrong et al., 2006), the internal consistency reliability of the MDASI-BT was demonstrated by Cronbach alpha coefficients for the six symptom factors and the interference scale of 0.87, 0.82, 0.72, 0.81, 0.69, 0.67 and 0.91, respectively, indicating a high level of reliability for these sets of items. These factors include both core and non-core items. In a sample of 205

patients with head and neck cancer (Rosenthal et al., 2007), Cronbach coefficient alpha reliabilities for the MDASI-HN were 0.88 and 0.92 for the 13 core symptom items and the 6 interference items, respectively.

In a sample of 156 patients with cancer and heart failure (Fadol et al., 2008), Cronbach coefficient alphas supported high internal consistency, with alphas of 0.89 for the 13 MDASI core symptoms and 0.92 for the 6 MDASI core interference items. Cronbach alpha values in a sample of 60 patients with thyroid cancer were 0.85 and 0.92 for the core symptom subscale, and interference subscale, respectively (Gning et al., 2009).

The core MDASI items and one additional item (bleeding) were tested in 100 patients with either multiple myeloma or non-Hodgkin's lymphoma and scheduled for autologous peripheral blood stem cell transplantation (Anderson et al., 2007). The MDASI demonstrated good internal reliability in this study, with coefficient values of 0.86 and 0.82 for the symptom and interference scales, respectively, at baseline and 0.91 for the symptom scale and 0.90 for the interference scale posttransplantation, at white blood cell count nadir.

In a study of 556 Taiwanese patients with various cancer diagnoses, good internal consistency was shown for the MDASI symptom items (Cronbach coefficient alpha = 0.89) and interference items (alpha = 0.94) (Lin et al., 2007). Among Taiwanese adolescents with cancer, Cronbach alpha coefficients for the symptom severity, the general symptoms, the gastrointestinal symptoms, and interference were 0.90, 0.88, 0.83, and 0.91, respectively, indicating good internal consistency (Tseng et al., 2008).

## **Validity of the M. D. Anderson Symptom Inventory**

Tests of the validity of a PRO instrument examine whether its items appear to measure the concepts they are intended to measure in a useful way and whether patients similar to those participating in the clinical trial have confirmed the completeness and relevance of all items.

## Content Validity

Content validity indicates that items and response options are relevant and comprehensive measures of the domain or concept. The focus groups, clinician review, and cognitive debriefing used in the development of the MDASI (Cleeland et al., 2000) and its modules (Armstrong et al., 2005; Armstrong et al., 2006; Fadol et al., 2008; Gning et al., 2009; Rosenthal et al., 2007) ensure that the content is both appropriate and relevant. Continuous validation of the MDASI core items in the modules and translations confirms the MDASI's content validity.

## Construct Validity

Construct validity establishes that relationships among items, domains, and concepts conform to what is predicted by the conceptual framework for the PRO instrument itself and its validation hypotheses. Tests of [known-group validity](#) and [concurrent validity](#) establish whether results distinguish one group from another, based on a prespecified variable that is relevant to the concept of interest. [Convergent validity](#) indicates whether results compare favorably with results from a similar but independent measure.

## Initial MDASI Validation Study

Principal axis factor analysis with oblimin rotation was used to test the [construct validity](#) of the MDASI (Cleeland et al., 2000). In the initial validation outpatient sample, the 13 core symptom items of the MDASI were found to measure two underlying constructs: a **general symptom severity factor** (*pain, fatigue, disturbed sleep, distress (emotional), shortness of breath, drowsiness, dry mouth, sadness, difficulty remembering, and numbness or tingling*) and a **gastrointestinal factor** (*nausea and vomiting*). *Lack of appetite* loaded on both constructs.

To cross-validate the factor loading of the data, we performed factor analysis on a second sample of outpatients, the cross-validation sample. We examined the differences between the reproduced correlations based on the two-factor solution and the observed correlations in the cross-validation sample.

In the MDASI validation study, symptom severity did not differ among patients undergoing bone marrow transplantation (BMT), patients receiving chemotherapy, and patients not treated within the last 3 months. However, differences in symptom

interference were observed between the BMT and chemotherapy groups compared with the no-treatment group. Further, *fatigue* and *numbness* did not differ between groups, although *nausea* and *vomiting* severity was greater for the chemotherapy group, and *lack of appetite* differentiated all groups. This study shows that symptom severity and interference are two different factors.

### Further MDASI Validation Studies

The M. D. Anderson Symptom Inventory continues to be validated in studies of patients with various cancer types, disease stages, and treatment regimens, as well as in studies of cancer patients in many countries and many languages. These studies have confirmed the high internal consistency and the robust nature of the MDASI. In summary, the MDASI has been shown to be very stable across different diseases.

Using pooled data from the original validation study of the MDASI and three psychometrically validated disease-specific modules of the MDASI (the brain tumor (Armstrong et al., 2006), head and neck (Rosenthal et al., 2007), and heart failure (Fadol et al., 2008) modules), we performed a factor analysis with direct oblimin rotation to determine whether a two-factor structure could be found for the core symptom items. Results showed that a general-severity factor and a gastrointestinal factor, consistent with the original validation study (**Table 1**).

Table 1. Factor analysis of MDASI core items (N=1062)

| Symptom Item           | Descriptive Statistics |       | Pattern Matrix <sup>a</sup> |                             |
|------------------------|------------------------|-------|-----------------------------|-----------------------------|
|                        | Mean                   | SD    | Factor 1 (General)          | Factor 2 (Gastrointestinal) |
| Distress               | 3.11                   | 3.164 | .792                        | -.058                       |
| Fatigue                | 4.40                   | 3.081 | .771                        | .007                        |
| Sadness                | 2.54                   | 3.032 | .735                        | -.094                       |
| Drowsiness             | 3.39                   | 3.112 | .686                        | .050                        |
| Difficulty remembering | 2.44                   | 2.795 | .677                        | -.123                       |
| Sleep disturbance      | 3.43                   | 3.221 | .597                        | .063                        |
| Shortness of breath    | 2.14                   | 2.886 | .556                        | .012                        |
| Numbness               | 2.09                   | 2.946 | .474                        | .017                        |
| Pain                   | 2.74                   | 3.180 | .459                        | .170                        |
| Dry mouth              | 3.25                   | 3.367 | .448                        | .110                        |
| Lack of appetite       | 2.77                   | 3.277 | .417                        | .351                        |
| Vomiting               | 0.79                   | 2.109 | -.036                       | .817                        |
| Nausea                 | 1.53                   | 2.644 | .090                        | .816                        |

<sup>a</sup> Rotation converged in 4 iterations.

The M. D. Anderson Symptom Inventory was validated in a sample of 201 patients with primary brain tumor (Armstrong et al., 2006). **Construct validity** was determined using principal component analysis with varimax rotation. The 22-item MDASI-BT was found to measure six underlying constructs: (1) an affective factor comprising distress, fatigue, sleep disturbance, sadness, and irritability; (2) a cognitive factor comprising difficulty understanding, difficulty remembering, difficulty speaking, and difficulty concentrating; (3) a focal neurologic deficit factor consisting of seizures, numbness, pain, and weakness; (4) treatment-related symptoms such as dry mouth, drowsiness, and appetite; (5) generalized/disease status symptoms, including change in appearance, change in vision, change in bowel patterns, and shortness of breath; and (6) a gastrointestinal factor consisting of nausea and vomiting. Model fit was confirmed using Harman's criterion (Harman, 1967). **Known-group validity** was shown in three different comparisons. The MDASI-BT discriminated between two patient groups dichotomized by good or poor Karnofsky Performance Status, with a significant difference in mean symptom severity (1.3 vs 2.79) and mean interference (1.75 vs 4.9,

P < .001). The instrument also discriminated between inpatients and outpatients, where inpatients had significantly worse mean symptom severity (2.4 versus 1.52) and mean symptom interference (4.33 versus 2.1).

We validated the MDASI in 205 patients with head and neck cancer (Rosenthal et al., 2007). **Construct validity** was tested using principal axis factoring with direct oblimin rotation. Model fit was confirmed using Harman's criterion in a comparison of the reproduced correlations based on the 2-factor solution and observed correlations in the sample. **Known-group validity** was tested in a comparison of patients with good performance status vs patients with poor performance status. As expected, these two patient groups differed significantly in their MDASI ratings of core symptom severity (1.72 vs 3.59, respectively) and mean interference (1.68 vs 4.55). The MDASI showed **concurrent validity** in comparison with another measure that is widely used for assessing cancer symptoms, the SF12v2. There was a significant correlation with the SF12v2 physical and mental component scores for both the symptom items (−0.526, −0.573, respectively) and the interference items (−0.567, −0.549, respectively).

The MDASI core items were validated in 156 patients with cancer and a concurrent diagnosis of heart failure (Fadol et al., 2008). Pearson product moment correlation was used to test for **concurrent validity**. High correlation was found with the Eastern Cooperative Oncology Group performance scale for the 13 core symptom items ( $r = 0.63$ ) and the 6 interference items ( $r = 0.65$ ), and with the New York Heart Association classification for the 13 core symptom items ( $r = 0.63$ ) and the interference items ( $r = 0.59$ ).

In a sample of 156 patients with cancer and heart failure (Fadol et al., 2008), the **concurrent validity** of the MDASI was examined using the Mann-Whitney U test to compare patients with B-type natriuretic peptide (BNP)  $\leq 100$  pg/mL (categorized as "normal") vs. patients with BNP > 100 pg/mL (categorized as "elevated"). As predicted, the MDASI-HF scores showed a significant difference in mean symptom severity and mean HF symptom severity between pts with normal and elevated BNP.

The M. D. Anderson Symptom Inventory has typically been used in adult populations. However, a recent study validated the MDASI in 108 Taiwanese adolescents with cancer (Tseng et al., 2008). **Construct validity** was established by

principal axis factor analysis with direct oblimin rotation, which resulted in a 2-factor solution for the 13 MDASI-T symptom items: a general symptoms factor (*pain, fatigue, sleep disturbance, distress, shortness of breath, difficulty remembering, drowsiness, dry mouth, sadness, and numbness*) and a gastrointestinal symptoms factor (*nausea, vomiting, and lack of appetite*). These two factors explained 51.7% of the total variance. Hierarchical cluster analysis results were consistent with the factor analysis. **Concurrent validity** was established by comparing symptom severity and interference scores with SF-36-T physical functioning and mental health subscales. The correlation coefficients for the related pairs were moderate, and included: pain/bodily pain items ( $r = -0.60$ ), fatigue/vitality items ( $r = -0.49$ ), distress/mental health items ( $r = -0.50$ ), and sadness/mental health items ( $r = -0.41$ ). **Known-group validity** was examined by comparing the MDASI scores between patients with low and high functional status and between patients currently undergoing treatment and those currently not undergoing treatment. As we hypothesized, patients with low functional status (KPS score  $\leq 80$ ) and those with a high functional status (KPS score  $> 80$ ) had significantly different MDASI scores. Similarly, adolescents who were currently undergoing treatment reported significantly higher levels of symptom severity and symptom interference than adolescents who were currently not undergoing treatment.

### **Predictive Validity**

Predictive validity is an indicator of whether future events or status can be predicted by changes in PRO scores. Several recent studies have begun to establish the MDASI's predictive validity. The MDASI-HN has been shown to predict the severity of radiation-induced mucositis (Rosenthal et al., 2008). The developers of the MDASI-BT tested its ability to predict recurrence (Armstrong et al., 2006). Patients were divided into three groups, 30 newly diagnosed, 58 with stable disease, and 113 with recurrent tumor. Patients with recurrent tumor had significantly worse mean symptom severity scores (both overall and brain-tumor-specific items) and interference scores than the other two groups. The newly diagnosed and recurrent tumor groups did not differ on the mean severity score on the core MDASI items. This supports the prognostic importance of the brain-tumor-specific items.

The MDASI was used to assess the correlation between hemoglobin and self-perceived cancer-related symptoms in a large patient population with chemotherapy-induced anemia (Gabrilove et al., 2007). Of 2401 patients that received at least 1 dose of darbepoetin-alfa, eighty percent (95% confidence limit, 78-82 patients) achieved target hemoglobin levels ( $>$  or  $=11$  g/dL) during the study. Improvement in MDASI scores was associated with an increase in hemoglobin concentration. In conclusion, treatment with darbepoetin-alfa was associated with improvement in symptom burden as measured by the MDASI, a simple tool that may improve symptom management for cancer patients with chemotherapy-induced anemia.

## Sensitivity of the M. D. Anderson Symptom Inventory

Ability to detect change is always specific to a time interval that must be appropriate for the study - Includes calculations of effect size and standard error of measurement, among others. Are scores stable when there is no change in the patient, and do they change in a predicted direction when notable change as evidenced by effect size?

### Initial MDASI Validation

Sensitivity of the MDASI was obtained by differentiating between disease severity and treatment status. In the initial MDASI validation study (Cleeland et al., 2000), patients were divided into two groups based on whether they had good performance status (ECOG PS = 0 or 1) or poor performance status (ECOG PS = 2+). There was a significant difference in mean symptom severity and mean symptom interference between patients with a good performance status and those with a poor performance status. Most of the symptoms on the core list of the MDASI were significantly more severe for the group with a poor performance status, with the exception of *numbness or tingling, vomiting, difficulty remembering, and shortness of breath*.

