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Symptom and Quality of Life Assessment in Ambulatory Oncology: the evaluation of a clinical assessment tool

by

Susan Elizabeth Anne Horsman

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Examining Committee

Dr. Kärin Olson, Ph.D., Faculty of Nursing, University of Alberta

Dr. Sunita Ghosh, Ph. D., Alberta Health Services

Dr. Heather-jane Au, M.D., Department of Oncology, Faculty of Medicine, University of Alberta

Dr Alex Clark, Ph. D., Faculty of Nursing, University of Alberta

Abstract

This study addressed gaps in the literature regarding the lack of information about the degree and extent of the relationships among symptom burden, specific symptoms, and health-related quality of life (HRQL). The sample included 89 adults receiving care for colorectal cancer in an outpatient setting. Data for this cross-sectional study were collected over a four month period using the Modified Ambulatory Care Flow Sheet (MACFS), the Rotterdam Symptom Checklist- Modified, numerical rating scales for pain and coping, and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Cancer 30. Results showed that the MACFS was reasonably valid and internally consistent and that symptom burden and number of symptoms were significantly abut weakly correlated with HRQL. Specific symptoms most significantly correlated with HRQL were insomnia, fatigue, pain, nausea and vomiting. Findings support the use of the MACFS to assess symptoms and HRQL in the study population.

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CHAPTER 1

Colorectal cancer is the fourth leading type of cancer in Canada, and the second leading cause of cancer death (Arndt, Merx, Stegmaier, Ziegler, & Brenner, 2006; Efficace, Bottomley, Vanvoorden, & Blazeby, 2004). In 2007, the Canadian Cancer Society estimates that 20,000 Canadians will be diagnosed with colorectal cancer, and 8,500 persons will die from this disease. The societal impact of this disease is not insignificant, as patients and families deal with both the stigma of a cancer diagnosis and the burden of cancer treatment. Recent advancements in treatment options have increased the median life expectancy from 8 months to 22 months for persons diagnosed with metastatic disease (de Kort, Willemse, Habraken, de Haes, Willems, & Richel, 2006).

Colorectal cancer treatment is multi-modal, utilizing surgery, radiation therapy, chemotherapy or a combination of the above treatments to achieve the optimal outcome. Cancer therapy may be used for either curative or palliative intent, and patients who receive treatment are monitored closely for the effects of their disease, potential side effects and symptoms related to cancer treatment and quality of life. From a clinical point of view, both healthcare providers and patients weigh implications for quality of life carefully when making treatment-related decisions. The focus of this study is on the relationship between symptoms and quality of life.

The collection of information regarding symptoms and quality of life in patients with colorectal cancer is important. Improvements in the treatment options for colorectal cancer have included the use of new laparoscopic surgery techniques, combination chemotherapy, oral chemotherapy drugs, and new biotherapies (Best et al., 2006; Díez-Fernández, Salinas Hernández, & Girón-Duch, 2006; Goldberg, 2005; Goldberg et al., 2007; H. Hurwitz et al., 2004; H. I. Hurwitz, Honeycutt, Haley & Favaro, 2006). The increase in the number of colorectal cancer treatment options reflects ongoing research into both overall survival and symptom palliation for patients with colorectal cancer. Both symptoms and quality of life may be altered by these new developments and by the disease process itself (Ragnhammar, Hafstrom, Nygren, Glimelius, & SBU Group, 2001).

Symptoms are terms used by patients to describe sensations they experience. Symptoms have been described as deviations from normal function, sensation or appearance, and as predictors of change in normal function experienced by patients (Armstrong 2003). For the purposes of this study, we will consider symptoms as indicators or evidence of changes related to disease or treatment.

Quality of life is the satisfaction a person has with his or her physical, spiritual emotional and social situation (Donnelly, Rybicki, & Walsh, 2001). Higginson and Carr (2001) discuss the transition of quality of life measures into the clinical setting, and found that these measures have

the potential to ensure that treatment and evaluation have a patient-centred focus, and to improve the effectiveness of the clinical encounter. Though there are several conceptualizations of health related quality of life measures (HRQL) (Moons, Budts & De Geest, 2006), HRQL are used extensively as a component of clinical research trials in oncology to gain important information about the impact of the disease and the therapies used for treatment (Gotay, 2004). Constraints of time in clinical practice make the collection of HRQL data at routine visits challenging, both in the amount of time and resources required to collect and process the data, and in the time required by the patients to complete the forms in the clinic setting. We do not routinely assess HRQL in our clinic. Rather, we assume that assessing and treating symptoms optimizes HRQL.

At the Cross Cancer Institute, a tertiary cancer treatment facility in western Canada, a documentation tool called the Ambulatory Care Flow Sheet (ACFS) was developed for use in the ambulatory care department. The purpose of the tool was to monitor patient symptoms during cancer treatment and follow-up. This tool lists common symptoms experienced during treatment and provides an area to note allergies, new medications, recent hospitalizations and concerns to be discussed with the clinician attending the clinic. Staff members report that the ACFS has been effective in improving the communication between the patient and family with the health care team, and in acting as a reminder of things to discuss or address at each visit. This tool, which is completed at every visit, provides a snapshot view of the patient condition on the day of clinic, and helps the health care team to assess changes in symptoms since the last visit. Understanding how patients cope with the rigors of cancer treatment enables health care providers to facilitate patients and their families' access to the appropriate resources during treatment and thus hopefully foster a good quality of life. Although useful, this tool has not undergone any testing for reliability or validity. The purpose of this study is to evaluate the newly developed symptom measure, the ACFS, and to explore the relationship between symptoms and quality of life.

Research Questions

1. Among individuals with colorectal cancer, to what extent do the symptom scores [difficulty sleeping, pain, tiredness /fatigue, shortness of breath, changes to skin, mouth sores, changes in appetite, nausea/vomiting, diarrhea/constipation, difficulty urinating, changes in sexuality/sexual function, difficulty coping] on the ACFS tool correlate with scores for similar symptoms on other assessment tools?
2. To what extent do symptom scores on the ACFS correlate with scores on measures of quality of life in this population?
3. What is the relationship between individual symptoms and quality of life?

Definitions

1. Colorectal cancer: Adenocarcinoma of the colon or rectum is the most common histology of colorectal cancers, accounting for 93-95% of colorectal cancer diagnosis (Ragnhammar, Hafstrom, Nygren, Glimelius, & SBU Group, 2001). Colorectal cancers are described through the use of staging, and the American Joint Commission (AJC) TNM (Tumour-Nodal-Metastasis) staging system 6th Edition will be used to differentiate stages of cancer in this study. Once a person's T, N, and M categories have been determined, through staging investigations or surgery, this information is used to assign a cancer stage. For the purposes of this study, I will focus on patients with stage III or IV cancer, as this population is standardly offered cancer treatment using chemotherapy or radiation. Although treatment may be offered as an option for discussion in cases with a lower stage, it is not standard practice at our treatment facility for all colon cancer patients /9it is standard for stage II rectal and routine for "high risk" stage II colon cancer), and study participants will be accrued from patients in the standard treatment group, recruited from those patients with Stage III or IV cancer.
    a. Stage 3 colorectal cancer is defined as a lesion in the colon or rectum which demonstrates the presence of a tumour with nodal involvement in the absence of distant cancer metastasis (any T, N1 M0) (Wang, Chen, & Su, 2006). At the tertiary cancer centre where this study was conducted, standard care for patients entails treatment with curative intent, using adjuvant chemotherapy (colon) or adjuvant radiation/chemotherapy (rectum) in conjunction with surgical excision. Several chemotherapy options exist, and the decision of which regimen to use is based on a number of patient characteristics, including comorbidities, performance status and patient preference.
    b. Stage 4 colorectal cancer is defined as a lesion in the colon or rectum which demonstrates the presence of a tumour, with or without nodal involvement and with distant cancer metastasis (any T, any N M1) (Wang et al., 2006). Standard treatment includes palliative chemotherapy for improvement in survival and control of symptoms. These patients may also be candidates for palliative radiotherapy for control of symptoms related to metastatic (bone) or local (rectal) disease.
2. Symptoms are terms used by patients to describe sensations they experience. Symptoms have been described as deviations from normal function, sensation or appearance, and as predictors of change in normal function experienced by patients (Armstrong, 2003), and can be considered the subjective evidence of disease. Anxiety, lower back pain and fatigue are all symptoms. For the purposes of this study, the term symptom will be used to describe the changes from normal function experienced by patients during treatment with respect to difficulty sleeping, pain, tiredness /fatigue, shortness of breath, changes to skin, mouth sores,

changes in appetite, nausea/vomiting, diarrhea/constipation, difficulty urinating, changes in sexuality/sexual function, difficulty coping.

3. Health-related quality of life (HRQL) incorporates the physical, psychological and social functioning aspects of life that are affected by treatment or disease, as assessed by the patient (Spilker & Revicki, 1996). HRQL measures can provide additional information to supplement traditional trial outcome endpoints (tumour response, disease free and overall survival, and the assessment of toxicities) and has increasingly become part of the assessment of patients during clinical trials (Aaronson, Cull, Kaasa, & Sprangers, 1996; Aaronson et al., 1993; Sprangers, 1999).

Organization of Thesis

In the remaining chapters of this thesis I will review the literature on tools for assessing symptoms and HRQL in cancer (Chapter 2), describe the methods used in this study (Chapter 3), present the study results (Chapter 4) and discuss the results in relation to current literature (Chapter 5). The final chapter (Chapter 6) will outline the implications for clinical practice, education, research and theory development, and policy.

CHAPTER 2: LITERATURE REVIEW

Symptoms and Symptom Assessment

Symptoms are terms used by patients to describe sensations they experience. Armstrong (2003) reviewed the concept of symptoms in oncology practice. Symptoms were described as deviations from normal function, sensation or appearance, and as predictors of change in normal function experienced by patients. These symptoms, which may occur singly or in clusters, often function as prompts for patients to seek medical intervention (Gift, 2007). Previous experiences with similar symptoms may lead some patients to be hypervigilent, assuming symptoms are equated with disease progression (Heidrich, Egan, Hengudomsub, & Randolph, 2006). For other patients the same symptoms might be associated with benign age related changes or chronic health conditions, and not given the same relative importance. It is the subjective nature of symptoms that creates difficulty in monitoring and assessing change, as each patient's perspective is unique (Gift, 2007; Williams et al., 2006). As symptoms may be directly related to disease, treatment, concurrent co-morbid conditions, or any combination of these factors, a systematic approach needs to be developed to adequately assess symptoms (Armstrong, 2003; Brown, 2001; Gift, 2007; Spilker & Revicki, 1996).