### Further MDASI Validation Studies

To demonstrate sensitivity of an instrument, we should be able to show that symptom score changes when we expect them to change. For example, we expected a group of 134 patients with head and neck cancer who were undergoing chemoradiation treatment to report more severe symptoms when they completed their treatment (**Table 2**, T2) than when they started treatment (T1) (Rosenthal et al., 2008).

Table 2. Change in mean MDASI symptom and interference scores over time

| MDASI-HN           | Number of patients | Mean (SD) at T1 | Mean (SD) at T2 |
|--------------------|--------------------|-----------------|-----------------|
| All items          | 128                | 1.41 (1.35)     | 3.51 (1.84)     |
| HN items           | 128                | 1.19 (1.39)     | 3.74 (2.10)     |
| Core items         | 128                | 1.55 (1.47)     | 3.34 (1.87)     |
| Interference items | 128                | 1.94 (2.11)     | 3.92 (2.81)     |

We expected that a group of patients who underwent autologous blood and marrow transplantation (Anderson et al., 2007) would report their worse symptoms during the nadir of white blood cell count after transplantation. Study data suggest that MDASI scores are sensitive to such trends (**Figure 4**).

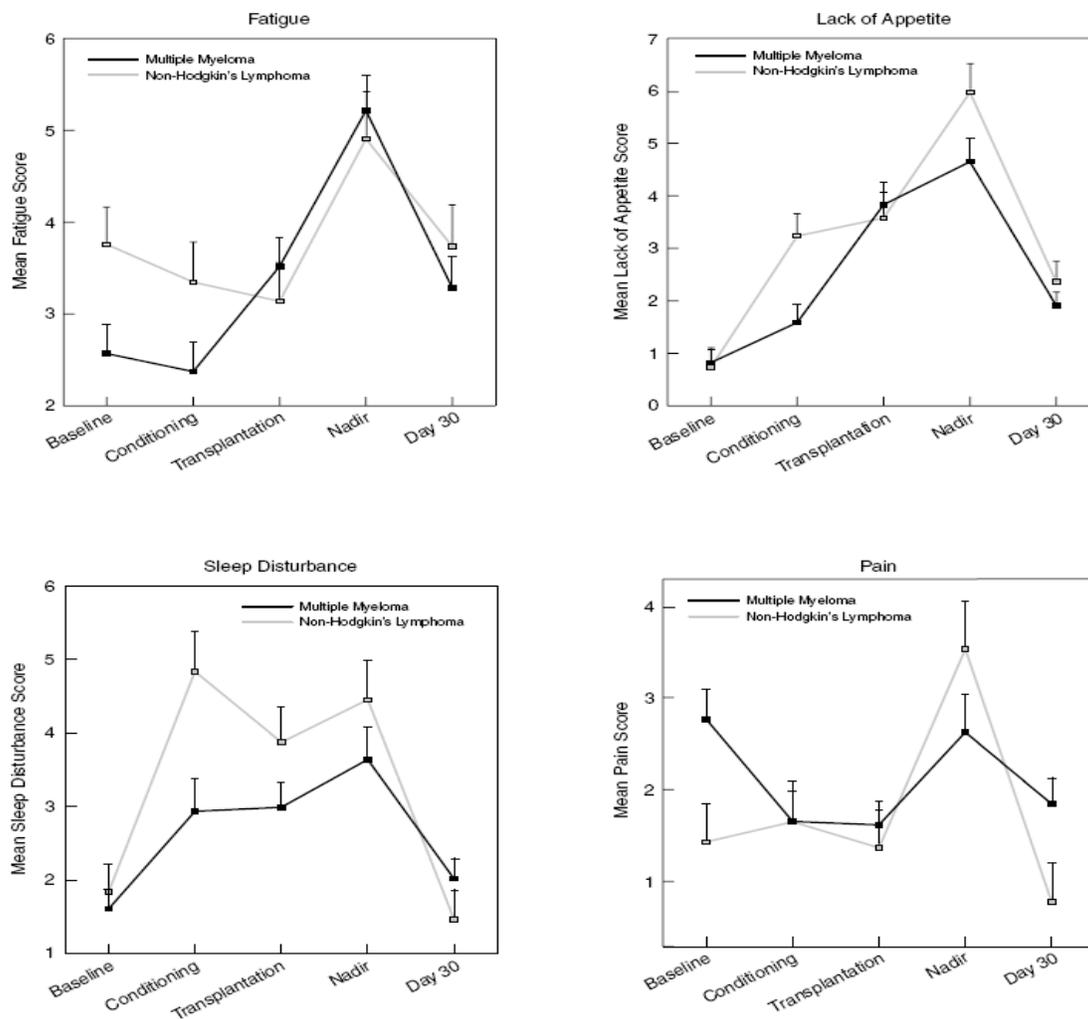


Figure 4. Mean symptom scores across time (N=100) (Anderson et al., 2007)

A group of patients undergoing allogeneic hematopoietic stem cell transplantation (allo-HSCT) would also be expected to show changes in symptom severity throughout the course of their treatment. A study by Wang et al (Wang et al., 2008) used the MDASI to track symptom severity over time and compared it to biological factors (**Figure 5**).

Finally, we examined the sensitivity of the MDASI in a sample of 20 Taiwanese cancer patients receiving chemotherapy (Lin et al., 2007). As expected, post-hoc Sheffe tests revealed that patients reported their lowest MDASI severity and interference scores before chemotherapy treatment and their highest scores during the treatment.

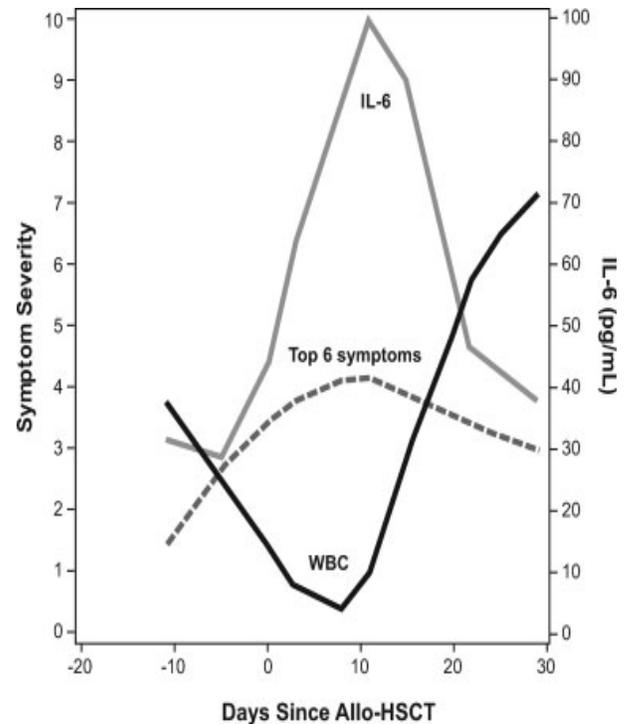


Figure 5. Severity levels of symptoms and cytokines (IL-6) relative to white blood cell count.

## Interpretability of the M. D. Anderson Symptom Inventory

Tests of interpretability examine the clinical meaningfulness of PRO score changes.

### Using Severity Descriptors: Mild, Moderate, and Severe

We have provisionally designated moderate pain and fatigue as those rated 5 or 6 on the MDASI's 0–10 scale and severe symptoms as those rated 7 or higher. These cut points were derived from our previous research on pain and fatigue, which suggested that 5–6 is the optimum range for a “moderate” designation and 7–10 is optimum a “severe” designation (Mendoza et al., 1999; Serlin et al., 1995). This categorization has been used in clinical practice guidelines for screening and managing pain and fatigue in Western countries (Benedetti et al., 2000; Mock et al., 2000). Cut points for mild, moderate, and severe categorization of MDASI symptoms other than pain and fatigue have not been investigated and can not be assumed to be the same as for pain or fatigue.

## Using a Responder Analysis

One of the applications of the mild, moderate, and severe categories for symptoms is to monitor shift in patient response. A responder definition is used to identify responders in clinical trials for analyzing differences in the proportion of responders between treatment arms. That is, it establishes the change in score that would be clear evidence that an individual patient experienced a treatment benefit.

For example, if a patient reported a severe pain level at baseline and a mild pain level after a month of treatment, then the patient can be considered as a responder. This kind of analysis was used in evaluating the effectiveness of an analgesic protocol in a multi-institutional ECOG trial (Cleeland et al., 2005).

## Summarizing Symptoms Over Time: The Area Under the Curve

The area under the curve (AUC) is a sensitive method for detecting differences by disease condition or treatment type for multiple symptoms. The AUC provides an excellent descriptive summary of MDASI severity ratings of multiple symptoms of patients while on treatment (or during a specified time period of interest). The MDASI-IVR system complements the AUC because it allows us to assess symptoms frequently during the course of the study.

The AUC charts shown below provide visual representation of a comparison of two disease conditions (**Figure 6**) and two treatment types (**Figure 7**) as reflected in

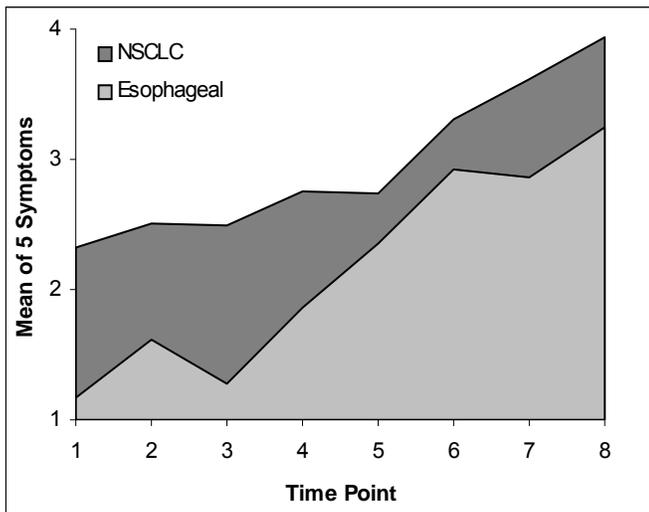


Figure 6. Average AUC Comparison of 5 Symptoms by Disease Condition with Chemoradiotherapy

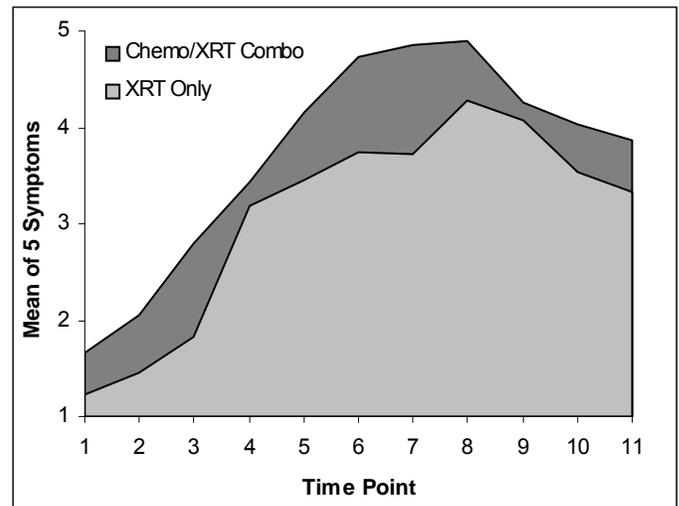


Figure 7. Average AUC Comparison of 5 Symptoms by Type of Treatment in Patients with Head & Neck Cancer

MDASI ratings of the severity of five symptoms (pain, fatigue, sleep disturbance, lack of appetite, and difficulty swallowing). Figure 6 presents the AUC comparisons for five selected symptoms (pain, fatigue, sleep disturbance, lack of appetite, drowsiness) between two cancers, esophageal and non-small cell lung cancer (NSCLC) being treated by chemoradiation therapy. Patients with NSCLC showed significantly larger AUC across 7 weeks of therapy than patients with esophageal cancer ( $P < .014$ ). Figure 7 presents the AUC comparisons for five selected symptoms (pain, fatigue, sleep disturbance, lack of appetite, difficulty swallowing) between different treatments, concurrent chemoradiation therapy (CXRT) and radiation therapy (XRT) alone. Patients with HNC undergoing CXRT demonstrated significantly larger AUC across 10 weeks than radiation patients ( $P < .028$ ).

### **Minimum Important Difference**

The smallest difference that is considered clinically important can be a specified difference (the minimum important difference, MID) or, in some cases, any detectable difference. The MID is used as a benchmark to interpret mean score differences between treatment arms in a clinical trial. A difference in mean score between treatment groups provides convincing evidence of a treatment benefit.

Several MIDs have been reported in the literature. Farrar and colleagues suggested that the MID for a 0–10 NRS is approximately a 33% reduction. This translates to at least a 3-point difference and is considered to be very liberal. Given that the standard deviation for pain at its worst is about 2.5, using Sloan et al, 1998 criteria of half standard deviation, the MID for a 0–10 NRS would be about 1.2 points.

Following guidelines used in the evaluation of the MID in health-related quality of life instruments, we tentatively set the MID for the MDASI to be about half a standard deviation (Sloan & Dueck, 2004). Given standard deviation values of 1.95 for the 13 core symptoms (Cleeland et al., 2000), 2.31 for the five most highly rated head and neck symptoms (Rosenthal et al., 2007), and 2.43 for five highly rated non-small cell lung cancer symptoms (unpublished data), it follows that the MID ranged from 0.98 to 1.21.

## Chapter 5

# Foreign-Language Versions of the M. D. Anderson Symptom Inventory

The MDASI has been translated into a number of languages; certification of the translation process is available for each. Of these, seven have been psychometrically validated: simplified Chinese (Wang et al., 2004), Filipino (Wang et al., 2006), Greek (Mystakidou et al., 2004), Japanese (Okuyama et al., 2003a), Korean (Yun et al., 2006), Russian (Ivanova et al., 2005), Spanish (unpublished data), and Taiwanese (Lin et al., 2007). Some of the MDASI modules are available in other languages.

New translations must undergo the translation procedures currently used by the Department of Symptom Research at MD Anderson Cancer Center, which include forward and back translation by native speakers (repeated until agreement is reached), pilot testing with cognitive debriefing, international harmonization to ensure conceptual equivalence, and proofreading by native translators.

The MDASI translations have most often mirrored the 2-factor structure and level of internal consistency of the original English MDASI (**Table 3**). A few of the translations have more than two factors.

**Table 3. MDASI translations with a two-factor structure**

| <b>Translation</b> | <b>Cronbach alpha: Severity</b> | <b>Cronbach alpha: Interference</b> |
|--------------------|---------------------------------|-------------------------------------|
| English            | 0.87                            | 0.91                                |
| Chinese            | 0.86                            | 0.84                                |
| Filipino           | 0.79                            | 0.77                                |
| Japanese           | 0.92                            | 0.93                                |
| Korean             | 0.91                            | 0.93                                |
| Taiwanese          | 0.89                            | 0.94                                |

## Example of the Validation of a Foreign-Language Version: The MDASI-Taiwanese

The MDASI-T was validated in 108 Taiwanese adolescents with cancer (Tseng et al., 2008). **Construct validity** was established by principal axis factor analysis with direct oblimin rotation, which resulted in a 2-factor solution for the 13 MDASI-T symptom items: a general symptoms factor (*pain, fatigue, sleep disturbance, distress, shortness of breath, difficulty remembering, drowsiness, dry mouth, sadness, and numbness*) and a gastrointestinal symptoms factor (*nausea, vomiting, and lack of appetite*). These two factors explained 51.7% of the total variance. Hierarchical cluster analysis results were consistent with the factor analysis. **Concurrent validity** was established by comparing symptom severity and interference scores with SF-36-T physical functioning and mental health subscales. The correlation coefficients for the related pairs were moderate, and included: pain/bodily pain items ( $r = -0.60$ ;  $P < .001$ ), fatigue/vitality items ( $r = -0.49$ ;  $P < .001$ ), distress/mental health items ( $r = -0.50$ ;  $P < .001$ ), and sadness/mental health items ( $r = -0.41$ ;  $P < .001$ ). **Known-group validity** was examined by comparing the MDASI-T total scores between patients with low and high functional status and between patients currently undergoing treatment and those currently not undergoing treatment. As we hypothesized, patients with low functional status (KPS score  $\leq 80$ ) and those with a high functional status (KPS score  $> 80$ ) had significantly different total MDASI-T scores. Similarly, adolescents who were currently undergoing treatment reported significantly higher levels of symptom severity and symptom interference than adolescents who were currently not undergoing treatment.

In a study of 556 Taiwanese patients with various cancer diagnoses, good internal consistency was shown for the MDASI symptom items (Cronbach coefficient  $\alpha = 0.89$ ) and interference items ( $\alpha = 0.94$ ). In the MDASI-T validation among adolescents with cancer, Cronbach alpha coefficients for the MDASI-T symptom severity, the general symptoms, the gastrointestinal symptoms, and interference were 0.90, 0.88, 0.83, and 0.91, respectively, indicating good internal consistency.

## Chapter 6

# The MDASI Modules

We recognized that particular cancer types, disease stages, or treatment modalities might require additional MDASI symptom items to achieve a comprehensive and accurate assessment. MDASI modules augment the 19 core MDASI symptom and interference items with additional items identified as unique to a particular patient population. MDASI modules may be disease-specific, disease-site-specific, or treatment-specific. For example, site-specific modules have been developed for brain tumors (Armstrong et al., 2006), head and neck cancer (Rosenthal et al., 2007), thyroid cancer (Gning et al., 2009), and lung cancer (unpublished data); others are in development. Treatment-specific modules are available for bone marrow transplantation, chemotherapy, radiotherapy, and bioimmunotherapy. Disease-specific modules are available for noncancer diseases, such as heart failure (Fadol et al., 2008).

## Examples of MDASI Module Development

### The MDASI Lung Cancer Module

The lung cancer module of the MDASI (MDASI-Lung) augments the core MDASI's 13 symptom and six interference items with three additional symptom items—*coughing*, *constipation*, and *sore throat*—specific to patients with lung cancer who are undergoing chemotherapy, radiation therapy, or both. The three lung-specific symptom items were originally identified through literature review and clinician input. Patient input on these items was solicited through cognitive debriefing.

The three lung-specific symptom items do not stand on their own, but derive their meaning when assessed in conjunction with the 13 MDASI core symptom items. For example, coughing, a lung-specific item, and shortness of breath, a core MDASI symptom item, would reasonably be highly correlated in patients with lung cancer. Thus, a severity subscale score (mean of the 13

core MDASI items plus the three lung-specific items) can be calculated. Symptom items can also be used individually or in subsets, without summary scoring.

We used three patient samples to demonstrate the reliability, validity, and sensitivity of the MDASI-Lung. Sample 1 comprised 102 patients with advanced lung cancer being treated with chemotherapy. The lung-specific symptom items presented to this sample were coughing and constipation. Sample 2 comprised 62 patients with locally advanced lung cancer who were undergoing chemotherapy, radiation, or a combination of both. The lung-specific symptom items presented to this sample were coughing and sore throat. We expected the patients receiving radiotherapy to report worsening sore throat. Data from Samples 1 and 2 were combined and provide the bulk of the data for the demonstration of reliability, validity, and sensitivity of the MDASI-Lung. The MDASI-Lung's test-retest reliability was examined in a third sample of 20 patients with either early-stage or advanced lung cancer being treated with chemotherapy, radiation, or a combination of both. On the basis of results from Samples 1 and 2, we presented all three lung-specific symptom items (coughing, sore throat, and constipation) to the 20 patients in Sample 3. Respondents completed the instrument twice, one day apart, and also underwent cognitive debriefing.

The three patient samples combined had an average age of about 61 years and were predominantly male and non-Hispanic white. The mean education level was grade 12.9. Most of the patients had a diagnosis of non-small cell lung cancer and most had good performance status. Approximately 18% had stage I or II disease.

Results of the cognitive debriefing indicated that the MDASI-Lung took about 2 minutes to complete, on average. All 20 respondents reported that the MDASI-Lung questionnaire was easy to complete, easy to understand, and not repetitive. They reported being very comfortable answering the questions and had no problems with the understanding, readability, or the quantity of the questions asked. Additionally, all 20 subjects were comfortable with the scoring system and found it easy to use and understand. Ninety-five percent of the respondents indicated that the MDASI-Lung was comprehensive and that no additional symptoms were needed.

The MDASI-Lung showed good [internal consistency reliability](#). Subscale Cronbach coefficient alpha values before treatment were 0.89 for the core MDASI

symptom items, at least 0.88 for the 16-item severity subscale, and 0.90 for the interference subscale. All subscale scores were at least 0.91 during treatment.

Correlations between MDASI subscales administered one day apart were at least 0.83. Test-retest reliabilities were 0.83 for the core MDASI symptom items, 0.88 for the 16-item severity subscale, and 0.84 for the interference subscale.

**Known-group validity** comparisons were made for the MDASI-Lung subscales in relation to ECOG PS. The MDASI-Lung discriminated between patients with good ECOG PS versus those with poor ECOG PS. Independent sample t-tests showed that patients with good ECOG PS had a significantly lower average core symptom scores (1.69, SD 1.51) than patients with poor ECOG PS (2.73, SD 1.88). Significant differences were also found in lung-cancer-specific symptoms, with a mean of 1.44 (SD 1.74) for the group of patients with a good ECOG PS, and a mean of 2.58 (SD 2.39) for the group of patients with poor ECOG PS. Similar results were seen for the severity subscale and the interference subscale. Effect-size differences were at least 0.65, which is considered to be a medium to large effect size (Cohen, 1992; Cohen, 1988).

To evidence **concurrent validity**, the MDASI subscales were correlated with the Beck Depression Inventory (BDI) and SF-12 scores. As expected, depression ratings were moderately correlated with symptom burden ( $r = 0.48$ ).

Because patients are supposedly more symptomatic when they are receiving chemoradiation, we demonstrated **sensitivity** by showing significant increases in the MDASI subscale ratings. The mean of the 13 core symptom items (1.69 vs 2.45,  $P < .024$ , effect size = 0.49), the mean of the 13 core symptoms plus three lung items (1.64 vs 2.50,  $P < .001$ , effect size = 0.61) and the mean of the symptom interference items (2.24 vs 3.24,  $P < .05$ , effect size = 0.40) were significantly higher during treatment when compared against ratings before treatment. These differences are also clinically important, as depicted by the magnitude of the effect sizes. Sloan et al (2004) suggest that differences of about one-half standard deviation are clinically meaningful.

In summary, these results are indicative of the validity, reliability and sensitivity of the MDASI-Lung for use in assessing symptom severity and symptom interference in patients with lung cancer.

### **The MDASI Head and Neck Module**

The MDASI Head and Neck Module (MDASI-HN) (Rosenthal et al., 2007) was developed to remedy various deficiencies in existing symptom-assessment measures, which either did not address relevant symptoms, symptom interference with daily functioning, or symptom-related distress, or else utilized less-desirable scales or recall periods. The initial items for the MDASI-HN were derived from a comprehensive literature review and focus-group input. Focus groups included patients with head and neck cancer; surgeons; radiation, medical, and dental oncologists and speech-language pathologists working with this patient population; and symptom researchers. Eleven potential symptoms specific to the head and neck cancer population were identified and provisionally added to the core MDASI items, for a total of 24 symptom items and 6 interference items.

The MDASI-HN was then tested in 205 patients with head and neck cancer. The number of symptoms in the module was further reduced based on examination of descriptive statistics for the severity and prevalence of symptoms, regression models to determine the greatest source of variability in predicting symptom interference, and clinician review. In general, items that showed the highest severity and that were reported to be moderate to severe by the greatest percentage of patients were retained. Several items were rated with low severity but were retained because clinicians believed them to be necessary for clinical assessment of patients receiving treatment for head and neck cancer. The nine items retained for the MDASI-HN include *mucus in the mouth and throat, difficulty swallowing/chewing, choking/coughing, difficulty with voice/speech, skin pain/burning/rash, constipation, problems with tasting food, mouth/throat sores, and problems with teeth or gums.*

**Construct validity** was tested using principal axis factoring with direct oblimin rotation. The 9 additional items in the module measured 2 underlying constructs, a factor comprising *mouth sores, tasting food, constipation, teeth or gum problems,* and

*skin pain*, and a factor comprising *problems with the voice, choking/coughing, swallowing/chewing, and mucus*. Model fit was confirmed using Harman's criterion in a comparison of the reproduced correlations based on the 2-factor solution and observed correlations in the sample. **Known-group validity** was tested in a comparison of patients with good performance status vs patients with poor performance status. As expected, these two patient groups differed significantly in their MDASI-HN ratings of core symptom severity (1.72 vs 3.59, respectively), mean head and neck symptom severity (1.85 vs 4.52), and mean interference (1.68 vs 4.55). The MDASI-HN showed **concurrent validity** in comparison with another measure that is widely used for assessing cancer symptoms, the SF12v2. There was a significant correlation between the core, head-and-neck specific, and interference subscales of the MDASI-HN and the physical and mental component scores of the SF12v2.

The **internal consistency reliability** of the MDASI-HN was evidenced by Cronbach coefficient alphas of 0.88, 0.72, 0.83, and 0.92 for the 13 core symptom items, the 2 factors of the 9 head and neck symptom items, and the 6 interference items, respectively.

## Chapter 7

# The MDASI in the Literature

### MDASI Translations

Gunnarsdottir S, Fridriksdottir N, Skuladottir F, Birgisdottir O, Fridriksdottir V. The psychometric properties of the Icelandic version of the MD Anderson Symptom Inventory (MDASI). *Oncology Nursing Forum* 2006;33:458.