The use of symptom measurement tools in clinical oncology practice is widespread. Models have been developed to consider the interaction of symptom assessment with the process of disease management. The study of integrated strategies to manage symptoms has promoted the development of a common understanding of the dimensions of symptom occurrence, distress and experience (Fu, LeMone, & McDaniel, 2004).

Models for Symptom Assessment and Intervention

Ongoing development of nursing models for symptom assessment and intervention includes the Integrated Approach to Symptom Management (IASM), which is currently in use in nursing education and research, primarily in Japan and the Symptom Management Model, developed by faculty and students at the University of California - San Francisco School of Nursing. The IASM model integrates the process of recognizing and understanding the mechanism of the symptom, understanding the patient's experience of that symptom, using a strategy for management that promotes patient self care, and evaluating outcomes. The work done on this model advances the idea that nurses are central in helping patients identify and manage symptoms, and have the opportunity to promote symptom management and patient self-care through health promotion (Larson et al., 1999).

The Symptom Management Model, developed by faculty and students at the University of California - San Francisco School of Nursing was designed on the understanding that effective management of a single symptom or a symptom cluster requires addressing the three dimensions

of symptom experience, symptom management and outcomes. This strategy uses signs and symptoms to evaluate disease status and to affirm the effectiveness of management strategies. Within the framework, there is recognition symptom clusters may occur, that some symptoms may be resolving as others develop, and that symptoms change over time. Thus, this model should be regarded as a general guideline for practice (Dodd, Miaskowski, & Paul, 2001; Miaskowski, Dodd, & Lee, 2004). Within this study I will focus on the dimension of symptom experience, and how we as health care providers assess and understand the way patients experience treatment.

Both the IASM and Symptom Management Model stress the interaction between disease processes, treatments and co-morbidities. Treatments may change as disease progresses, and evolve and as com-morbidities ebb and wane, highlighting the importance of ongoing symptom assessment using valid and reliable tools.

Symptom Assessment Tools

Understanding the symptom experience of patients through use of appropriate assessment and management tools helps patients and clinicians make treatment decisions. Numerous tools have been developed to facilitate the collection of information about symptoms from patients. These tools, designed to allow patients to communicate more effectively about treatment or disease effects with health care providers, need to be reliable, comprehensive and accurate. Adequate review of tools used for symptom monitoring must be carried out to ensure that they meet stringent requirements for reliability and validity (Cleeland et al., 2000; Kirkova et al., 2006).

Evaluating Common Symptom Assessment Tools

In their comprehensive review of symptom assessment instruments, Kirkova et al. (2006) identified five criteria for consideration when choosing a symptom assessment instrument: the contents of the tool, the scale of measurement, the validity of the tool, the process by which the tool was completed and the information obtained. Data collected must be comprehensive in nature, capturing symptom prevalence, severity and distress, and must identify symptom clusters. Measurement scales must be easy to comprehend and complete, be of clinical utility, be useful for statistical analysis, and be sensitive to change over time. The validity of tools must be assessed through comparison with other tested symptom measures and the tools must produce results that are reliable, reproducible, and stable between different raters and over time. Tools must present a minimal burden for completion and use, and must provide information that is adequate for decision-making, while enabling initial and ongoing symptom control. This template for considering the components of an ideal symptom assessment tool provides a framework that can be used to evaluate symptom assessment tools (Kirkova et al., 2006).

Within the field of oncology, numerous symptom assessment tools are used in research and clinical practice to monitor symptom experience. These tools vary in the number and type of symptoms they monitor, and the functionality that they represent. The first four criteria developed by Kirkova et al. (2006) were used to assess six of the symptom assessment tools most commonly used in the oncology setting. The fifth criteria, information obtained, would include a list of the actual symptoms assessed by each tool and was not included in order to keep all remaining information on one page. A list of the symptoms included in each tool is included in Appendix A.

Rotterdam Symptom Checklist

The Rotterdam Symptom Checklist (RSC) is a 31-item scale that also measures both physical and psychological aspects of quality of life. This patient-completed tool measures numerous symptoms, and asks patients to rate the extent to which they have been bothered by the symptom in the past 3 days, or in the past week. Possible answers range from not at all to very much. This tool has been used widely in several countries with cancer patients, and the reliability and structure have been studied in numerous settings with different patient populations (de Haes & Olschewski, 1998; Stein, Denniston, Baker, Dent, Hann, Bushhouse and West, 2003). Advantages of this scale include the ability to customize the RSCL for use in different patient groups by adding or deleting specific items. Disadvantages of this tool include the verbal rating system, which may make it more difficult for some patients to understand, and the length of the tool. The majority of questions on the RSCL refer to physical symptoms, and, although designed as a measure for quality of life, it might be better described as a symptom measure (Hardy, Edmonds, Turner, Rees, & A'Hern, 1999). Within the palliative setting, there was a lack of correlation between overall QOL measures and both performance status (rs= 0.15) and visual analogue scale scores (rs=0.03) (Hardy et al., 1999). The RSCL was developed for use with early stage cancer patients, and may not be appropriate for use in advanced cancer, when patients are less able to complete the forms (Cleeland, 2000; Hardy et al., 1999; Philip, Smith, Craft, & Lickiss, 1998). Content and construct validity were assessed through factor analysis (de Haes & Olschewski, 1998). A large group of 752 patients from medical oncology and healthy controls were examined in the validation study, and further studies validated the RSC in multicultural settings (de Haes and Olschewski, 1998).

Rotterdam Symptom Checklist-Modified

A modified version of the RSC (RSC-M) was developed to address perceived shortcomings of the original measure (Stein et al., 2003). The RSC-M was modified through the addition of 6 items to assess patient distress, and the resultant 28-item measure underwent psychometric testing in a population of 1,005 patients, representing a broad range of cancer

diagnoses. Reliability testing yielded a coefficient alpha of 0.88 for the sample as a whole, and was found to be equally reliable for male (α= 0.87) and female (α = 0.89) patients. Internal consistency was noted within the original 22 item RSCL when compared with the additional 6 item of the modified scale.

Convergent and discriminant validity were examined through comparison with other physical measures of health reported through use of the Medical Outcomes Study 36- Item Short Form (MOS SF-36). Discriminant validity was assessed by examining the relationship of the tool with measures that examined spiritual well being, and social support (Functional Assessment of Chronic Illness Therapy-Spiritual Well-Being Scale (FACIT-Sp) and the Multidimensional Scale of perceived Social Support (MSPSS). Moderate inverse correlations were noted between the RSC-M and the MOS SF-36 physical functioning scale (r = -0.59) and general health scale(r = -0.61). Weak inverse correlations were noted between the RSC-M and both the FACIT-Sp (r = -0.21) and the MSPSS (r = -0.31), which was attributed to the high scores on RSC-M being associated with physical distress, and high scores in the other scales being associated with better levels of function.

ANCOVA analysis across 10 different cancer diagnoses indicated a significant difference in distress when controlled for age and comorbidities. ($F=7.060$, $df=9$, $p<0.001$). As well, the RSCL-M could differentiate among patients with different treatment profiles ($F=13.171$, $df=6$, $P<0.001$) when controlled for age and comorbidities. The RSCL-M was sensitive to differences in symptom distress between genders (($t=3.957$, $p<0.0001$) and a difference was noted in the scores of patients undergoing active treatment when compared to those who had completed therapy ($t=3.677$, $P<0.0001$).

Advantages of the RSCL-M include the more comprehensive list of symptoms, and ease of completion of the measure. The validation study of the RSC-M was done in a large and diverse population of cancer patients within the United States, and indicates the broad applicability of this tool within that population (Stein et al., 2003).

Memorial Symptom Assessment Scale (MSAS)

The Memorial Symptom Assessment Scale (MSAS) is a 32-item scale that is used to measure symptoms, grouped into domains of physical and psychological symptoms. Patients are asked to rate their symptoms over the previous week using Likert-type scales, rating the frequency, severity and level of distress generated by symptoms. The rating scheme varies among the descriptors of symptoms. The frequency of symptoms is rated on a 4-point Likert-scale from rarely (1) to almost constantly (4), severity of symptoms on a 4-point scale from slight (1) to very severe (4). Symptom distress is rated on a 5-point Likert-scale from not at all (0) to very much (5). This scale also has a Global Distress Index (GDI), generated as the mean of 10 frequently endorsed items. The validation studies for the MSAS indicated the GDI and the physical and

psychological subscale scores were significantly correlated with indicators of clinical function and quality of life. The physical function subscale was also shown to be an independent predictor of survival, complementing the predictive value of Karnofsky performance status (KPS) (Chang et al., 1998; Chang, Hwang, Feuerman, Kasimis, & Thaler, 2000; Cleeland et al., 2000).

An updated version of the MSAS, the Memorial Symptom Assessment Scale Short Form (MSAS-SF), measures each of the 32 items with respect to distress or frequency alone. This abbreviated version was validated in a cancer population of 299 cancer inpatients and outpatients. Comparing the MSAS with the characteristics of the ideal assessment instrument (Kirkova et al., 2006), the MSAS-SF demonstrated a Cronbach's alpha ranging from 0.76 to 0.87. The MSAS demonstrated content validity, construct validity (factor analysis) and construct validity compared to performance status, the Functional Living Index-Cancer, the Revised Rand Mental Health Inventory and the Mood Visual Analogue scale. The MSAS-SF subscales demonstrated convergent validity with FACT subscales, performance status, inpatient status and extent of disease. The test-retest correlation coefficients for the MSAS-SF subscales ranged from 0.86 to 0.94 at 1 day and 0.40 to 0.84 at 1 week. (Chang, Hwang, Feuerman, Kasimis et al., 2000; Kirkova et al., 2006)

M.D. Anderson Symptom Inventory

The M.D. Anderson Symptom Inventory (MDASI) was developed to measure both the severity and the impact of cancer-related symptoms. It consists of 13 core symptom items that are rated based on presence and severity of symptoms, and 6 interference items that are rated based on the levels of interference with function. The MDASI is easy to complete, requiring less than 5 minutes for most patients to complete, and uses a familiar 1-10 rating system. It can be completed through self-assessment, or through interview. The multi-dimensional nature of assessment provides information that is of clinical utility. Reliability of the MDASI is confirmed through internal consistency, with Cronbach's alpha of 0.87 to 0.94 (Cleeland et al., 2000). Validity of the tool was demonstrated through content validity and construct validity noted when compared to ECOG. Tested in a large sample of 660 cancer patients, the MDASI also demonstrated discriminative construct validity in examining a subset of five symptoms that were expected to be more severe during chemotherapy treatment (Armstrong, Cohen, Eriksen, & Cleeland, 2005; Kirkova et al., 2006).