Ivanova MO, Ionova TI, Kalyadina SA, Uspenskaya OS, Kishitovich AV, Guo H, Mendoza TR, Novik A, Cleeland CS, Wang XS. Cancer-related symptom assessment in Russia: validation and utility of the Russian M. D. Anderson Symptom Inventory. *J Pain Symptom Manage* 2005;30:443-453.

Lin CC, Chang AP, Cleeland CS, Mendoza TR, Wang XS. Taiwanese version of the M. D. Anderson symptom inventory: symptom assessment in cancer patients. *J Pain Symptom Manage* 2007;33:180-188.

Mystakidou K, Cleeland C, Tsilika E, Katsouda E, Primikiri A, Parpa E, Vlahos L, Mendoza T. Greek M.D. Anderson Symptom Inventory: validation and utility in cancer patients. *Oncology* 2004;67:203-210.

Okuyama T, Wang XS, Akechi T, Mendoza TR, Hosaka T, Cleeland CS, Uchitomi Y. Japanese version of the MD Anderson Symptom Inventory: a validation study. *J Pain Symptom Manage* 2003;26:1093-1104.

Wang XS, Wang Y, Guo H, Mendoza TR, Hao XS, Cleeland CS. Chinese version of the M. D. Anderson Symptom Inventory: validation and application of symptom measurement in cancer patients. *Cancer* 2004;101:1890-1901.

Wang XS, Laudico AV, Guo H, Mendoza TR, Matsuda ML, Yosuiico VD, Fragante EP, Cleeland CS. Filipino version of the M. D. Anderson Symptom Inventory: validation and multisymptom measurement in cancer patients. *J Pain Symptom Manage* 2006;31:542-552.

Yun YH, Mendoza TR, Kang IO, You CH, Roh JW, Lee CG, Lee WS, Lee KS, Bang SM, Park SM, Cleeland CS, Wang XS. Validation study of the Korean version of the M. D. Anderson Symptom Inventory. *J Pain Symptom Manage* 2006;31:345-352.

### The MDASI in Research Studies

Abernethy AP, Herndon JE, Wheeler JL, et al. Improving Health Care Efficiency and Quality Using Tablet Personal Computers to Collect Research-Quality, Patient-Reported Data. *Health Serv Res*, e-pub ahead of print 2008.

Anderson KO, Giralt SA, Mendoza TR, et al. Symptom burden in patients undergoing autologous stem-cell transplantation. *Bone Marrow Transplant* 2007;39(12):759-766.

Armstrong T, Mendoza T, Cohen M, et al. Reliability and validity of the M.D. Anderson symptom inventory (MDASI-BT) in the primary brain tumor patient population. *Oncology Nursing Forum* 2005;32(2):476-477.

Armstrong TS, Mendoza T, Cohen MZ, et al. Reliability and validity of the M.D. Anderson symptom inventory (MDASI-BT) in the primary brain tumor patient population. *Neuro-Oncology* 2004;6(4):355-356.

Armstrong TS, Cohen MZ, Eriksen L, Cleeland C. Content validity of self-report measurement instruments: an illustration from the development of the Brain Tumor Module of the M.D. Anderson Symptom Inventory. *Oncol Nurs Forum* 2005;32(3):669-676.

Armstrong TS, Mendoza T, Gning I, et al. Validation of the M.D. Anderson Symptom Inventory Brain Tumor Module (MDASI-BT). *J Neurooncol* 2006;80(1):27-35.

Armstrong TS, Gning I, Mendoza TR, et al. Clinical Utility of the MDASI-BT in Patients with Brain Metastases. *J Pain Symptom Manage* 2008.

Campagnaro E, Saliba R, Giralt S, et al. Symptom burden after autologous stem cell transplantation for multiple myeloma. *Cancer* 2008;112(7):1617-1624.

Chen ML, Tseng HC. Symptom clusters in cancer patients. *Support Care Cancer* 2006;14(8):825-830.

Chen ML, Lin CC. Cancer symptom clusters: a validation study. *J Pain Symptom Manage* 2007;34(6):590-599.

Cleeland CS, Mendoza TR, Wang XS, et al. Assessing symptom distress in cancer patients: the M.D. Anderson Symptom Inventory. *Cancer* 2000;89(7):1634-1646.

Fadol A, Mendoza T, Gning I, et al. Psychometric testing of the MDASI-HF: a symptom assessment instrument for patients with cancer and concurrent heart failure. *J Card Fail* 2008;14(6):497-507.

Fan G, Filipczak L, Chow E. Symptom clusters in cancer patients: a review of the literature. *Curr Oncol* 2007;14(5):173-179.

Gabrilove JL, Perez EA, Tomita DK, Rossi G, Cleeland CS. Assessing symptom burden using the M. D. Anderson symptom inventory in patients with chemotherapy-induced anemia: results of a multicenter, open-label study (SURPASS) of patients treated with darbepoetin-alpha at a dose of 200 microg every 2 weeks. *Cancer* 2007;110(7):1629-1640.

Ivanova MO, Ionova TI, Kalyadina SA, et al. Cancer-related symptom assessment in Russia: validation and utility of the Russian M. D. Anderson Symptom Inventory. *J Pain Symptom Manage* 2005;30(5):443-453.

Kwon YC, Yun YH, Lee KH, et al. Symptoms in the lives of terminal cancer patients: which is the most important? *Oncology* 2006;71(1-2):69-76.

Lin CC, Chang AP, Cleeland CS, Mendoza TR, Wang XS. Taiwanese version of the M. D. Anderson symptom inventory: symptom assessment in cancer patients. *J Pain Symptom Manage* 2007;33(2):180-188.

Mystakidou K, Cleeland C, Tsilika E, et al. Greek M.D. Anderson Symptom Inventory: validation and utility in cancer patients. *Oncology* 2004;67(3-4):203-210.

Mystakidou K, Tsilika E, Parpa E, et al. Psychometric properties of the brief fatigue inventory in Greek patients with advanced cancer. *J Pain Symptom Manage* 2008;36(4):367-373.

Navari RM, Einhorn LH, Passik SD, et al. A phase II trial of olanzapine for the prevention of chemotherapy-induced nausea and vomiting: A Hoosier Oncology Group study. *Supportive Care in Cancer* 2005;13(7):529-534.

Navari RM, Einhorn LH, Loehrer PJ, et al. A phase II trial of olanzapine, dexamethasone, and palonosetron for the prevention of chemotherapy-induced nausea and vomiting: a Hoosier oncology group study. *Supportive Care in Cancer* 2007;15(11):1285-1291.

Okuyama T, Wang XS, Akechi T, et al. Japanese version of the MD Anderson Symptom Inventory: a validation study. *J Pain Symptom Manage* 2003;26(6):1093-1104.

Okuyama T, Wang XS, Akechi T, et al. Adequacy of cancer pain management in a Japanese Cancer Hospital. *Jpn J Clin Oncol* 2004;34(1):37-42.

Paice JA. Assessment of symptom clusters in people with cancer. *J Natl Cancer Inst Monogr* 2004;(32):98-102.

Reyes-Gibby CC, Chan W, Abbruzzese JL, et al. Patterns of self-reported symptoms in pancreatic cancer patients receiving chemoradiation. *J Pain Symptom Manage* 2007;34(3):244-252.

Rosenthal DI, Mendoza TR, Chambers MS, et al. Measuring head and neck cancer symptom burden: the development and validation of the M. D. Anderson symptom inventory, head and neck module. *Head Neck* 2007;29(10):923-931.

Rosenthal DI, Mendoza TR, Chambers MS, et al. The M.D. Anderson Symptom Inventory-Head and Neck Module, A Patient-Reported Outcome Instrument, Accurately Predicts The Severity of Radiation-Induced Mucositis. *Int J Radiat Oncol Biol Phys* 2008.

Shih YC, Wang XS, Cantor SB, Cleeland CS. The association between symptom burdens and utility in Chinese cancer patients. *Qual Life Res* 2006;15(8):1427-1438.

Tseng TH, Cleeland CS, Wang XS, Lin CC. Assessing cancer symptoms in adolescents with cancer using the Taiwanese version of the M. D. Anderson Symptom Inventory. *Cancer Nurs* 2008;31(3):E9-16.

Valdres RU, Escalante C, Manzullo E. Fatigue: a debilitating symptom. *Nurs Clin North Am* 2001;36(4):685-94, vi.

Wang SY, Tsai CM, Chen BC, Lin CH, Lin CC. Symptom clusters and relationships to symptom interference with daily life in Taiwanese lung cancer patients. *J Pain Symptom Manage* 2008;35(3):258-266.

Wang XS, Wang Y, Guo H, et al. Chinese version of the M. D. Anderson Symptom Inventory: validation and application of symptom measurement in cancer patients. *Cancer* 2004;101(8):1890-1901.

Wang XS, Ferrajoli A, Broadway JB, et al. Symptom assessment in patients with chronic lymphocytic leukemia: Validation and application of the M.D. Anderson Symptom Inventory. *Blood* 2005;106(11):331B.

Wang XS, Laudico AV, Guo H, et al. Filipino version of the M. D. Anderson Symptom Inventory: validation and multisymptom measurement in cancer patients. *J Pain Symptom Manage* 2006;31(6):542-552.

Wang XS, Fairclough DL, Liao Z, et al. Longitudinal study of the relationship between chemoradiation therapy for non-small-cell lung cancer and patient symptoms. *J Clin Oncol* 2006;24(27):4485-4491.

Wang XS, Laudico AV, Guo H, et al. Filipino version of the M. D. Anderson Symptom Inventory: validation and multisymptom measurement in cancer patients. *J Pain Symptom Manage* 2006;31(6):542-552.

Wang XS, Shi Q, Williams LA, et al. Serum interleukin-6 predicts the development of multiple symptoms at nadir of allogeneic hematopoietic stem cell transplantation. *Cancer* 2008;113(8):2102-2109.

Yamagishi A, Morita T, Miyashita M, Kimura F. Symptom Prevalence and Longitudinal Follow-Up in Cancer Outpatients Receiving Chemotherapy. *J Pain Symptom Manage* 2008.

Yun YH, Mendoza TR, Kang IO, et al. Validation study of the Korean version of the M. D. Anderson Symptom Inventory. *J Pain Symptom Manage* 2006;31(4):345-352.

Zhao Y, Wang XS, Li PP. Investigation of common symptoms of cancer and reliability analysis. *Chin J Integr Med* 2007;13(3):195-199.

## Appendix A. The M. D. Anderson Symptom Inventory

Date: \_\_\_\_\_

Institution: \_\_\_\_\_

Subject Initials: \_\_\_\_\_

Hospital Chart #: \_\_\_\_\_

Study Subject #: \_\_\_\_\_

### M. D. Anderson Symptom Inventory (MDASI) Core Items

#### Part I. How severe are your symptoms?

People with cancer frequently have symptoms that are caused by their disease or by their treatment. We ask you to rate how severe the following symptoms have been *in the last 24 hours*. Please fill in the circle below from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.

|   | Not Present           | As Bad As You Can Imagine |                       |                       |                       |                       |                       |                       |                       |                       |                       |
|---|-----------------------|---------------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
|   | 0                     | 1                         | 2                     | 3                     | 4                     | 5                     | 6                     | 7                     | 8                     | 9                     | 10                    |
| 1. Your <b>pain</b> at its WORST?                                 | <input type="radio"/> | <input type="radio"/>     | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 2. Your <b>fatigue (tiredness)</b> at its WORST?                  | <input type="radio"/> | <input type="radio"/>     | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 3. Your <b>nausea</b> at its WORST?                               | <input type="radio"/> | <input type="radio"/>     | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 4. Your <b>disturbed sleep</b> at its WORST?                      | <input type="radio"/> | <input type="radio"/>     | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 5. Your feelings of being <b>distressed (upset)</b> at its WORST? | <input type="radio"/> | <input type="radio"/>     | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 6. Your <b>shortness of breath</b> at its WORST?                  | <input type="radio"/> | <input type="radio"/>     | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 7. Your problem with <b>remembering things</b> at its WORST?      | <input type="radio"/> | <input type="radio"/>     | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 8. Your problem with <b>lack of appetite</b> at its WORST?        | <input type="radio"/> | <input type="radio"/>     | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 9. Your feeling <b>drowsy (sleepy)</b> at its WORST?              | <input type="radio"/> | <input type="radio"/>     | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |
| 10. Your having a <b>dry mouth</b> at its WORST?                  | <input type="radio"/> | <input type="radio"/>     | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> | <input type="radio"/> |

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Date: \_\_\_\_\_

Institution: \_\_\_\_\_

Subject Initials: \_\_\_\_\_

Hospital Chart #: \_\_\_\_\_

Study Subject #: \_\_\_\_\_

|  | Not Present           |                       |                       |                       |                       |                       |                       |                       |                       |                       | As Bad As You Can Imagine |  |
|--|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|---------------------------|--|
|  | 0                     | 1                     | 2                     | 3                     | 4                     | 5                     | 6                     | 7                     | 8                     | 9                     | 10                        |  |
| 11. Your feeling <b>sad</b> at its WORST?          | <input type="radio"/>     |  |
| 12. Your <b>vomiting</b> at its WORST?             | <input type="radio"/>     |  |
| 13. Your <b>numbness or tingling</b> at its WORST? | <input type="radio"/>     |  |

**Part II. How have your symptoms interfered with your life?**

Symptoms frequently interfere with how we feel and function. How much have your symptoms interfered with the following items in the last 24 hours:

|  | Did Not Interfere     |                       |                       |                       |                       |                       |                       |                       |                       |                       | Interfered Completely |  |
|--|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|--|
|  | 0                     | 1                     | 2                     | 3                     | 4                     | 5                     | 6                     | 7                     | 8                     | 9                     | 10                    |  |
| 14. <b>General activity?</b>                       | <input type="radio"/> |  |
| 15. <b>Mood?</b>                                   | <input type="radio"/> |  |
| 16. <b>Work (including work around the house)?</b> | <input type="radio"/> |  |
| 17. <b>Relations with other people?</b>            | <input type="radio"/> |  |
| 18. <b>Walking?</b>                                | <input type="radio"/> |  |
| 19. <b>Enjoyment of life?</b>                      | <input type="radio"/> |  |

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## Appendix B. Sample Cognitive Debriefing Form

|  |  |  |
|--|--|--|
| <br>64899 | Date: <input type="text"/> / <input type="text"/> / <input type="text"/><br>(month) (day) (year)         | Study Title: Validation of the M. D.<br>Anderson Symptom Inventory -<br>Thyroid Module |
|  | Participant's Initials: _____  | Protocol #: BS99-094   |
|  | Participant Study #: <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> | PI: Charles Cleeland, PhD  |
| PLEASE USE A<br>BLACK INK PEN  |  | Revised: 07-17-07  |

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**Cognitive Debriefing - MDASI-Thyroid**

**INSTRUCTIONS:**

After the participant completes the MDASI-Thyroid, the data collector asks the following questions and records the participant's responses. The participant is given a copy of the MDASI-Thyroid with no responses entered as a reference while these questions are being asked.

**Time taken to complete the MDASI-Thyroid:**   min. (Noted by data collector)

**1. Ease of Completion:**

1.a. On a scale of 0 to 10 with 0 being "Very easy" and 10 being "Very hard", how easy was it to complete the questions?  0  1  2  3  4  5  6  7  8  9  10  
Very easy Very hard

1.b. Were the words and numbers easy to see?  Yes  No

1.c. Should the words and numbers be larger or easier to read?  Yes  No

1.d. Are there too many questions?  Yes  No



Date:  /  /   
(month) (day) (year)

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**2. Comprehensibility:**

2.a. On a scale of 0 to 10 with 0 being "Very easy" and 10 being "Very hard", how easy were the questions to understand?  0  1  2  3  4  5  6  7  8  9  10  
Very easy Very hard

2.b. Were there any questions that were difficult to understand?  Yes  No

2.c. What specific questions were difficult to understand? (Check all that apply)

|                                     | 2.d. What was difficult about the question? | 2.e. Can you suggest a way to make the question easier to answer? |
|-------------------------------------|---|---|
| <input type="radio"/> 1.Pain        | .....                                       | .....   |
| <input type="radio"/> 2.Fatigue     | .....                                       | .....   |
| <input type="radio"/> 3.Nausea      | .....                                       | .....   |
| <input type="radio"/> 4.Sleep       | .....                                       | .....   |
| <input type="radio"/> 5.Distress    | .....                                       | .....   |
| <input type="radio"/> 6.SOB         | .....                                       | .....   |
| <input type="radio"/> 7.Remember    | .....                                       | .....   |
| <input type="radio"/> 8.Appetite    | .....                                       | .....   |
| <input type="radio"/> 9.Drowsy      | .....                                       | .....   |
| <input type="radio"/> 10.Dry Mouth  | .....                                       | .....   |
| <input type="radio"/> 11.Sad        | .....                                       | .....   |
| <input type="radio"/> 12.Vomiting   | .....                                       | .....   |
| <input type="radio"/> 13.Numbness   | .....                                       | .....   |
| <input type="radio"/> 14.Hoarseness | .....                                       | .....   |
| <input type="radio"/> 15.Feel Hot   | .....                                       | .....   |
| <input type="radio"/> 16.Heartbeat  | .....                                       | .....   |
| <input type="radio"/> 17.Feel Cold  | .....                                       | .....   |
| <input type="radio"/> 18.Swallow    | .....                                       | .....   |
| <input type="radio"/> 19.Diarrhea   | .....                                       | .....   |
| <input type="radio"/> 20.Activity   | .....                                       | .....   |
| <input type="radio"/> 21.Mood       | .....                                       | .....   |
| <input type="radio"/> 22.Work       | .....                                       | .....   |
| <input type="radio"/> 23.Relations  | .....                                       | .....   |
| <input type="radio"/> 24.Walking    | .....                                       | .....   |
| <input type="radio"/> 25.Enjoy Life | .....                                       | .....   |



Date:  /  /   
(month) (day) (year)

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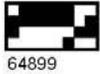
**3. Acceptability:**

3.a. On a scale of 0 to 10 with 0 being "Very comfortable" and 10 being "Very uncomfortable", how comfortable were you in answering the questions?  0  1  2  3  4  5  6  7  8  9  10  
Very comfortable Very uncomfortable

3.b. Were there any questions that you were uncomfortable in answering?  Yes  No

3.c. What questions were you not comfortable in answering? (Check all that apply)

|                                     | 3.d. What was uncomfortable about answering the question? | 3.e. Can you suggest a way to make the question more comfortable to answer? |
|-------------------------------------|---|---|
| <input type="radio"/> 1.Pain        | -----   | -----   |
| <input type="radio"/> 2.Fatigue     | -----   | -----   |
| <input type="radio"/> 3.Nausea      | -----   | -----   |
| <input type="radio"/> 4.Sleep       | -----   | -----   |
| <input type="radio"/> 5.Distress    | -----   | -----   |
| <input type="radio"/> 6.SOB         | -----   | -----   |
| <input type="radio"/> 7.Remember    | -----   | -----   |
| <input type="radio"/> 8.Appetite    | -----   | -----   |
| <input type="radio"/> 9.Drowsy      | -----   | -----   |
| <input type="radio"/> 10.Dry Mouth  | -----   | -----   |
| <input type="radio"/> 11.Sad        | -----   | -----   |
| <input type="radio"/> 12.Vomiting   | -----   | -----   |
| <input type="radio"/> 13.Numbness   | -----   | -----   |
| <input type="radio"/> 14.Hoarseness | -----   | -----   |
| <input type="radio"/> 15.Feel Hot   | -----   | -----   |
| <input type="radio"/> 16.Heartbeat  | -----   | -----   |
| <input type="radio"/> 17.Feel Cold  | -----   | -----   |
| <input type="radio"/> 18.Swallow    | -----   | -----   |
| <input type="radio"/> 19.Diarrhea   | -----   | -----   |
| <input type="radio"/> 20.Activity   | -----   | -----   |
| <input type="radio"/> 21.Mood       | -----   | -----   |
| <input type="radio"/> 22.Work       | -----   | -----   |
| <input type="radio"/> 23.Relations  | -----   | -----   |
| <input type="radio"/> 24.Walking    | -----   | -----   |
| <input type="radio"/> 25.Enjoy Life | -----   | -----   |



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**4. Redundancy:**

4.a. On a scale of 0 to 10 with 0 being "Not repetitive at all" and 10 being "Completely repetitive", how repetitive were the questions?  0  1  2  3  4  5  6  7  8  9  10  
Not repetitive at all Completely repetitive

4.b. Were there any questions that you found repetitive?  Yes  No

4.c. What questions did you find repetitive? (Check all that apply)

- |                                  |                                    |                                     |                                     |
|----------------------------------|------------------------------------|-------------------------------------|-------------------------------------|
| <input type="radio"/> 1.Pain     | <input type="radio"/> 8.Appetite   | <input type="radio"/> 14.Hoarseness | <input type="radio"/> 20.Activity   |
| <input type="radio"/> 2.Fatigue  | <input type="radio"/> 9.Drowsy     | <input type="radio"/> 15.Feel Hot   | <input type="radio"/> 21.Mood       |
| <input type="radio"/> 3.Nausea   | <input type="radio"/> 10.Dry Mouth | <input type="radio"/> 16.Heartbeat  | <input type="radio"/> 22.Work       |
| <input type="radio"/> 4.Sleep    | <input type="radio"/> 11.Sad       | <input type="radio"/> 17.Feel Cold  | <input type="radio"/> 23.Relations  |
| <input type="radio"/> 5.Distress | <input type="radio"/> 12.Vomiting  | <input type="radio"/> 18.Swallow    | <input type="radio"/> 24.Walking    |
| <input type="radio"/> 6.SOB      | <input type="radio"/> 13.Numbness  | <input type="radio"/> 19.Diarrhea   | <input type="radio"/> 25.Enjoy Life |
| <input type="radio"/> 7.Remember |                                    |                                     |                                     |

4.d. Which questions would you suggest getting rid of because they are repetitive?  None

- |                                  |                                    |                                     |                                     |
|----------------------------------|------------------------------------|-------------------------------------|-------------------------------------|
| <input type="radio"/> 1.Pain     | <input type="radio"/> 8.Appetite   | <input type="radio"/> 14.Hoarseness | <input type="radio"/> 20.Activity   |
| <input type="radio"/> 2.Fatigue  | <input type="radio"/> 9.Drowsy     | <input type="radio"/> 15.Feel Hot   | <input type="radio"/> 21.Mood       |
| <input type="radio"/> 3.Nausea   | <input type="radio"/> 10.Dry Mouth | <input type="radio"/> 16.Heartbeat  | <input type="radio"/> 22.Work       |
| <input type="radio"/> 4.Sleep    | <input type="radio"/> 11.Sad       | <input type="radio"/> 17.Feel Cold  | <input type="radio"/> 23.Relations  |
| <input type="radio"/> 5.Distress | <input type="radio"/> 12.Vomiting  | <input type="radio"/> 18.Swallow    | <input type="radio"/> 24.Walking    |
| <input type="radio"/> 6.SOB      | <input type="radio"/> 13.Numbness  | <input type="radio"/> 19.Diarrhea   | <input type="radio"/> 25.Enjoy Life |
| <input type="radio"/> 7.Remember |                                    |                                     |                                     |

4.e. Which questions would you suggest keeping because they are not repetitive?  All

- |                                  |                                    |                                     |                                     |
|----------------------------------|------------------------------------|-------------------------------------|-------------------------------------|
| <input type="radio"/> 1.Pain     | <input type="radio"/> 8.Appetite   | <input type="radio"/> 14.Hoarseness | <input type="radio"/> 20.Activity   |
| <input type="radio"/> 2.Fatigue  | <input type="radio"/> 9.Drowsy     | <input type="radio"/> 15.Feel Hot   | <input type="radio"/> 21.Mood       |
| <input type="radio"/> 3.Nausea   | <input type="radio"/> 10.Dry Mouth | <input type="radio"/> 16.Heartbeat  | <input type="radio"/> 22.Work       |
| <input type="radio"/> 4.Sleep    | <input type="radio"/> 11.Sad       | <input type="radio"/> 17.Feel Cold  | <input type="radio"/> 23.Relations  |
| <input type="radio"/> 5.Distress | <input type="radio"/> 12.Vomiting  | <input type="radio"/> 18.Swallow    | <input type="radio"/> 24.Walking    |
| <input type="radio"/> 6.SOB      | <input type="radio"/> 13.Numbness  | <input type="radio"/> 19.Diarrhea   | <input type="radio"/> 25.Enjoy Life |
| <input type="radio"/> 7.Remember |                                    |                                     |                                     |





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Date: [ ] [ ] / [ ] [ ] / [ ] [ ] [ ]  
(month) (day) (year)

Participant's Initials: \_\_\_\_\_

Participant Study #: [ ] [ ] [ ] [ ] [ ] [ ]

Study Title: Validation of the M. D. Anderson Symptom Inventory - Thyroid Module

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**7. Content Domain Confirmation:**

7.a. Are there any other questions about your symptoms that should be included?  Yes  No

(If Yes) What are those questions?

- 1. \_\_\_\_\_
- 2. \_\_\_\_\_
- 3. \_\_\_\_\_
- 4. \_\_\_\_\_

7.b. Is there anything else you would like us to know about measuring your symptoms and how these symptoms interfere with normal activities?  Yes  No

(If Yes) What else would you like us to know?

- 1. \_\_\_\_\_
- 2. \_\_\_\_\_

7.c. Are there other questions about your symptoms that you think we should ask?  Yes  No

(If Yes) What other questions:

- 1. \_\_\_\_\_
- 2. \_\_\_\_\_
- 3. \_\_\_\_\_
- 4. \_\_\_\_\_



Date:  /  /   
 (month) (day) (year)

Participant's Initials: \_\_\_\_\_

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**8. Recall Period:**

8.a. Was it easy to remember your symptoms over the past 24 hours?  Yes  No

8.b. On a scale of 0 to 10 with 0 being "Very easy" and 10 being "Very hard", how easy was it to remember symptoms over the past 24 hours?  
 0  1  2  3  4  5  6  7  8  9  10  
 Very easy Very hard

8.c. On a scale of 0 to 10 with 0 being "Very easy" and 10 being "Very hard", how easy would it be to remember symptoms over the past week?  
 0  1  2  3  4  5  6  7  8  9  10  
 Very easy Very hard

## Appendix C. Sample Instructions for MDASI Administration

The following instructions pertain to the paper and pencil version of the MDASI. A sample IVR instruction booklet is included in Appendix D.