Worthington Chemotherapy Questionnaire (WCQ)

The Worthing Chemotherapy Questionnaire (WCQ) is a 64-item symptom assessment tool designed for use in oncology, in which questions are arranged into physical and psychological domains. Symptoms are measured in 4 aspects, examining the presence, severity, frequency and duration of symptoms, using a 5-point Likert type scale. This questionnaire was tested in a group

of 147 medical oncology patients, and demonstrated content validity. Factor analysis confirmed construct validity, and discriminative construct validity was noted in the validation study (Kirkova et al., 2006; Sitzia, Dikken, & Hughes, 1997). Drawbacks of this tool include the length of time required to complete 64 questions, which may lead to respondent fatigue and make it an impractical tool for clinical application.

Chemotherapy Symptom Assessment Scale (C-SAS)

The Chemotherapy Symptom Assessment Scale (C-SAS) is a scale designed for routine clinical use in outpatient oncology. Development of the tool originated with the same item pool as in the WCQ, and resulted in a 24-item tool intended for clinical practice. The items evaluate symptoms based on their incidence, severity and the bother they cause patients. Severity and bother scales were rated using 3- and 4-point Likert scales. Validity was noted through correlations with the RSC and MSAS (Brown et al., 2001; Brown, 2001). Construct validity was based on evidence of the relationship between cytotoxic agent use and the incidence of stomatitis and alopecia, through factor analysis. Reliability testing was completed using test-retest and internal consistency. Brown et al. (2001) stated that as symptoms constantly change, they might not be stable over even short periods of time. Acceptable levels of agreement were noted when patients completed the C-SAS pre-treatment and 24-hours post treatment, but the authors hypothesized a higher level of agreement might be obtained if the testing was completed mid-chemotherapy treatment cycle. Internal consistency (IC) was evaluated by comparing expected and observed occurrence of symptoms with specific chemotherapy protocols, and a value of 0.75 was observed (Brown et al., 2001). Validation testing was completed in a sample group of 120 medical oncology patients and 23 health care professionals (Brown et al., 2001; Brown, 2001; Kirkova et al., 2006).

Edmonton Symptom Assessment System (ESAS)

The Edmonton Symptom Assessment System (ESAS) was first developed as a tool to assess patients in palliative care (Bruera, Kuehn, Miller, Selmser, & Macmillan, 1991), but has been validated in a variety of settings (Chang, Hwang, & Feuerman, 2000; Davison, Jhangri, & Johnson, 2006a; Davison, Jhangri, & Johnson, 2006b). Designed as a series of 9 bi-polar visual analogue scales, the ESAS is completed by patient self-report, or can be completed by proxy (a family member or health care provider). The items include pain, nausea, depression, anxiety, drowsiness, appetite sensation, well-being and shortness of breath. The items can be grouped into physical and psychological domains, and adding the individual item scores can generate a general symptom distress score. The advantages of the ESAS tool are multiple: it is brief and easy to complete, and measures clusters of symptoms in patients with cancer (Paice, 2004).

Nekolaichuk, Maguire, Suarez-Almazor, Rogers, & Bruera, (1999) reviewed the reliability of symptom assessments using the ESAS, comparing multiple raters, and found reliability

estimates were higher using multiple raters, over multiple time periods (Nekolaichuk et al., 1999). Analysis of individual symptom scores was found to be more meaningful than that of total symptom distress ratings. A disadvantage of the ESAS tool may be the multiple visual analogue scales (Rees, Hardy, Ling, Broadley, & A'Hern, 1998). Modified versions of the ESAS tool have included additional items (pain relief) and replacement of the visual analogue rating scale, with a combination of a 100 mm horizontal line, with a 1 to 10 numeric range included below the line, which may be easier for patients to understand and complete (Chang, Hwang, & Feuerman, 2000; Cleeland, 2000; Kirkova et al., 2006).

In a validation of modified ESAS in which it was compared to the Rotterdam Symptom Checklist and Brief Pain Inventory completed by Philip et al. (1998) found directly comparable indices had weighted kappa's ranging from 0.45 to 0.61, demonstrating convergent validity (Philip et al., 1998). Chang, Hwang and Feuerman (2000) examined construct validity of the ESAS, comparing the tool with physician assessed performance status and studied the ability of the tool to discriminate between different levels of symptom experience. Main validation studies for the ESAS were completed in groups of 135 palliative cancer patients, as well as 282 medical oncology in- and out- patients (Kirkova et al., 2006). Modified versions of the ESAS with additional items were studied and content and concurrent validity proven in the palliative cancer population (Phillip et al. 1998). Further ESAS versions with modified response options have been developed, but reliability and validity data has not been reported (Chang, Hwang, & Feuerman, 2000; Kirkova et al., 2006).

A comparison of the six tools reviewed above using the factors recommended by Kirkova et al. (2006) is shown in Table 2.1.

Table 2.1 Comparison of selected symptom assessment tools

	Contents of tool	Scale of measurement	Validity (V) and reliability	Process
RSCL-M *	31 items Extent bothered by symptoms in the past week Measure of physical distress	Verbal rating system from "not at all" to "very much"- higher score correlates with more bother	V=Content Construct (factor analysis) .59 with SF36 physical functioning, score, .61 with SF36 general health status R= internal consistency Cronbach's alpha 0.88	Self administered
MSAS **	32 items Symptom frequency, severity and level of distress from symptom	4- and 5-point Likert scale, higher scale correlates with increased frequency, severity, and distress	V=Content Construct (factor analysis, convergent/divergent) R= Cronbach's alpha .76-.87 (Kirkova) test-retest= .86-.94 at one day, .40-.86 at 1 week (Chang et al)	Self administered
MDASI***	19 items symptom presence, severity and interference with life	Symptoms measured on a 0-10 scale, higher score indicates increased frequency, severity and interference	V=Content, Construct (factor analysis, convergent/divergent, discriminative) R= internal consistency Cronbach's alpha .87-.94 (Cleeland)	Self administered
CSAS ****	24 items Symptom incidence, severity and bother	4- and 5-point Likert scale, higher score correlates with increased incidence, severity and bother	V=Criterion, Construct: discriminative .60-.71 correlation with MSAS R= internal consistency Cronbach's alpha .75 , test-retest weighted kappa (*wk*)-incidence .61 SD .17, severity *wk* .60, SD .23, bother *wk* .56, SD .23	Self administered or proxy
ESAS*****	9 items Symptom severity at the time of assessment, can generate a mean distress score	Numerical rating scales, higher score indicates increased severity	V=Construct : convergent *wk* .45-.61/divergent, discriminative; Concurrent- .85 correlation with FACT pain, .83 correlation with MSAS pain (Chang) R= internal consistency Cronbach's alpha .79, test-retest Spearman Correlation Coefficient .86 P<.0001 at 2 days, .46, P<.05 at 1 week (Chang)	Self administered or proxy

* Data on the Rotterdam Symptom Assessment scale from Stein et al. 2003
** Data for the MSAS from Chang, Hwang, Feuerman, Kasimis et al., 2000 and Kirkova et al., 2006
***Data for the MDASI from Cleeland et al.2000, Armstrong et al., 2005, and Kirkova et al., 2006
****CSAS data obtained from Brown et al., 2001, Brown, 2001, and Kirkova et al., 2006
***** ESAS data obtained from Nekolaichuk et al. 1999, Chang, Hwang & Feuerman, 2000, Kirkova et al. 2006

From reviewing the assessment tools above, it is clear that while all meet the requirements identified by Kirkova et al., each also has some disadvantages. In order to be comprehensive, some tools are longer than others. The ESAS is the shortest and most simple but it lacks information about duration and interference/distress associated with each symptom, From the standpoint of clinical practice, Kirkova et al. failed to include an important feature of symptom assessment- whether the symptom was improved or worse than at the previous assessments; none of the instruments reviewed collected this kind of information.

Quality of Life

Quality of life (QOL) is a concept which has been used increasingly both in research and clinical practice over the past 40 years. It has been used to evaluate the effectiveness and quality of health outcomes, but consensus on how to define and evaluate quality of life has been elusive. QOL as an umbrella term encompasses many concepts, from functioning, health status, and perceptions, to life conditions, behaviour, happiness, lifestyle and symptoms (Simko, 1999). Quality of one's life may be influenced by a number of factors, both internal and external to the individual and range in scope of impact, from social issues related to education, levels of crime or environments of warfare, to quality of life issues related to health care and mental health (Dolan & Peasgood, 2007; Giacaman et al., 2007). The diversity of approaches to quality of life has complicated the use of this concept in health care outcome evaluation, as the lack of consensus in the conceptual approaches causes a lack of clarity about the subject.

Moons, Budts & De Geest (2006) reviewed the multitude of conceptual approaches to quality of life, and noted six conceptual problems which influence how we think about quality of life. These conceptual problems included: QOL vs. health status, the objective-subjective appraisal of QOL, indicators or determinants, changes over time, improving or deteriorating factors and the idea of health related quality of life. The distinction between quality of life and health status has been historically challenging, and these terms have been used interchangeably in the past, despite their substantive differences. The subjective-objective nature of quality of life is reflected in the differences between observable symptoms and patient perception, leading to increased differences in how QOL is described or rated by both individuals and their proxies. Indicators are the conditions or events which characterize a condition, while determinants are those factors external to the individual which may influence the QOL experience. QOL is not a static state, it changes according to a multitude of factors, and consideration of QOL must include the assessment of this fluctuation. Finally, health related quality of life (HRQL) focuses on the individual experience that relates to health, disease, disability and impairment. The concern in focusing on HRQL is that by focusing solely on the health related aspects of QOL, health care providers may either over- or under-estimate the impact of adverse health on overall quality of life. Within these approaches to

quality of life, Moons et al. (2006) stated that quality of life can be best defined in terms of life satisfaction, which Donnelly et al (2001) further defined as a function of physical, spiritual, emotional and social factors. The remainder of this chapter focuses on HRQL as it is most consistent with the study objectives.