### Instructions for Beginning MDASI Administration via Interview

| Instructions   | Dialogue   |
|--|--|
| <p>It is important to get the research participant's honest answers to the MDASI without any outside influences. It is important to approach and respond to each research participant in a similar manner and to be friendly but neutral so as not to influence the research participant's answers (this includes verbal and non-verbal communications). Approach the research participant by saying:</p>  | <p><b>Thank you for agreeing to tell us about your symptoms. In this interview, there are no right or wrong answers. So do not worry about whether your answers are correct. When it comes to your symptoms, you are the expert, and <i>your</i> answers are the <i>right</i> answers.</b></p>   |
| <p>Family members, friends, or health care providers can also influence the research participant's answers. It is best to conduct the symptom interview in a private area with no one else around. If you are in an examination room with the research participant, but one or two other people are in the room, assess the situation and determine if it would be possible to ask the other people in the room to leave. You can say:</p>   | <p><b>I have a few questions that I need to ask Mr./Mrs./Ms./Miss _____ (research participant's last name). Usually family or friends may stay in the room when patients are asked about their health. However, I need a few minutes alone with Mr./Mrs./Ms./Miss _____ (research participant's last name). Would you mind leaving us alone for just a few minutes? If you like, you may wait in the hall. I will let you know as soon as I am finished. This should take no more than 10 minutes.</b></p> |
| <p>If, after appraising the situation, you think that asking the other people to leave may upset the research participant or a family member, then do not ask them to do so. In other cases, such as in a large waiting area, it is not always practical to ask people to leave you and the research participant alone. Therefore, if anyone else is in the area when the research participant is completing the symptom inventory, before beginning the inventory it is important to say:</p> |  |

| Instructions   | Dialogue   |
|--|--|
|  | <p><b>Because symptoms are things that a patient experiences, you, the patient, are the only one who can tell us about your symptoms. Please answer these questions about your symptoms without any help from anyone else.</b></p> |
| <p>Determine the manner in which the research participant will complete the MDASI by saying:</p> | <p><b>The symptom questions are on this two page form. Would you like to fill out the form yourself or would you like me to ask you the questions?</b></p>   |

### Instructions for Research Participants Who Complete the MDASI Themselves

| Instructions   | Dialogue   |
|--|--|
| <p>If research participants chose to complete the MDASI the themselves, say:</p>   | <p><b>We use special computer forms to collect your answers. Because of that, I am going to go over a few tips that will help you in completing the form.</b></p> <p><b>We will not use your name on the form and only the study staff will know who completed each form.</b></p> <p><b>Complete each symptom item by marking only one circle in each row. You may completely fill in the circle or make an X or a check mark. Keep your mark only in one circle. Don't let your mark move into other circles.</b></p> <p><b>Let me know if you want to change your answer or if you make a mark in a wrong circle by accident. I will make a note to show which marks were made by mistake on your form.</b></p> <p><b>After you have completed the form, I will check over the form. I want to be sure that you have not skipped any of the items or marked more than one answer for an item. If there are any items that you do not wish to answer, please leave them blank. When I check the form, you can let me know that you left that item blank on purpose.</b></p> |
| <p>It is important that research participants rate the severity of any symptom that they have experienced in the last 24 hours regardless of what they think is causing the symptom.</p> <p>Research participants must select a single whole number as an answer. They may not mark part way between two numbers.</p> <p>Hand the MDASI form to the research participant along with a black ballpoint pen and say:</p> |  |

| Instructions   | Dialogue  |
|--|---|
|  | <p><b>Let's start the survey. How severe are your symptoms? People with cancer frequently have symptoms that are caused by their disease or by their treatment. We ask you to rate how severe the following symptoms have been <i>in the last 24 hours</i>.</b></p> <p><b>Please rate the worst severity of each symptom that you experienced in the last 24-hours, regardless of whether you think it was related to cancer, treatment, or another cause. If you did not experience the symptom at all in the last 24 hours, rate the severity as 0.</b></p> <p><b>Please fill in the circle below from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.</b></p> <p><b>When you have finished answering the symptom items, let me know.</b></p> |
| <p>Research participants should base their interference ratings only on the interference caused by the symptoms and not on interference due to other causes, such as being away from home.</p> <p>When the research participant has completed the symptom items say:</p> | <p><b>Good. Now we have just a few more questions. You will complete these questions the same way that you completed the symptom items. We are interested in the way that the symptoms you have just rated interfered with things you wanted or needed to do. Answer these questions based only on how much your symptoms have interfered.</b></p> <p><b>How have your symptoms interfered with your life? Symptoms frequently interfere with how we feel and function. How much have your symptoms interfered with the following items <i>in the last 24 hours</i>?</b></p>  |
| <p>When the research participant has completed the interference items say:</p>   | <p><b>Good. Now just let me look over this form to be sure I understand all of your answers.</b></p>  |
| <p>Once you have checked the form and clarified any multiple answers to a single item or any blank items say:</p>  | <p><b>We are finished with the symptom survey now. Thank you for taking the time to complete the symptom assessment today. Remember that this assessment is only for research purposes, so if you have reported any symptoms that bother you, please remember to tell your doctor or nurse about those symptoms. Do you have any questions?</b></p>   |

## Instructions for Research participants Who Have the MDASI Read to Them

| Instructions   | Dialogue  |
|--|---|
| <p>It is important that research participants rate the severity of any symptom that they have experienced in the last 24 hours regardless of what they think is causing the symptom.</p> <p>If research participants choose to have the MDASI read to them, say:</p>   | <p><b>I am now going to ask you how severe your symptoms are. Please rate the worst severity of each symptom that you experienced in the last 24-hours, regardless of whether you think it was related to cancer, treatment, or another cause. If you did not experience the symptom at all in the last 24 hours, rate the severity as 0.</b></p> <p><b>People with cancer frequently have symptoms that are caused by their disease or by their treatment. We ask you to rate how severe the following symptoms have been <i>in the last 24 hours</i>. Please give me a number from 0 (the symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.</b></p> <p><b>Your <i>pain</i> at its WORST.</b></p> |
| <p>Wait for the research participant to answer. You may repeat the item or rating scale for the research participant. If it is convenient, you also may sit next to the research participant and allow the research participant to view the form to see the rating scale while answering. Do not give the research participant any information other than what is in the item. You may remind the research participant that the rating asked for is pain at its WORST in the last 24 hours.</p> <p>When the research participant responds, make a mark in the correct circle. Do not make any stray marks in other circles. If a mark is made in an incorrect circle, mark through that circle with a single straight line, carefully write "Error" over the circle, initial, and date.</p> <p>Move on to the next item.</p> | <p><b>Your <i>fatigue (tiredness)</i> at its WORST.</b></p>   |
| <p>When the research participant has answered, and you have recorded the answer in the same manner, continue on to each of the remaining symptom severity items in the same manner. Read the items exactly as they appear on the form and in the order they appear. If a research participant is having difficulty answering an item, you may move on and return to it after you have completed the other symptom severity items. If the research participant chooses not to answer an item, carefully write a note</p>  |   |

| Instructions   | Dialogue   |
|--|--|
| <p>in the margin that the research participant chose not to answer, initial, and date.</p> <p>When all symptom severity items have been completed, move on to the 6 interference items. Research participants should base their interference ratings only on the interference caused by the symptoms and not on interference due to other causes, such as being away from home.</p> <p>When all symptom severity items have been completed, say:</p>   | <p><b>Now I'm going to ask you how your symptoms have interfered with your life. We are interested in the way that the symptoms you have just rated interfered with things you wanted or needed to do. Answer these questions based only on how much your symptoms have interfered.</b></p> <p><b>Symptoms frequently interfere with how we feel and function. How much have your symptoms interfered with the following items in the last 24 hours? Please give me a number from 0 (symptoms did not interfere) to 10 (symptoms interfered completely) for each item.</b></p> <p><b>General activity.</b></p> |
| <p>Wait for the research participant to answer. You may repeat the item or rating scale for the research participant. If it is convenient, you also may sit next to the research participant and allow the research participant to view the form to see the rating scale while answering. Do not give the research participant any information other than what is in the item. You may remind the research participant that the rating asked for is how much symptoms have interfered in the last 24 hours.</p> <p>When the research participant responds, make a mark in the correct circle. Do not make any stray marks in other circles. If a mark is made in an incorrect circle, mark through that circle with a single straight line, carefully write "Error" over the circle, initial, and date.</p> <p>Move on to the next item.</p> | <p><b>Mood.</b></p>  |
| <p>When the research participant has answered, and you have recorded the answer in the same manner, continue on to each of the remaining symptom interference items in the same manner. Read the items exactly as they appear on the form and in the order they appear. If a research participant is having difficulty answering an item, you may move on and return to it after you have completed the other symptom interference items. If the research participant chooses not to answer an item, carefully</p>   |  |

| Instructions   | Dialogue  |
|--|---|
| <p>write a note in the margin that the research participant chose not to answer, initial, and date.</p> <p>Once all of the items have been completed, say:</p> | <p><b>We are finished with the symptom inventory now. Thank you for taking the time to complete the symptom assessment today. Remember that this assessment is only for research purposes, so if you have reported any troublesome symptoms, please remember to tell your doctor or nurse about those symptoms.</b></p> |

### Instructions for Completing the MDASI by Personal Phone Call

| Instructions  | Dialogue  |
|---|---|
| <p>When the research participant answers the phone, say:</p>  | <p><b>Good day, Mr./Ms./Miss _____ (research participant's last name). I am _____ (your first and last name) from _____ (name of institution). I am calling today to ask you to how your symptoms are for _____ (brief description of study for which symptom assessment is being collected, e.g. the breast cancer treatment study in which you are participating). This will take 5 to 10 minutes. Is this a convenient time for you, or would you prefer that I call back later?</b></p> |
| <p>When the research participant has confirmed that this is a good time to complete the MDASI, say:</p>   | <p><b>Do you have any questions about why we are doing the symptom assessment?</b></p>  |
| <p>Answer any questions the research participant may have.</p> <p>It is important that research participants rate the severity of any symptom that they have experienced in the last 24 hours regardless of what they think is causing the symptom.</p> <p>When you are ready to start the symptom assessment questionnaire, say:</p> | <p><b>Let's get started with the symptom assessment. If you have a copy of the MDASI with you, you may want to get it out and follow along with me.</b></p> <p><b>I am now going to ask you how severe your symptoms are. Please rate the worst severity of each symptom that you experienced in the last 24-hours, regardless of whether you think it was related to cancer, treatment, or another cause. If you did not experience the symptom at all in the</b></p>                      |

| Instructions  | Dialogue  |
|---|---|
|   | <p>last 24 hours, rate the severity as 0.</p> <p><b>People with cancer frequently have symptoms that are caused by their disease or by their treatment. We ask you to rate how severe the following symptoms have been <i>in the last 24 hours</i>. Please give me a number from 0 (the symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.</b></p> <p><b>Your <i>pain</i> at its WORST.</b></p> |
| <p>Wait for the research participant to answer. You may repeat the item or rating scale for the research participant. Do not give the research participant any information other than what is in the item. You may remind the research participant that the rating asked for is pain at its WORST <i>in the last 24 hours</i>.</p> <p>When the research participant responds, make a mark in the correct circle. Do not make any stray marks in other circles. If a mark is made in an incorrect circle, mark through that circle with a single straight line, carefully write "Error" over the circle, initial, and date.</p> <p>Move on to the next item.</p>   | <p><b>Your <i>fatigue (tiredness)</i> at its WORST.</b></p>   |
| <p>When the research participant has answered, and you have recorded the answer in the same manner, continue on to each of the remaining symptom severity items in the same manner. Read the items exactly as they appear on the form and in the order they appear. If a research participant is having difficulty answering an item, you may move on and return to it after you have completed the other symptom severity items. If the research participant chooses not to answer an item, carefully write a note in the margin that the research participant chose not to answer, initial, and date.</p> <p>When all symptom severity items have been completed, move on to the 6 interference items. Research participants should base their interference ratings only on the interference caused by the symptoms and not on interference due to other causes, such as being away from home. Say:</p> | <p><b>Now I'm going to ask you how your symptoms have interfered with your life. We are interested in the way that the symptoms you have just rated interfered with things you wanted or needed to do. Answer these questions based only on how much your symptoms have interfered.</b></p> <p><b>Symptoms frequently interfere with how we feel and function. How much have your symptoms interfered with the following items in the last 24</b></p>   |

| Instructions  | Dialogue   |
|---|--|
| <p>Wait for the research participant to answer. You may repeat the item or rating scale for the research participant. Do not give the research participant any information other than what is in the item. You may remind the research participant that the rating asked for is <i>how much symptoms have interfered in the last 24 hours</i>.</p> <p>When the research participant responds, make a mark in the correct circle. Do not make any stray marks in other circles. If a mark is made in an incorrect circle, mark through that circle with a single straight line, carefully write "Error" over the circle, initial, and date.</p> <p>Move on to the next item.</p> | <p><b>hours? Please give me a number from 0 (symptoms did not interfere) to 10 (symptoms interfered completely) for each item.</b></p> <p><b>General activity.</b></p>   |
| <p>When the research participant has answered, and you have recorded the answer in the same manner, continue on to each of the remaining symptom interference items in the same manner. Read the items exactly as they appear on the form and in the order they appear. If a research participant is having difficulty answering an item, you may move on and return to it after you have completed the other symptom interference items. If the research participant chooses not to answer an item, carefully write a note in the margin that the research participant chose not to answer, initial, and date.</p> <p>Once all of the items have been completed, say:</p>      | <p><b>Mood.</b></p> <p><b>We are finished with the symptom inventory now. Thank you for taking the time to complete the symptom assessment today. Remember that this assessment is only for research purposes, so if you have reported any troublesome symptoms, please remember to tell your doctor or nurse about those symptoms. I will call you again in (time frame for MDASI collection, e.g., 2 days, a week, a month) for another symptom assessment. Can I reach you at this phone number then?</b></p> |