Kaplan (2003) reviewed the importance of quality of life measurement in medical care. He noted that the shift in the model of care from a model which focused on disease identification and treatment to a model aimed at helping patients live longer and better lives has also lead to an increased focus on quality of life (Kaplan, 2003). Evaluating not only survival benefits of specific treatments, but also the life expectancy adjusted for quality of life allows the integration of morbidity and mortality data. Koller & Lorenz (2002) proposed a three-component outcome model that would include classical endpoints of survival, health status and biochemical indices, hermeneutic endpoints of quality of life, expectations and coping, and a third endpoint, including value judgements of clinical relevance. The paradigm shift from a solely medical model to an outcomes model including patient reported outcomes (PRO's) has led to the development of guidelines designed to facilitate evaluation of quality of life instruments (Lipscomb, Snyder, & Gotay, 2007).

Utilizing PRO's requires a clear understanding of what they entail, and how the information is collected. Marshall et al. (2006) define PROs as measures designed to record the patients' perspective of health, illness and the effects of health care interventions in a manner that is not only reliable and valid, but also acceptable and feasible. Schwartz and Sprangers (2002) state that PROs address the fundamental aspect of treatment, the way it is experienced by the patient. By asking the patient about their experience, patients can share firsthand knowledge of the personal benefit versus cost of therapy, and may inform physicians on side effects of treatment otherwise unreported. The enhanced aspect of communication between patient and clinician is an important aspect of the use of PROs, as clinicians often misjudge the severity of treatment-related symptoms experienced by patients (Fromme, Eilers, Mori, Hsieh, & Beer, 2004; Strömgren et al., 2001). PRO tools are completed by patients or their proxies, and can be completed in a paper and pen format, by personal interview, or through the use of computer questionnaire. The information gathered is a rich data source, allowing clinicians to assess patients' experiences of treatment, and learn more about treatment response, current levels of physical psychological and social functioning, health status and quality of life (Chang, Hwang, & Kasimis, 2002; Detmar, Muller, Schornagel, Wever, & Aaronson, 2002).

Anderson & Burckhardt (1999) reviewed the concept of quality of life as a PRO. The authors noted that traditional assessment and intervention directed toward QOL issues may be

difficult if the definition of QOL to be used is not carefully selected from among those that are available, based on project objectives.

HRQL has been defined as those parts of quality of life that are affected by disease or treatment, as assessed by the patient (Spilker & Revicki, 1996). HRQL incorporates physical, psychological, spiritual and social functioning aspects, and is an indicator of the patient's interpretation of their own well-being in relation to these factors (Spilker & Revicki, 1996). HRQL assessment has become a frequent component of clinical research trials in oncology, as clinicians strive to understand the impact of various treatments on patients (Detmar et al., 2002; Sloan et al., 2002).

Assessment of HRQL has increasingly become a standard component of the evaluation of patients receiving chemotherapy treatment during chemotherapy trials including colorectal cancer as an additional method to identify differences in treatment alternatives (Gunnars, Nygren, Glimelius, & SBU Group, 2001; Detmar et al., 2002; Sloan et al., 2002).

Research trials use HRQL measures to evaluate the treatment experience. HRQL measures can provide significant information to healthcare providers and patients, assisting in the decision making process when benefits of therapy may be limited, and the impact of treatment on quality of life becomes the focus of care (Davidson-Homewood, Norman, Küchler, Cunningham, & Watson, 2003; Kavadas et al., 2003). Trial outcomes of tumour response, disease free and overall survival, and the assessment of toxicities can thus be supplemented by a formal assessment of the functional, psychological and social impact of cancer treatment (Aaronson, Cull, Kaasa, & Sprangers, 1996; Aaronson et al., 1993; Sprangers, 1999). Bottomley, Efficace & Fayers (2002) reviewed the use of HRQL measures and concluded that they were a vital component of cancer clinical trial research programs, and noted that they provide additional information required in treatment making decisions. This is consistent with the later work of Conroy and colleagues (2003, 2007) who reported that clinicians often underestimate the impact or severity of patient's symptoms when compared to patients reports. Despite the usefulness of HRQL information (Higginson & Carr, 2001), it is not routinely collected in clinical settings outside of clinical trials.

Conroy, Uwer, & Deblock (2007) discussed the potential of HRQL measures as a prognostic indicator in colorectal cancer, and found that post treatment completion, most cancer survivors reported good overall QOL, as measured using the EORTC QLQ C30 measure, but may experience persistent deficits with fatigue, dyspnea and altered bowel function, lasting in some cases for years.

HRQL is one of several prognostic factors for survival of colorectal cancer. Recent studies have examined patient self-reported HRQL, and noted that the EORTC-QLQ C-30 social functioning subscale score is an independent prognostic factor for survival, while

performance status or the global quality of life/health status subscale were not significant predictors for survival (Efficace et al., 2006).

The "Clinical Significance of Quality of Life Measures in Cancer Patient Symposium", held in 2000, was designed to bring together experts in the field of HRQL, and to improve the understanding of clinicians of both the validity and usefulness of HRQL measures in clinical practice (Donaldson, 2004). A key benefit of HRQL for clinical practice was reported by several authors was the improvement in communication between physician and patient when HRQL measures are used (Fromme et al., 2004; Schwartz & Sprangers, 2002; Strömgren et al., 2001).

The relationship between patient reported outcome (PRO) measures such as HRQL and clinical practice provides a foundation for considering barriers to successful implementation of this type of tool in clinical practice. Greenhalgh, Long and Flynn (2005) reported that the many tools already in use are perceived to provide clinicians with the same type of information as HRQL measures, making the collection of specific HRQL data redundant. Nevertheless Greenhalgh and colleagues identified the following ways in which HRQL assessment could be helpful in clinical practice: prompting discussions between care providers and patients about HRQL, optimizing the detection of unreported problems, and adapting management strategies to address HRQL concerns. The monitoring of HRQL may also influence patient behaviour, and lead to improvements in health status and satisfaction with care. Greenhalgh and colleagues suggested that the primary barrier to the use of HRQL tools in clinical practice was that they were designed to provide a "one-time" or snapshot of quality of life, rather than the long term view required in clinical practice. Such an approach would address the concerns raised by Bliven, Kaufman and Spertus (2001) and Sloan et al. (2002), who noted that in the context of busy clinical settings, current HRQL assessment may be perceived as a burden by healthcare providers, due to the lack of time to discuss or fully consider the implications of the information the tools provide. HRQL tools specially designed for clinical practice may also address concerns noted by Osoba and colleagues (1998) and Velikova & Wright (2005) who noted that the use of HRQL assessment in clinical practice could be limited by lack of information about its potential clinical utility. Arndt et al. (2006) elaborated on this point by noting that the format of tools for routine use should be designed in a way that complements and coordinates with decision making and treatment management, with clear methods of interpretation and analysis (Arndt et al., 2006).

Evaluating Health Related Quality of Life Tools

As there are many different HRQL measures that have been developed and are currently in use within the cancer population, the selection of tool is dependent upon which elements of HRQL one measures and how one uses the information (Cooley et al., 2005). Use of a

framework to evaluate potential questionnaires can ensure the suitability of tools for a particular patient profile or clinical study (Efficace et al., 2003; Lipscomb et al., 2007).

The Medical Outcomes Trust (MOT) framework was published in 2002 as a guide to evaluating health status and quality of life measures, and was subsequently adopted by the National Cancer Institute (NCI). Examining the numerous available measures for cancer populations, the NCI working group found that many tools demonstrate reliability, validity, responsiveness, feasibility and adaptability to different languages and cultures (Lipscomb et al., 2007). The use of the MOT framework allows clinicians to evaluate current available tools, and select the measure most appropriate tool for their requirements. This framework was used to evaluate three quality of life tools commonly used in oncology settings.

EORTC-QLQ-C30

The EORTC-QLQ-C30 is a disease-specific quality of life measure designed to measure cancer patients' physical, psychological and social functions, and is composed of both multi-item and single item questions. The scale includes five functional scales (physical, role, emotional, cognitive, and social scales), a single item global health status quality of life scale and three symptom domains. It has been proven a valid tool in the oncology population (McDowell, 2006) and a practical tool for measuring quality of life in patients with advanced disease (Kaasa et al., 1995). The EORTC-QLQ- C30 has a demonstrated ability to detect clinically important differences in patients undergoing cancer therapy, and has been shown to be feasible for use in a variety of oncology settings (Strömgren et al., 2001). The EORTC QLQ C-30 has been used to assess HRQL deficits in colorectal cancer, in immediate and long-term follow-up, and is able to identify deficits post therapy in different domains of function, as well as specific symptoms limiting HRQL (Arndt, Merx, Stegmaier, Ziegler, & Brenner, 2004; Arndt et al., 2006). The core module of the EORTC program, the QLQ-C30 has been used in multiple international clinical trials, demonstrating the cross-cultural applications of this tool (Osoba, Aaronson, Zee, Sprangers, & te Velde, 1997). The modular nature of the EORTC system has led to disease specific components that address cancer-specific deficits of the core instrument (Ulander, Jeppsson, & Grahn, 1997).

Functional Assessment of Cancer Therapy (FACT-G)

The Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System was developed as a collection of HRQL scales designed to facilitate chronic disease management. Tools have been developed for use in cancer, as well as human immunodeficiency virus infection and multiple sclerosis. The core instrument, the FACT-G, consists of a 27-item questionnaire, organized into four domains of health: physical, functional, social and emotional well-being. Studies to examine the validity and reliability of the core instrument have been completed. Results

of these studies indicate that the core measure is sensitive to change in health status over time, and is an acceptable measure for use in evaluating HRQL (Cella, 2000). In addition to the core module, additional disease, symptom and treatment specific modules may be used to assess specific populations.

In a population of patients that are acutely ill, the potential exists for actual scores to range widely, and some scores may not be adequately measured. Studying the measurement of symptom burden in the severely ill haemodialysis patient, the FACIT measurement system was seen to be less susceptible to floor and ceiling effects than the MOS SF-36 QOL measure, as the FACIT system is designed to assess QOL in the chronically ill and in very sick populations of patients (Weisbord et al., 2003).

Functional Living Index-Cancer (FLIC)

The Functional Living Index- Cancer (FLIC) is a 22-item quality of life questionnaire that uses 7- point visual analogue scale for response options (Cheung, Goh, Thumboo, Khoo & Wee, 2005). Scoring is completed through summation of individual items scores, with higher scores representing better levels of health (range-22-154). Psychometric studies have shown that the FLIC items can be grouped into five domains: physical, mental and social function, general well being and gastrointestinal symptoms. Subscale scores range from 14 to 35 points. Validation studies comparing the FLIC with the RAND SF-36 found the subscales of physical, mental and social function to be comparable, with greatest differences within the domain of general well being (King, Dobson & Harnett, 1996; Schipper, Clinch, McMurray, & Levitt, 1984). Wilson, Hutson, & VanStry (2005), in their review of the RAND SF-36 Item health inventory and the FLIC, found that the condition specific may be more sensitive to psychological factors that influence health and well being compared to the generic SF36. There are currently 21 language translations available for the FLIC measure (*ProQolid: Patient Reported Outcome and Quality of Life Instruments Database,* 2007), and shortened versions have been developed and validated for use in English and Chinese languages (King, Dobson & Harnett, 1996; Schipper et al., 1984). Validation studies of the FLIC tool used factor analysis, which showed construct validity and high internal consistency in stable groups of patients, and has been used with multiple cancer diagnoses (Breitbart et al., 1996; Seidman & Portenoy, 1995).

In Table 2.2, three tools that assess HRQL are evaluated using criteria proposed by Efficace et al. (2003) and Lipscomb et al. (2001).

Table 2.2 Comparison of selected Quality of Life assessment tools

	Number of questions, type of measurement	Validity and reliability of the tool	Process of completion	Cross cultural use	Feasibility
EORTC QLQ C-30 *	*30 questions, 28/30 questions 4-point Likert scales, 2 questions 7-point Likert scales *High global scores and lower symptom scores indicate better function and lower symptom distress *Summary score	V= content, criterion, concurrent R= ICC 0.73 to 0.88	Self Administered paper or interviewer administered	Available in multiple languages	Average survey completion 10.3 minutes, 83% able to complete form without help
FACT G **	27 items, measured with a 5-point Likert-type scale *High global scores and lower symptom scores indicate better function and lower symptom distress *Summary score	V= construct (convergent/ divergent, discriminant , concurrent R= ICC 0.88	Self Administered Paper based Or interviewer administered	Available in multiple languages	Average completion of survey 10 -20 minutes Rated as easy
FLIC ***	22 items with 7-point Likert scores High total score = improved HRQL Summary score available	V=concurrent, Factor analysis R= ICC 0.91	Self administered , interview or proxy	Available in multiple languages	Average completion less than 10 minutes, patients able to answer all questions

* Data for the EORTC QLQ C-30 taken from McDowell, 2006, Strömgren et al., 2001 and Sprangers, te Velde, & Aaronson, 1999

**Data for the FACT-G taken from Cella et al., 1993, Weisbord et al. 2003 and *ProQolid: Patient Reported Outcome and Quality of Life Instruments Database,* 2007

***FLIC data obtained from King, Dobson & Harnett, 1996; Schipper, Clinch, McMurray, & Levitt, 1984, Breitbart et al., 1996; Seidman & Portenoy, 1995 and *ProQolid: Patient Reported Outcome and Quality of Life Instruments Database,* 2007

HRQL Measures Summary

HRQL tools cover a wide range of general and specific populations, and the information they provide can be used in many different ways. Some general tools may be good indicators of deviation from normal levels of HRQL in healthy individuals, but less applicable in populations with changes related to progression of disease, with significant HRQL deficits at initial assessment. The type of information gathered from the measures needs to be accurate, providing data that can be used to inform the decision making process. The burden of completion for the measure needs to be considered, particularly in studies involving patients with potentially extensive disease.

The measures reviewed present as very similar in many aspects. The cancer specific HRQL tools take approximately the same length of time to complete, and cover the same range of domains. The way questions are asked, and the type of resulting data differ. Patients may find questions with word answer options (very much, not at all) more difficult to complete if they have lower levels of English language competency, or with fewer years of formal education. The forms may seem straight forward when patients are well, but with exacerbation of symptoms, obtaining complete measures may be more difficult.

The Symptom: HRQL Relationship

Hassan et al. (2006) reviewed the use of quality of life outcomes in a population of patients with advanced colorectal malignancies. They found that central to the effectiveness of any HRQL tool was its ability to assess key symptoms known to affect quality of life. Clinical observations suggest that the following symptoms be included: bowel function, fatigue, anxiety, and spiritual well-being. The FACT-C and EORTC colorectal cancer module are two measures that incorporate bowel function, in addition to questions addressing fatigue, anxiety and general well being.

Many tools that collect data regarding symptom experience also collect data about the quality of life during cancer treatment. The relationship between individual symptoms and quality of life has been studied in many different cancer populations. The studies reviewed below used mixed cancer populations unless otherwise specified.

Symptom: Chemotherapy Induced Nausea and HRQL

Ballatori and Roila (2003) evaluated observational and double blind randomized clinical trials (RCT) examining the relationship between chemotherapy-induced nausea and vomiting (CINV) and the quality of life during chemotherapy. CINV appears to have a short-term effect on HRQL, and appropriate assessment may affect clinical decision-making. The introduction of antiemetic prophylaxis, with better control of nausea and vomiting in the first 24 hours post chemotherapy treatment was shown to lead to an improvement on HRQL (Ballatori & Roila, 2003). The development of acute and delayed CINV was found to have a significantly negative

impact on daily functioning of patients undergoing chemotherapy treatment (Bloechl-Daum, Deuson, Mavros, Hansen, & Herrstedt, 2006; Cohen, de Moor, Eisenberg, Ming, & Hu, 2006).

Symptom: Anemia, Fatigue and HRQL

Fatigue is a commonly reported symptom of cancer and cancer therapy. The specific cause of fatigue during cancer treatment is not completely understood, but anemia was considered by many researchers to be a significant cause of fatigue in this population (Holzner et al., 2002; Portenoy & Itri, 1999). More recently, researchers have closely examined the relationship between hemoglobin levels as indicators of fatigue, the administration of erythropoietin, and fatigue. This research has established the relationship between anemia and hemoglobin, but the relationship between anemia and fatigue remains inconclusive (Bohlius, Wilson, Seidenfeld, Piper, Schwarzer, Sandercock et al. 2006a; Turner, Anglin, Burkes, Couture, Evans, Goss et al. 2001). Bohlius et al. (2006b) in their Cochrane review stated that there is suggestive evidence that erythropoietin or Darbopoetin, which increase hemoglobin levels, may improve HRQL, but also noting the increased relative risk of thrombo-embolic complications. These findings suggest a more complex cause of fatigue in cancer patients than previously suggested. A number of studies and reviews have been completed to examine the relationship between symptom experience and quality of life within the colorectal cancer population. Numerous other symptoms related to both cancer and its treatment influence quality of life. By reviewing the studies within the colorectal population, we can better understand some of the challenges and advantages inherent in the application of HRQL measures in a clinical setting.

Symptom: Pain and HRQL

Pain is a common problem for patients with colorectal cancer, related to type of surgical procedure, presence of disease, or the process of treatment (Esnaola, Cantor, Johnson, Mirza, Miller, Curley, et al., 2002) and was ranked as the second most frequent symptom or concern for patients with colorectal cancer in a survey of healthcare providers (Cella, Paul, Yount, Winn, Chang, Banik, et al., 2003). Pain has been noted to have a negative impact on HRQL, with respect to physical and functional well-being, (Esnaola et al. 2002) and in a patient survey of HRQL 6 months postoperatively (Kopp, Bauhofer, & Koller, 2004).

Bruce & Krukowski (2006) reviewed the relationship between pain and HRQL in the context of gastrointestinal surgery. They determined that patients who experienced chronic pain after surgery had significantly poorer quality of life scores, and compared to those who were pain free, had poorer levels of function, poorer HRQL and more severe symptoms (Bruce & Krukowski, 2006). Pain may be related to the progression of disease, and is a concerning symptom (Harris et al., 2003).

Symptom: Reduced Nutrition and HRQL

There is a growing body of literature on relationships between symptoms that may have an impact on nutritional status and HRQL. Nutritional status during cancer therapy can increase morbidity and mortality in advanced cancer. Gupta et al. (2006) reviewed the relationship between nutritional status and HRQOL in colorectal cancer, and determined that 41% of the patients studied experienced malnutrition. Well-nourished patients had significantly improved HRQL scores on global, physical and role function scales, compared to malnourished patients. Ravasco, Monteiro-Grillo, Vidal, & Camilo (2005) determined that dietary counselling improved the outcomes of colorectal cancer patients, and had longer lasting benefit than did protein supplementation during treatment. Following a review of HRQL tools in colorectal cancer, Conroy et al. (2007) stated that nutrition is a key determinant of HRQL in colorectal patients.

Mucositis is an inflammation of the mucous membranes, which may include ulcerations or erosions. This inflammation is not limited to the oral cavity but may be present in the entire gastrointestinal tract. Mucositis can seriously impair the ability to eat and drink, be a significant cause of pain and infection and adversely affect patient functioning and HRQL. Consensus on standard treatment protocols to prevent or treat oral mucositis has not been achieved, but clinicians agree that ongoing systematic assessment with valid assessment tools facilitates intervention and management of mucositis (Dodd, Miaskowski, & Paul, 2001; Eilers, 2004). Mucositis is often associated with colorectal cancer therapies utilizing 5-fluorouracil (5FU) based chemotherapy (Van Gerpen, 2004): the recent introduction of capecitabine, an oral fluoropyridamine has resulted in less mucositis, neutropenia and alopecia, but with a rise in the incidence of hand foot syndrome (Nicum, Midgley & Kerr, 2003).

Symptom: Altered Sexual Function and HRQL

Quality of life, and sexual function post rectal cancer surgery was examined by Breukink et al. (2007). In this study it was noted that patients showed improvements in general quality of life outcomes, despite a decrease in sexual functioning. The degree of sexual dysfunction was dependant on the type of surgical intervention (low anterior resection patients had less dysfunction than the patients who had undergone an abdominoperineal resection (Breukink et al., 2007).

Symptom: Altered Bowel function and HRQL

Diarrhea is a specific side effect of chemotherapy drugs used in the treatment of colorectal cancer, namely 5FU and irinotecan, but can also be related to post surgical changes (Goldberg Arnold et al., 2005; Nicum et al., 2003; Van Gerpen, 2004; Wickham & Lassere, 2007). Many factors influence the development of diarrhea during chemotherapy treatment, including dosage, route of chemotherapy administration, combination chemotherapy and concurrent radiation therapy. Diarrhea onset can be early post therapy, requiring immediate intervention, or

late onset, requiring patients to begin a specific anti-diarrhea regimen until diarrhea has resolved (Hallquist Viale & Sommers, 2007). Diarrhea can be a limiting factor for patient quality of life, as patients reduce their social activities due to a fear of having diarrhea when away from home (Dunn et al., 2006).