## Responding to Patient Questions During MDASI Administration

| Instructions  | Dialogue   |
|---|--|
| <p>If a research participant asks you a question while completing the symptom or interference items, be pleasant, but remind them that their understanding and answers are correct. For example, if a research participant asks, “What do you mean by problem with remembering things?” Reply:</p>  | <p><b>“Problem with remembering things” is whatever you think it is. Please rate your problem with remembering things at its worst in the last 24 hours.</b></p> |
| <p>Research participants will sometimes continue to ask questions or try to explain things to you. Remain pleasant, but redirect them to answer the item as it is written. It is sometimes helpful to remind the research participant:</p>  | <p><b>Don’t worry about your answer. You are the expert and whatever you think is the best answer is correct.</b></p>  |
| <p>Do not define any symptom for a research participant or explain what any question means. Giving a research participant that information may influence their answer and cause them to answer differently than a research participant who did not have the same information. Always remain calm and pleasant when answering research participant questions, no matter how many they ask.</p> <p>Research participants may ask how they should answer if they had a symptom several days ago but did not have it in the last 24 hours. Say:</p> | <p><b>Answer the question based on your experience in the last 24 hours.</b></p>   |
| <p>If a research participant says that s/he experienced a symptom that s/he knows was related to another disease (“My knee hurts, but that’s just my arthritis”) or treatment (“I couldn’t sleep because I got steroids before my chemotherapy yesterday”), remind them that they should rate the severity of the symptom as they experienced it regardless of what they believe the cause to be. Say:</p>  | <p><b>Please rate the severity of the symptom as you experienced it in the last 24 hours, no matter what you think caused you to have that symptom.</b></p>      |
| <p>When answering the interference items, if a research participant says that s/he is unable to do something because s/he is away from home or in the hospital, ask the participant to base their interference ratings only on the way that symptoms interfere. Say:</p>  | <p><b>Please rate the way that the symptoms interfere, the best that you are able.</b></p>   |

| Instructions  | Dialogue  |
|---|---|
| If a research participant seems to be having an unreasonable amount of trouble answering a certain item or if a research participant seems unusually upset by a certain item say: | <b>Would you like to skip this item and continue answering the other items?</b> |
| After the research participant has completed the entire MDASI, say:   | <b>Would you be able to complete the item that you skipped earlier?</b>         |
| If the research participant still has an unreasonable amount of trouble answering the item or if a research participant seems unusually upset by the item, say:                   | <b>That's okay. We'll just skip that item today.</b>                            |
| Then make a note on the form that the research participant was upset by the item and was not able to answer it.   |   |

## Appendix D. Sample IVR Instruction Booklet

### IVR TELEPHONE SYSTEM

#### PATIENT INSTRUCTIONS



#### Protocol 2006-0000

Longitudinal Assessment of Arthralgia and Related Symptoms in Breast Cancer Patients Receiving Aromatase Inhibitors

- When to expect calls
- Personal ID and password
- Other instructions

### WHEN THE IVR SYSTEM CALLS YOU

**1. WHAT YOU HEAR:**

This is the Automated Survey. Is this \_\_\_\_\_? Please press 1 for "Yes" or 2 for "No."

**WHAT YOU DO:**

Using the touch-tone keypad on your telephone: Press "1" for yes or "2" for no.

**2. WHAT YOU HEAR:**

Please enter your patient ID.

**WHAT YOU DO:**

Enter your patient ID: \_\_\_\_\_

**3. WHAT YOU HEAR:**

Please enter your PIN number.

**WHAT YOU DO:**

Enter your PIN: \_\_\_\_\_

**4. WHAT YOU HEAR:**

Answer the questions on a 0-10 scale, with 0 meaning that the symptom has not been present and 10 meaning that the symptom was as bad as you can imagine it could be.

**WHAT YOU DO:**

To move more quickly through the survey, if your response is "1," please enter "01." If you enter only "1," there will be a three-second pause before the system

advances to the next question. If your response is "10," please enter only "10" (no leading zero).

*You may interrupt the script by entering your answer at any time during the prompt.*

If you miss your call or do not complete the survey, the system will call you two more times at 60-minute intervals.

If you miss the call or will not be available, you may also call the system within \_\_\_\_\_ (e.g., 1 hour/24 hours/1 week [STUDY SPECIFIC]) of this call at the number below:

\_\_\_\_\_

If you have any questions or problems with the IVR system or you want the survey calls stopped, please call your data coordinator \_\_\_\_\_

at \_\_\_\_\_.

**YOUR CALL SCHEDULE:**

Day(s): \_\_\_\_\_

Time: \_\_\_\_\_

ZIP code: \_\_\_\_\_

Phone number: \_\_\_\_\_

**Please remember that this IVR system is for research purposes only. If you experience severe symptoms, please call your clinic, visit the emergency room, or call 911.**

*Thank you for participating!*

2006-0000 – BREAST

Updated July 25, 2008

## Literature Cited

Abernethy AP, Herndon JE, Wheeler JL, et al. Improving health care efficiency and quality using tablet personal computers to collect research-quality, patient-reported data. *Health Serv Res* 2008;43(6):1975-1991.

American Educational Research Association, American Psychological Association, National Council on Measurement in Education, Joint Committee on Standards for Educational and Psychological Testing. *Standards for Educational and Psychological Testing*, 2nd ed. Washington, DC: American Educational Research Association, 1999.

Anderson KO, Giralt SA, Mendoza TR, et al. Symptom burden in patients undergoing autologous stem-cell transplantation. *Bone Marrow Transplant* 2007;39(12):759-766.

Armstrong TS, Cohen M, Eriksen L, Cleeland C. Content validity of self-report measurement instruments: an illustration from the development of the brain tumor module of the M. D. Anderson Symptom Inventory. *Oncol Nurs Forum* 2005;32(3):669-676.

Armstrong TS, Mendoza T, Gning I, et al. Validation of the M. D. Anderson Symptom Inventory brain tumor module (MDASI-BT). *J Neurooncol* 2006;80(1):27-35.

Bar-Sela G, Atid L, Danos S, Gabay N, Epelbaum R. Art therapy improved depression and influenced fatigue levels in cancer patients on chemotherapy. *Psychooncology* 2007;16(11):980-984.

Beecher HK. *Measurement of Subjective Responses: Quantitative Effects of Drugs*. New York: Oxford University Press, 1959.

Benedetti C, Brock C, Cleeland C, et al. NCCN practice guidelines for cancer pain. *Oncology (Huntington)* 2000;14(11A):135-150.

Borden EC, Parkinson D. A perspective on the clinical effectiveness and tolerance of interferon-alpha. *Semin Oncol* 1998;25(1 Suppl 1):3-8.

Breivik EK, Björnsson GA, Skovlund E. A comparison of pain rating scales by sampling from clinical trial data. *Clin J Pain* 2000;16(1):22-28.

- Bruera E, Kuehn N, Miller MJ, Selmser P, Macmillan K. The Edmonton Symptom Assessment System (ESAS): a simple method for the assessment of palliative care patients. *J Palliat Care* 1991;7(2):6-9.
- Caraceni A, Cherny N, Fainsinger R, et al. Pain measurement tools and methods in clinical research in palliative care: recommendations of an Expert Working Group of the European Association of Palliative Care. *J Pain Symptom Manage* 2002;23(3):239-255.
- Caraceni A, Mendoza TR, Mencaglia E, et al. A validation study of an Italian version of the Brief Pain Inventory (Breve Questionario per la Valutazione del Dolore). *Pain* 1996;65(1):87-92.
- Chang YJ, Lee JS, Lee CG, et al. Assessment of clinical relevant fatigue level in cancer. *Support Care Cancer* 2007;15(7):891-896.
- Cleeland CS. Symptom burden: multiple symptoms and their impact as patient-reported outcomes. *J Natl Cancer Inst Monogr* 2007;37:16-21.
- Cleeland CS. Measurement of pain by subjective report. In: Chapman CR, Loeser JD, eds. *Issues in Pain Measurement, Advances in Pain Research and Therapy, Vol. 12*. New York: Raven Press, 1989:391-403.
- Cleeland CS. Assessment of pain in cancer: measurement issues. In: Foley KM, Bonica JJ, Ventafridda V, eds. *Proceedings of the Second International Congress on Cancer Pain, Advances in Pain Research and Therapy, Vol. 16*. New York: Raven Press, 1990:47-55.
- Cleeland CS. Pain assessment in cancer. In: Osoba D, ed. *Effect of Cancer on Quality of Life*. Boca Raton: CRC Press, Inc., 1991:293-305.
- Cleeland CS, Bennett GJ, Dantzer R, et al. Are the symptoms of cancer and cancer treatment due to a shared biologic mechanism? *Cancer* 2003;97(11):2919-2925.
- Cleeland CS, Gonin R, Hatfield AK, et al. Pain and its treatment in outpatients with metastatic cancer. *N Engl J Med* 1994;330(9):592-596.
- Cleeland CS, Ladinsky JL, Serlin RC, Nguyen CT. Multidimensional measurement of cancer pain: comparisons of US and Vietnamese patients. *J Pain Symptom Manage* 1988;3(1):23-27.
- Cleeland CS, Mendoza TR, Wang XS, et al. Assessing symptom distress in cancer patients: the M. D. Anderson Symptom Inventory. *Cancer* 2000;89(7):1634-1646.

- Cleeland CS, Nakamura Y, Mendoza TR, et al. Dimensions of the impact of cancer pain in a four country sample: new information from multidimensional scaling. *Pain* 1996;67(2-3):267-273.
- Cleeland CS, Portenoy RK, Rue M, et al. Does an oral analgesic protocol improve pain control for patients with cancer? An intergroup study coordinated by the Eastern Cooperative Oncology Group. *Ann Oncol* 2005;16(6):972-980.
- Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. *Ann Acad Med Singapore* 1994;23(2):129-138.
- Cohen J. *Statistical Power Analysis for the Behavioral Sciences (2nd Ed.)*. Hillsdale, NJ: Lawrence Earlbaum Associates, 1988.
- Cohen J. A power primer. *Psychol Bull* 1992;112(1):155-159.
- Constant A, Castera L, Dantzer R, et al. Mood alterations during interferon-alfa therapy in patients with chronic hepatitis C: evidence for an overlap between manic/hypomanic and depressive symptoms. *J Clin Psychiatry* 2005;66(8):1050-1057.
- Daut RL, Cleeland CS. The prevalence and severity of pain in cancer. *Cancer* 1982;50(9):1913-1918.
- Daut RL, Cleeland CS, Flanery RC. Development of the Wisconsin Brief Pain Questionnaire to assess pain in cancer and other diseases. *Pain* 1983;17(2):197-210.
- De Conno F, Caraceni A, Gamba A, et al. Pain measurement in cancer patients: a comparison of six methods. *Pain* 1994;57(2):161-166.
- de Haes JC, van Knippenberg FC, Neijt JP. Measuring psychological and physical distress in cancer patients: structure and application of the Rotterdam Symptom Checklist. *Br J Cancer* 1990;62(6):1034-1038.
- Dodd MJ, Miaskowski C, Paul SM. Symptom clusters and their effect on the functional status of patients with cancer. *Oncol Nurs Forum* 2001;28(3):465-470.
- Du Pen SL, Du Pen AR, Polissar N, et al. Implementing guidelines for cancer pain management: results of a randomized controlled clinical trial. *J Clin Oncol* 1999;17(1):361-370.