Symptom: Neurotoxicity and HRQL

Neurotoxicity is a specific side effect of oxaliplatin; a chemotherapy agent used in combination with 5FU for the treatment of colorectal cancer, and is a dose-limiting toxicity of this chemotherapy (Simpson, Dunn, Curran, & Goa, 2003). Neurotoxicity may be acute and transient in nature accompanied by jaw pain, jaw tightness, or muscle cramping, with the potential of pharyngolaryngeal dysesthesia, a rare presentation with a sensation of perceived difficulty breathing, throat tightening and dysesthesia. Acute neurotoxicity is cold induced, through drinking cold water, touching cold objects or breathing cold air. The chronic or accumulated neurotoxicity presents as a gradually increasing numbness or tingling to the extremities, and may result in impaired ability to perform actions of daily living. Adequate assessment of the degree of sensation and motor activity to the extremities is an important component of the baseline assessment, to determine if patients have pre-existing conditions that increase their risk of impairment (such as from diabetes) and promote optimal function. Significant alterations to HRQL may result if significant nerve damage occurs, preventing normal levels of activity (Choi, Kong, Mozaffar, & Holcombe, 2006; Grothey, 2005; Simpson et al., 2003).

Symptom: Altered Psychosocial Well-being and HRQL

Much has been written on the impact of stress and coping in serious illness (Park & Folkman, 1997, Fitzsimmons et al. 1999, Dunn et al. 2006, Lee, 2008). Lazarus & Folkman (1984) examined coping, which they defined as "the constantly changing cognitive and behavioural efforts to manage specific external and or internal demands that are appraised as taxing or exceeding the resources of the person". They described the available coping mechanisms for coping with stressful situations, and commented that a person who is sick, or debilitated has less energy to expend on coping than does a healthy person. Although the presence of health and energy can enable coping, the authors point out that people who are seriously ill can cope with stressful events when necessary, and reviewed the literature which examines this phenomena (Lazarus & Folkman, 1984) Numerous coping strategies were reviewed that could hinder or improve individual coping, including beliefs, problem solving, social skills, social supports, and material resources. Mårtensson, Carlsson & Lampic (2008) examined patient and nurse agreement on coping resources and quality of life during cancer therapy. The study findings indicated that nurses who overestimated emotional distress underestimated coping resources and quality of life. Coping and the search for meaning has been described as a key determinant of QOL (Lee, 2008).

Fitzsimmons et al.(1999), in examining the relationship between perceptions of nurses and patients, found that staff nurses had a mechanistic view of quality of life (QOL is proportional to symptom severity), while patients regarded the risk or threat of each symptom, and the mediating effect of coping strategies on QOL. Lethborg, Aranda, Cox & Kissane (2007) discussed the adaptation to cancer and noted that both physical and existential distresses were positively correlated with psychological distress. The adequate management of physical symptoms was an important part of patients regaining a sense of control and hope, and a vital part of the adaptation process (Lethborg, Aranda, Cox & Kissane, 2007).

Dunn et al. (2006) examined the descriptive data on quality of life and psychosocial variables most pertinent to colorectal cancer patients. Through a process of in-depth interviews and focus groups, patients reported quality of life issues the authors grouped into five broad areas: physical function, social well-being, sexual function, psychological well-being and work or vocational function. Psychological well-being was decreased in half the participants, related to depression and anxiety (related to the fear of disease recurrence). Half the study participants reported loss of strength endurance and fatigue reported physical impairment. Some participants reported deceased social activity; some related this to anxiety about access to toilet facilities, while others reported fatigue and the social stigma of cancer diagnosis as limitations to activity. Levels of work or employment were not routinely reported as concerns, due to the age of participants, as most of those who were previously employed were able to return to work after extended sick leave. A loss of sexual function or concern about sexual self-concept was noted in younger study participants (Dunn et al., 2006). Ramsey examined the long-term quality of life issues in colorectal cancer patients (Ramsey et al., 2000; Ramsey, Berry, Moinpour, Giedzinska, & Andersen, 2002). Patients achieving a long-term remission experience a relatively high quality of life, but some symptoms like diarrhea and depression may persist for a long time.

Hassan et al. (2006) examined quality of life outcomes in patients with advanced colorectal malignancies. This review suggested that key symptoms can be identified which are highly linked to deterioration in HRQL. From clinical observations, the authors suggest that bowel function, fatigue, anxiety, and spiritual well-being are key symptoms of interest in this population, which should be included in any measure examining issues of HRQL. Whitford, Olver & Peterson (2008) studied the assessment of spirituality as a core domain in the assessment of quality of life in oncology. The results of their study supported the assessment of spirituality as a core domain of QOL, but the clinical utility of this assessment was unclear. Davis & Kirkova (2007) reviewed that concept of symptom burden in patients with advanced cancer. The authors identified 37 separate symptoms experienced by patients with incurable cancer, five of which (fatigue, pain, lack of energy, weakness and appetite loss) occurred in more than fifty percent of

patients. Hassan et al. (2006) also discussed the issue of patient burden, and recommended that researchers consider the length and timing of HRQL assessments, in an effort to obtain key information that influences treatment decisions.

Conclusion

Both symptom assessments and quality of life assessments provide important information about the experience of treatment from the patients' point of view. With the gradual shift to an outcomes-focused model of care, there is no question about the importance of information assessing perceived symptoms and HRQL; this kind of information is critical to both patients and health care providers responsible for making on-going treatment decisions.

In the process of reviewing the literature, two gaps were identified. first the oncology literature presumes that a relationship exists between HRQL and symptom burden, but to date no research has further examined the degree and extent of the relationship. Research questions one and two were designed to address this gap. Understanding the relationship between individual symptoms and quality of life may enable health care providers to identify patients requiring modification of overall treatment/symptom management plan sooner in the treatment trajectory, and direct interventions to the symptoms of greatest impact. Hassan et al. (2006) hypothesized that certain individual symptoms have the greatest influence on HRQL in patients with advanced colorectal malignancies, but no further research has been published which addresses this assertions. The third research question was designed to address this gap.

CHAPTER 3: METHOD

This study examined the relationship between symptoms and quality of life. The study was developed in two stages, the pilot study, and the main study.

Pilot study of Modified-ACFS (MACFS)

Some problems with the format of the ACFS had been identified by staff nurses. Following consultation with them the ACFS was modified based on their feedback. The pilot study was conducted to assess the ease of use of the modified version, to determine the acceptability of the new response format and to determine the length of time required to complete the symptom assessment portion of the MACSF measure. The symptom checklist portion of the MACFS asks patients to indicate the presence or absence of twelve symptoms, and if symptoms are present, to rate the severity of each symptom by indicating whether the symptom is improving, staying the same or deteriorating compared to their previous clinic visit.. The MACFS was pilot tested in a group of 10 patients currently undergoing cancer treatment at a tertiary cancer facility in Western Canada. Participants were asked to answer a brief 4-item questionnaire after completing the modified version of the ACFS.

Main Study: the Ambulatory Symptom Checklist Evaluation (ASCmE)

Design: This study used an observational cross-sectional design.

Sample and Setting

Patients were recruited from the Cross Cancer Institute, a tertiary cancer facility in Northern Alberta, between October 1 and December 15, 2008. Although MACFS is used throughout the ambulatory care department for patients on treatment and follow up for many diverse cancer diagnoses, the sample for the evaluation was limited to a smaller target group of patients receiving treatment for colorectal cancer. Inclusion criteria were: adult patients with a diagnosis of colorectal adenocarcinoma, (colon, rectum or rectosigmoid) with stage 3 or 4 cancer, on active treatment with chemotherapy, radiation therapy or combination therapy (chemotherapy and radiation therapy) and ability to read and write English. Exclusion criteria included the presence of uncontrolled pre-existing co-morbidities that interfere with quality of life, such as arthritis, heart disease or diabetes.

Sample size calculations were conducted based on the work of Dell, Holleran & Ramakrishnan (2002) as required for correlational analysis. A sample size of 88 participants was required for a moderate effect size of 0.3 with a significance level of 0.05 and a power of 80% (based on a normal distribution). Sample size calculation was conducted using the formula $n=1+2C(d/s)^2$, where n represents sample size, C is a constant calculated based on the level of significance and the desired power and $(d/s)^2$ represents the effect size (Dell et al. 2002). Accounting for potential participant mortality, the study enrolment was planned to continue until

100 patients were enrolled. Target population estimates were obtained through the Population Health Initiative at the Alberta Cancer Board, using the OncQT program. This program was developed to enable researchers to view aggregate data from the Cancer Registry and ICCN/ARIA Oncology Information systems. Developed in conjunction with the information management systems provider for the Cancer Board, the program allows the end user to specify inclusion criteria and then select variables related to the population that are of interest for review. Target population data was reviewed and this information indicated that within the identified population (colorectal cancer, stage 3 or 4), approximately 368 patients in Northern Alberta were reviewed at the Cross Cancer Institute in 2005 and would be eligible for the study, with current inclusion/exclusion criteria.

Data Collection

Recruitment

This study was submitted to the Health Research Ethics Committee at the University of Alberta and the Alberta Cancer Board Research Ethics Committee and commenced after approval was received from both boards. The issue of justice was addressed by including the study in the Pain and Symptom Study list, presented to all new patients, and by providing an information sheet about the study to all eligible patients currently on treatment.

Those who indicated an interest in learning about the study were asked to check off the study on the list and return it to the nursing desk or nurse in clinic. All individuals expressing an interest in the study were reviewed for eligibility, then contacted by the principle investigator (PI) and given an opportunity to ask questions. Patients recruited through the returning patient clinics were identified through chart review and through review of active treatment clinic schedules. Eligible patients were given an information sheet during the clinic, and advised about the study. If interested, patients returned the information sheet to the clinic nurse or clerk that day. Interested participants were then contacted by the PI and further explanation of the study was given. Patients who indicated interest in participating in the study completed a consent form (see Appendix B) and arrangements were made to commence data collection. Data collection was coordinated to occur either on the day of study enrolment, or when patients returned to the cancer clinic for assessment prior to the subsequent cycle of chemotherapy.

Measures

A number of measures were used in this study. These measures collected information about symptom incidence and quality of life experienced by study participants. Demographic data were collected using a demographic information sheet designed by the principle investigator for the purpose of this study (see Appendix C).

Modified-Ambulatory Care Flow Sheet (MACFS).

All participants were asked to complete the MACFS (see Appendix D). The MACFS was developed by the staff nurses at the Cross Cancer Institute and its psychometric properties have not been established.

The MACFS as a novel measure of symptoms has previously not had a scoring mechanism devised by which a total score could be determined. For the purpose of this study, a scoring manual was devised to allow calculation of a composite symptom burden score, and to provide a set of scoring rules to deal with missing data (Appendix H). The MACFS provides severity scores for individual symptoms and a composite symptom burden score may be calculated by adding the severity scores of all the symptoms and dividing by the number of symptoms. $\left(\sum \frac{symptompresence \times symptomseverity}{symptompresence}\right)$. The ability to calculate an overall score was intended to facilitate comparison with other measures used in the ASCmE study.

Rotterdam Symptom Checklist- Modified (RSCL-M).

The Rotterdam Symptom Checklist-Modified (RSCL-M) is a symptom assessment measure that has been shown to be a valid and reliable tool in a wide range of oncology populations within Europe (deHaes and Olschewski 1998) and the United States (Stein et al. 2003), and proven to be sensitive to differences in physical distress. Results from the validation trials of the RSC-M noted excellent reliability, with a Cronbach's alpha of α= 0.88 for the sample as a whole, and for the 10 distinct treatment groups in the validation study, a Cronbach's alpha ranging from 0.83 to 0.90. (Stein et al, 2003). The measure was equally reliable for men (α 0.870) and women (α=0.89). Tests of convergent and discriminant validity showed moderate correlations with physical functioning scales of two general quality of life measures (the MOS SF-36 physical functioning scale r = -0.59, and the MOS SF 36 General health scales r = -0.61) , while exhibiting a moderate negative correlation with measures of social support and spiritual well being (the Multidimensional Scale of Perceived Social Support r = -0.21, and the Functional Assessment of Chronic Illness Therapy –Spiritual Well-Being Scale r = -0.31), two scales that were anticipated to measure constructs conceptually different from physical distress.

The RSCL-M symptom assessment measure was chosen for several reasons. The modified version of this tool has recently undergone validity testing in a culture similar to the proposed MACFS evaluation (Stein et al. 2003). Of the symptom assessment tools reviewed, it contains the highest number of symptom domains also measured in the MACFS. To reduce participant burden, ideally the measurement tool being used to compare with the MACFS would contain the same symptom questions. The only two questions from the MACFS that are not included in the RSCL-M are pain and coping. The RSCL-M does not have a general pain item. It does include mouth pain, abdominal aches, and low back pain, but does not include pain with no

other descriptors. For this reason, additional measures were used for correlations of these two items. See Appendix E for the study version of the RSCL-M.

In preparing for the analysis of the study, no RSCL-M scoring manual was available (Stein 2003). The scoring of the RSC-M was completed using the methods of the original RSCL scoring manual (de Haes & Olschewski, 1998). The method of calculating the individual item scores, physical distress score and the overall total score was derived from this manual (See appendix H). The original RSCL-M was designed to examine physical symptoms, psychological distress and quality of life. The RSC-M does not contain any of the psychological symptoms or a quality of life rating. In order to compare the results of the RSCL-M, both the physical distress symptom subscale and the overall score of the RSCL-M were calculated. The physical distress score was calculated using the symptoms from the RSCL-M which were included in the original RSCL: lack of appetite, tiredness, sore muscles, lack of energy, low back pain, nausea, difficulty sleeping, headaches, vomiting, dizziness, decreased sexual interest, abdominal aches, constipation, diarrhea, heartburn, shivering, tingling hands or feet, sore mouth, loss of hair, burning sore eyes, shortness of breath and dry mouth. The items of the physical distress subscale and total RSC-M score were very strongly correlated ($\rho = 0.965$, $p < 0.0001$). Based on this degree of agreement between the subscale and the measure as a whole, the total RSCL-M score was used in the comparisons with the other "total score" measures of symptom experience.

Pain and Coping measures.

Selection of other measures for comparison to adequately validate pain and coping required consideration of both the burden of study participation, and the type of information necessary for analysis. Several measures of coping exist, including the Jalowiec Coping Scale, and the Ways of Coping Checklist (WCC), but these tools have 40- and 66-items respectively to assess thoughts and actions individuals use to cope with stress in everyday situations (Backer, Bakas, Bennett, & Pierce, 2000). The Jalowiec Coping Scale continues to undergo testing for validation and sensitivity for use in chronically ill populations. The Jalowiec Coping Scale was not used because of its length. A shorter measure of coping, the 20-item SECope (Johnson & Neilands, 2007), has been developed to examine the incidence of- and strategies of dealing with stress in patients undergoing antiretroviral treatment, but has not yet been studied in the oncology population. In order to minimize participant burden two numerical rating scales (NRS) were used to provide a second measure of these two concepts, without greatly increasing patient burden. The numerical rating scales in this study used a 100mm line with anchors at each end of the line to indicate the extreme end-point of each symptom, and 10 equally spaced numbers along the scale which patients were instructed to circle to indicate symptom intensity.

A series of numerical rating scales are used in the ESAS symptom measurement tool, an instrument currently used at the cancer centre as one component of the new patient history package, so the format of a numerical rating scale was familiar to study participants. The NRS measure for pain in this study was written in the same manner as in the ESAS tool, with patients asked to rate pain in the past week using a 10-point graded 100mm line, with zero representing" no pain", and 10 representing the "worst possible pain". Coping was assessed over the same time frame (in the past week) and with similar wording. Zero represented "no problems coping" and 10 represented "worst possible coping".

EORTC-QLQ C30.

The EORTC QLQ C-30 tool is a quality of life measure widely used in oncology (Osoba et al., 1997). The core module (C-30) version 2.0 has been assessed for reliability and validity (Role functioning scale Cronbach's α 0.88, overall global QOL scale Cronbach's α 0.92)(Osoba, et al., 1997). The EORTC-QLQ-C30 tool was chosen because the wording of question stems in the EORTC QLQ C-30 closely correspond with the wording of the ACFS symptoms, and it was anticipated that the symptom measures of the ACFS would represent the same types of concerns as in the EORTC QLQ C30. Scoring of the EORTC QLQ C-30 measure was completed using the statistical software syntax for SPSS, as provided by the tool developers.

Data Analysis

Mean and standard deviation was obtained for continuous data and median (range) and frequency were obtained for categorical data. Pearson's correlation was used to determine the correlation between two normally distributed continuous variables. If the assumption of normality was not satisfied, then Spearman's rho (ϱ) was used instead.

Normality assumption of the data variables were analyzed using the skewness and kurtosis measure. An examination of the age histogram indicated that a single outlier (age 20) was present which prevented the data from fitting a normal distribution curve (age > 2.5 SD from mean). Further examination of the global health score and ACFS composite burden scores revealed that the data failed to achieve a normal distribution within these categories, with levels of kurtosis and skewness that were outside the acceptable parameters (total skewness exceeded 2x standard error of skewness, total kurtosis exceeded 2x standard error of kurtosis). Cronbach's alpha was used to determine the internal consistency among different items of the MACFS questionnaire. All statistical analysis was conducted using statistical software, SPSS version 17. A p-value of 0.05 was considered significant for the statistical tests.

Correlations were used to compare the study data with the general oncology population data, using information collected both in the course of this study and using the OncQT program. Pearson's correlations were used to determine whether the patients in this study could be

considered representative of the target population. The correlation between the study participants with stage 3 cancers and the target population in the Alberta cancer registry was 0.700, ($p=0.005$). The correlation between the study participants with stage 4 cancers and the target population in the Alberta cancer registry was 0.912 ($p<0.0001$) or very strong. This indicates a high degree of similarity between the study participants and the target population, and suggests study findings would be applicable to other cancer patients with stage 3 or 4 colorectal cancer not involved in the study.

Choice of Statistical Procedures

The first research question examined the relationship between measures of individual symptoms. This question was answered by calculating the correlations among symptoms on the MACFS, the RSCL-M, the NRS measures of pain and coping and the EORTC QLQ C30.

Question two examined the relationship between symptoms as measured in each of the above tools, and HRQL. As a first step, the internal consistency of the MACFS was calculated using Cronbach's alpha (Salkind 2006). The calculation of Cronbach's alpha enables the researcher to examine the correlation among variables within the data set. An alpha score of zero indicates that the true score is not measured, and only error has been captured, whereas an alpha of 1.0 indicates that all items measure only the true score and there is no error (Garson 2009). Common accepted benchmarks have been established to describe acceptable levels of alpha. An alpha level of 0.60 is acceptable for experimental research, a level above 0.70 indicates that the internal consistency if the instrument is sufficient for use in routine practice, and the level of 0.80 is used as a bench mark or cut-off criteria in describing a good scale (Garson 2009). Correlations were then calculated between HRQL as measured on the EORTC QLQ C30 and the total symptom score measured on each of the symptom assessment tools (MACFS, the RSCL-M, the NRS measures of pain and coping, EORTC QLQ C30).

The third question, which arose during this study, concerned the relationship between specific symptoms and QOL. This was assessed using the specific symptoms and HRQL as measured by the EORTC QLQ C30 measure.

CHAPTER 4: RESULTS

Pilot Study Evaluation of MACFS

The pilot study portion of this project was designed to review the ease of use and functionality of the revised Ambulatory Care Flow sheet, and the time required for completion of the checklist portion. In this phase of the study, 10 patients were selected from the eligible patient population group for the study and asked to complete the ACFS symptom checklist, and to complete a short questionnaire. In the questionnaire patients were asked several questions about the symptom questionnaire: "Is there was anything we could to make questions more clear", "Are there any words you don't understand", "How long did it take to complete the form", and "Any further questions or comments". Participants in the pilot were chosen in a convenience sample from patients currently on treatment with chemotherapy for colorectal cancer within the tertiary cancer center ambulatory care department, being seen in clinic for assessment prior to chemotherapy. Patients were equally distributed between men and women, with 70% of participants diagnosed with colon cancer, and 30% rectal cancer (See Table 4.1.).

Pilot Study Results

Table 4.1. Results of Pilot Project Ambulatory Care Flowsheet

Gender			Diagnosis		
Male	5	50%	Colon	7	70%
Female	5	50%	adenocarcinoma		
			Rectal adenocarcinoma	3	30%
Treatment			Chemotherapy		
Adjuvant	2	20%	Single agent	3	30%
palliative	8	80%	combination	7	70%
Average length of time to complete forms			4.3 minutes (range 1-9 minutes)		

Patient Comments on the ACFS Pilot

"New format is so much better because it explains in more detail and gives a more accurate result of how the symptoms are"

"I like the addition of the ratings- it gives 5 options to rate symptoms."