- Dworkin RH, Turk DC, Farrar JT, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain* 2005;113(1-2):9-19.
- Fadol A, Mendoza T, Gning I, et al. Psychometric testing of the MDASI-HF: a symptom assessment instrument for patients with cancer and concurrent heart failure. *J Card Fail* 2008;14(6):497-507.
- Fedorenko DA, Kishtovich AV, Ionova TI, et al. The use of the Brief Fatigue Inventory in systemic rheumatic patients [abstract]. International Society for Quality of Life Research 11th Annual Conference, Hong Kong, October 16-19, 2004. *Qual Life Res* 2004;13(9):1523.
- Ferraz MB, Quaresma MR, Aquino LR, et al. Reliability of pain scales in the assessment of literate and illiterate patients with rheumatoid arthritis. *J Rheumatol* 1990;17(8):1022-1024.
- Food and Drug Administration. *Guidelines for Industry (draft). Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*. Rockville MD: U.S. Department of Health and Human Services, 2006.
- Gabrilove JL, Perez EA, Tomita DK, Rossi G, Cleeland CS. Assessing symptom burden using the M. D. Anderson symptom inventory in patients with chemotherapy-induced anemia: results of a multicenter, open-label study (SURPASS) of patients treated with darbepoetin-alpha at a dose of 200 mug every 2 weeks. *Cancer* 2007;110(7):1629-1640.
- Gagliese L, Weizblit N, Ellis W, Chan VW. The measurement of postoperative pain: a comparison of intensity scales in younger and older surgical patients. *Pain* 2005;117(3):412-420.
- Ger LP, Ho ST, Sun WZ, Wang MS, Cleeland CS. Validation of the Brief Pain Inventory in a Taiwanese population. *J Pain Symptom Manage* 1999;18(5):316-322.
- Gning I, Trask PC, Mendoza TR, et al. Development and initial validation of the thyroid cancer module of the M. D. Anderson Symptom Inventory. *Oncology* 2009;76(1):59-68.
- Harman HH. *Modern Factor Analysis*, 2nd revised ed. Chicago: University of Chicago Press, 1967.
- Harsh JR, Hayduk R, Rosenberg R, et al. The efficacy and safety of armodafinil as treatment for adults with excessive sleepiness associated with narcolepsy. *Curr Med Res Opin* 2006;22(4):761-774.

- Hollen PJ, Gralla RJ, Kris MG, et al. A comparison of visual analogue and numerical rating scale formats for the Lung Cancer Symptom Scale (LCSS): does format affect patient ratings of symptoms and quality of life? *Qual Life Res* 2005;14(3):837-847.
- Ivanova MO, Ionova TI, Kalyadina SA, et al. Cancer-related symptom assessment in Russia: validation and utility of the Russian M. D. Anderson Symptom Inventory. *J Pain Symptom Manage* 2005;30(5):443-453.
- Jensen MP, Karoly P, Braver S. The measurement of clinical pain intensity: a comparison of six methods. *Pain* 1986;27(1):117-126.
- Klepstad P, Loge JH, Borchgrevink PC, et al. The Norwegian Brief Pain Inventory questionnaire: translation and validation in cancer pain patients. *J Pain Symptom Manage* 2002;24(5):517-525.
- Kramer L, Hofer H, Bauer E, et al. Relative impact of fatigue and subclinical cognitive brain dysfunction on health-related quality of life in chronic hepatitis C infection. *AIDS* 2005;19(Suppl 3):S85-S92.
- Kurzrock R. The role of cytokines in cancer-related fatigue. *Cancer* 2001;92(6 Suppl):1684-1688.
- Larue F, Colleau SM, Brasseur L, Cleeland CS. Multicentre study of cancer pain and its treatment in France. *BMJ* 1995;310(6986):1034-1037.
- Lasagna L. Analgesic methodology: a brief history and commentary. *J Clin Pharmacol* 1980;20(5-6 Pt 2):373-376.
- Laudico AV, Mendoza TR, Siguan SS, Cleeland CS. Measuring cancer pain intensity and its effect on daily functioning: validation of the Cebuano version of the Brief Pain Inventory (BPI-Ce). *Philipp J Surg Spec* 2002;57(3):94-99.
- Lee MK, Son BH, Hwang SY, et al. Factors affecting health-related quality of life in women with recurrent breast cancer in Korea. *Qual Life Res* 2007;16(4):559-569.
- Li L, Liu X, Herr K. Postoperative pain intensity assessment: a comparison of four scales in Chinese adults. *Pain Med* 2007;8(3):223-234.
- Lin CC, Chang AP, Chen ML, et al. Validation of the Taiwanese version of the Brief Fatigue Inventory. *J Pain Symptom Manage* 2006;32(1):52-59.

Lin CC, Chang AP, Cleeland CS, Mendoza TR, Wang XS. Taiwanese version of the M. D. Anderson Symptom Inventory: symptom assessment in cancer patients. *J Pain Symptom Manage* 2007;33(2):180-188.

McCorkle R, Young K. Development of a symptom distress scale. *Cancer Nurs* 1978;1(5):373-378.

McNair DM, Lorr M, Droppleman LF. *Manual for the Profile of Mood States*. San Diego CA: Educational and Industrial Testing Service, 1992.

Mead G, Lynch J, Greig C, et al. Evaluation of fatigue scales in stroke patients. *Stroke* 2007;38(7):2090-2095.

Mendoza T, Mayne T, Rublee D, Cleeland C. Reliability and validity of a modified Brief Pain Inventory short form in patients with osteoarthritis. *Eur J Pain* 2006;10(4):353-361.

Mendoza TR, Chen C, Brugger A, et al. The utility and validity of the modified Brief Pain Inventory in a multiple-dose postoperative analgesic trial. *Clin J Pain* 2004;20(5):357-362.

Mendoza TR, Wang XS, Cleeland CS, et al. The rapid assessment of fatigue severity in cancer patients: use of the Brief Fatigue Inventory. *Cancer* 1999;85(5):1186-1196.

Mock V, Atkinson A, Barsevick A, et al. NCCN Practice Guidelines for Cancer-Related Fatigue. *Oncology (Huntington)* 2000;14(11A):151-161.

Mystakidou K, Cleeland C, Tsilika E, et al. Greek M. D. Anderson Symptom Inventory: validation and utility in cancer patients. *Oncology* 2004;67(3-4):203-210.

Mystakidou K, Mendoza T, Tsilika E, et al. Greek Brief Pain Inventory: validation and utility in cancer pain. *Oncology* 2001;60(1):35-42.

Nunnally JC, Bernstein IH. *Psychometric Theory*, 3rd ed ed. New York: McGraw-Hill, 1994.

Okuyama T, Wang XS, Akechi T, et al. Japanese version of the M. D. Anderson Symptom Inventory: a validation study. *J Pain Symptom Manage* 2003a;26(6):1093-1104.

Okuyama T, Wang XS, Akechi T, et al. Validation study of the Japanese version of the Brief Fatigue Inventory. *J Pain Symptom Manage* 2003b;25(2):106-117.

- Paice JA, Cohen FL. Validity of a verbally administered numeric rating scale to measure cancer pain intensity. *Cancer Nurs* 1997;20(2):88-93.
- Papakostas GI, Petersen TJ, Burns AM, Fava M. Adjunctive atomoxetine for residual fatigue in major depressive disorder. *J Psychiatr Res* 2006;40(4):370-373.
- Portenoy RK, Thaler HT, Kornblith AB, et al. The Memorial Symptom Assessment Scale: an instrument for the evaluation of symptom prevalence, characteristics and distress. *Eur J Cancer* 1994;30A(9):1326-1336.
- Radbruch L, Loick G, Kiencke P, et al. Validation of the German version of the Brief Pain Inventory. *J Pain Symptom Manage* 1999;18(3):180-187.
- Radbruch L, Sabatowski R, Elsner F, et al. Validation of the German version of the Brief Fatigue Inventory. *J Pain Symptom Manage* 2003;25(5):449-458.
- Rosenthal DI, Mendoza TR, Chambers MS, et al. Measuring head and neck cancer symptom burden: The development and validation of the M. D. Anderson Symptom Inventory, head and neck module. *Head Neck* 2007;29(10):923-931.
- Rosenthal DI, Mendoza TR, Chambers MS, et al. The M. D. Anderson Symptom Inventory-Head and Neck Module, a patient-reported outcome instrument, accurately predicts the severity of radiation-induced mucositis. *Int J Radiat Oncol Biol Phys* 2008;e-pub ahead of print.
- Roth T, Rippon GA, Arora S. Armodafinil improves wakefulness and long-term episodic memory in nCPAP-adherent patients with excessive sleepiness associated with obstructive sleep apnea. *Sleep Breath* 2008;12(1):53-62.
- Saxena A, Mendoza T, Cleeland CS. The assessment of cancer pain in north India: the validation of the Hindi Brief Pain Inventory--BPI-H. *J Pain Symptom Manage* 1999;17(1):27-41.
- Serlin RC, Lapsley DK. Rational appraisal of methodological research and the good-enough principle. In: Keren G, Lewis C, eds. *A Handbook for Data Analysis in the Behavioral Sciences: Statistical Issues*, Vol. 2. Hillsdale NJ: L. Erlbaum Associates, 1993.
- Serlin RC, Mendoza TR, Nakamura Y, Edwards KR, Cleeland CS. When is cancer pain mild, moderate or severe? Grading pain severity by its interference with function. *Pain* 1995;61(2):277-284.

- Shi Q, Wang XS, Mendoza TR, Pandya KJ, Cleeland CS. Assessing persistent cancer pain: a comparison of current pain ratings and pain recalled from the past week. *J Pain Symptom Manage* 2008;e-pub ahead of print.
- Simmonds MJ, Novy D, Sandoval R. The differential influence of pain and fatigue on physical performance and health status in ambulatory patients with human immunodeficiency virus. *Clin J Pain* 2005;21(3):200-206.
- Sloan JA, Dueck A. Issues for statisticians in conducting analyses and translating results for quality of life end points in clinical trials. *J Biopharm Stat* 2004;14(1):73-96.
- Sze FK, Chung TK, Wong E, et al. Pain in Chinese cancer patients under palliative care. *Palliat Med* 1998;12(4):271-277.
- Tseng TH, Cleeland CS, Wang XS, Lin CC. Assessing cancer symptoms in adolescents with cancer using the Taiwanese version of the M. D. Anderson Symptom Inventory. *Cancer Nurs* 2008;31(3):E9-16.
- Turk DC, Dworkin RH, Allen RR, et al. Core outcome domains for chronic pain clinical trials: IMMPACT recommendations. *Pain* 2003;106(3):337-345.
- Turner RR, Quittner AL, Parasuraman BM, Kallich JD, Cleeland CS. Patient-reported outcomes: instrument development and selection issues. *Value Health* 2007;10(Suppl 2):S86-S93.
- Uki J, Mendoza T, Cleeland CS, Nakamura Y, Takeda F. A brief cancer pain assessment tool in Japanese: the utility of the Japanese Brief Pain Inventory--BPI-J. *J Pain Symptom Manage* 1998;16(6):364-373.
- Uronis HE, Herndon II JE, Coan A, et al. E-tablets to collect research-quality, patient-reported data [abstract]. American Society of Clinical Oncology 2008 Annual Meeting, Chicago IL, May 30 - June 3, 2008. *J Clin Oncol* 2008;26(15 Suppl).
- Valentine AD, Meyers CA. Cognitive and mood disturbance as causes and symptoms of fatigue in cancer patients. *Cancer* 2001;92(6 Suppl):1694-1698.
- Wallenstein SL. Measurement of pain and analgesia in cancer patients. *Cancer* 1984;53(10 Suppl):2260-2266.
- Wang XS. Validation study of the Chinese version of the Brief Fatigue Inventory (BFI-C). Hao XS, Wang Y, Guo H, Jiang YQ, Mendoza TR, Cleeland CS, editors. *J Pain*

Symptom Manage. 27[4]:322-332. 2004.  
Ref Type: Generic

Wang XS, Laudico AV, Guo H, et al. Filipino version of the M. D. Anderson Symptom Inventory: validation and multisymptom measurement in cancer patients. *J Pain Symptom Manage* 2006;31(6):542-552.

Wang XS, Mendoza TR, Gao SZ, Cleeland CS. The Chinese version of the Brief Pain Inventory (BPI-C): Its development and use in a study of cancer pain. *Pain* 1996;67(2-3):407-416.

Wang XS, Shi Q, Williams LA, et al. Serum interleukin-6 predicts the development of multiple symptoms at nadir of allogeneic hematopoietic stem cell transplantation. *Cancer* 2008;113(8):2102-2109.

Wang XS, Wang Y, Guo H, et al. Chinese version of the M. D. Anderson Symptom Inventory: validation and application of symptom measurement in cancer patients. *Cancer* 2004;101(8):1890-1901.

Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992;30(6):473-483.

Yun YH, Mendoza TR, Heo DS, et al. Development of a cancer pain assessment tool in Korea: a validation study of a Korean version of the Brief Pain Inventory. *Oncology* 2004;66(6):439-444.

Yun YH, Mendoza TR, Kang IO, et al. Validation study of the Korean version of the M. D. Anderson Symptom Inventory. *J Pain Symptom Manage* 2006;31(4):345-352.

Yun YH, Wang XS, Lee JS, et al. Validation study of the Korean version of the Brief Fatigue Inventory. *J Pain Symptom Manage* 2005;29(2):165-172.