"I think the new format would benefit the patient and be a great help for the doctors."

"Checklist is easier to deal with than having to explain problems. It can be hard to fill out rows of checkboxes."

"Printing could be larger on the checkboxes."

Questions about the form were open ended, and patients were encouraged to give suggestions and comments about the form to the primary researcher. Most patients stated they found the new format to be self explanatory, and easy to complete. The time required to complete

the form was not considered to be excessive compared to the current form. The overall review of the ASCF-modified was considered to be positive, and the next portion of the ASCmE study was commenced using the modified version. Although some comments were made with regards to the text size, current formatting restricts the available space for the patient symptom assessment on the ACFS sheet. Future revisions to this document should consider both print layout and font with a goal to increase readability of this section of the document.

Main Study Results

Sample Description of the ASCmE Study

The sample population (n=89) consisted of patients currently on treatment for colorectal cancer, undergoing treatment with chemotherapy or chemoradiation. A flow diagram showing the recruitment process is shown in Figure 4.1. Patient demographic data is presented in Tables 4.2 and 4.2. At completion of the study period 101 patients were enrolled in the Ambulatory Symptom Checklist evaluation study between October and December 2008. Potential study participants were identified in both new patient and current treatment groups through chart review, and were initially approached by clinic staff. If interested in further information, they were then contacted by the PI to discuss the study further. Of the patients who were enrolled in the study, a total of 5 patients withdrew from the study: 2 patients withdrew from the study after enrolment due to the perceived burden of completing the questionnaires, and three patients who after enrolment did not submit completed forms, and did not respond to further requests for further information regarding. Two patients submitted duplicate forms. A further 5 patients had significant quantities of missing data, as they failed to complete one or more of the study questionnaires, and the ACFS form (the main questionnaire for the study) was one of the questionnaires not completed. Thus analysis was completed on results from 89 patients. Further description of the study population is found in Tables 4.2 and 4.3.

Chart 4.1: Flow diagram: Patient enrollment in ASCmE study

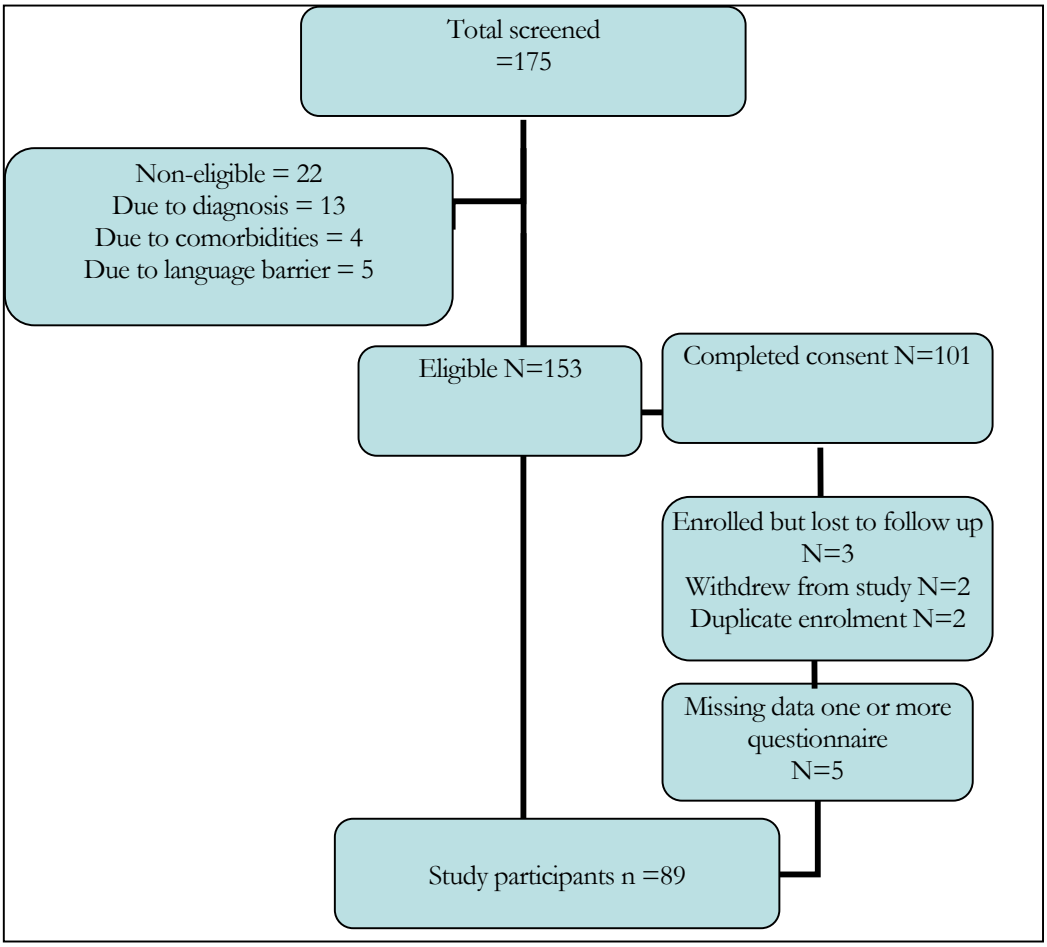

Table 4.2: Demographic summary for ASCmE Study participants

Age (years)	Mean (SD)	Median (range)
Mean(SD) and median(range) presented for continuous data	61.11 (10.2)	62 (20-82)
Gender	Frequency	(%)
Male	62	69.7
Female	27	30.3
Marital status		
Single	8	9
Common-law	8	9
Married	57	64
Widowed	9	10.1
Divorced/separated	7	7.9
Diagnosis		
Colon adenocarcinoma	60	67.4
Rectal adenocarcinoma	27	30.3
Rectosigmoid adenocarcinoma	2	2.2
Stage		
Stage 3 'curative'	35	39.3
Stage 4'palliative'	54	60.7
Treatment type		
Single agent:		
Capecitabine	30	33.7
Irinotecan	5	5.6
Combination:		
FOLFOX	16	18
CAPOX	5	5.6
FOLFIRI	15	16.9
FOLFIRI+BEVACIZUMAB	1	1.1
CHEMO/RT	17	19.1
Karnofsky performance status		
100	15	16.9
90	59	66.3
80	11	12.4
70	4	4.5

Question 1: Correlations of Symptom Measurement

The objective of this study was to examine the ability of the MACFS to validly assess a set of symptoms. We assessed this validity by comparing the MACFS to other validated assessment tools. The analysis related to question one examined correlations between the MACFS symptom scores and symptom scores on other measures. Correlations were also calculated between values of individual items and subscale scores. Using the scheme of Salkind (2006), correlations will be described as "weak or no relationship" 0-0.2, "weak" 0.21-0.40, "moderate" 0.41-0.60, "strong" 0.61-0.80, and 0.81-1 "very strong".

Relationships Among Measures of Pain

The correlations among the MACFS pain items, pain NRS scale and EORTC pain item and the EORTC pain subscale were moderate to strong, positive, and highly significant ($p<.0001$) as shown in Table 4.3. Interestingly, a higher correlation was noted when the analysis was completed using the MACFS pain presence score than with the pain severity score.

Table 4.3 Correlations among pain measures in the ASCmE Study

			MACFS presence pain	MACFS pain Severity score	NRS Pain	EORTC pain	EORTC Pain subscale
Spearman's rho	MACFS pain presence	Correlation Coefficient	1.000	.736**	.539**	.629**	.674**
		Sig. (2-tailed)	.	.000	.000	.000	.000
		N	89	89	89	88	89
	MACFS pain Severity score	Correlation Coefficient		1.000	.406**	.439**	.483**
		Sig. (2-tailed)		.	.000	.000	.000
		N		89	89	88	89
	NRS Pain	Correlation Coefficient			1.000	.773**	.830**
		Sig. (2-tailed)			.	.000	.000
		N			89	88	89
	EORTC pain	Correlation Coefficient				1.000	.963**
		Sig. (2-tailed)				.	.000
		N				88	88
	EORTC Pain subscale	Correlation Coefficient					1.000
		Sig. (2-tailed)					.
		N					89

**. Correlation is significant at the 0.01 level (2-tailed).

Relationships Among Measures of Coping

The correlations for coping were calculated using the MACFS coping items, the NRS coping score, and the EORTC subscales for social function and emotional function. The MACFS coping item was positively correlated with NRS coping (ρ =0.472 $p<0.0001$), but the correlation between the social functioning subscale of the EORTC measure and the MACFS coping item was both negative and non-significant (ρ =-0.147, p=0.061). This correlation is negative because the MACFS measure equates a higher score with higher symptom presence, whereas the EORTC measure uses a higher score to indicate a better quality of life, with less impairment (Fayers et al. 2001). The MACFS coping presence item had a moderate negative correlation (ρ =-0.409, $p<0.0001$) with EORTC emotional subscale (see Table 4.4). The correlations were consistently higher than when the same correlations were calculated using the coping severity item.

Table 4.4: Correlates of coping in the ASCmE study

			MACFS cope presence	MACFS cope score	NRS coping	EORTC Social Function	EORTC Emotional Function
Spearman's rho	MACFS cope presence	Correlation Coefficient	1.000	.570**	.472**	-.147	-.409**
		Sig. (2-tailed)	.	.000	.000	.169	.000
		N	89	89	89	89	89
	MACFS cope score	Correlation Coefficient		1.000	.363**	-.199	-.288**
		Sig. (2-tailed)		.	.000	.061	.006
		N		89	89	89	89
	NRS coping	Correlation Coefficient			1.000	-.407**	-.632**
		Sig. (2-tailed)			.	.000	.000
		N			89	89	89
	EORTC Social Function	Correlation Coefficient				1.000	.371**
		Sig. (2-tailed)				.	.000
		N				89	89
	EORTC Emotional Function	Correlation Coefficient					1.000
		Sig. (2-tailed)					.
		N					89

**. Correlation is significant at the 0.01 level (2-tailed).

Relationships Among Measures of Fatigue

The correlations for fatigue were calculated using the MACFS fatigue items, the EORTC fatigue items for tiredness and fatigue, and the RSCL-M items for lack of energy and tiredness. The correlations between the MACFS fatigue presence score and the EORTC and RSCL-M items were all positive, moderate and highly significant ($p<.0001$) (see Table

4.5). Once again these correlations were higher than when the same calculations were conducted using the MACFS fatigue severity score, except for the correlation between the MACFS fatigue score and the RSCL-M tiredness score.

Table 4.5 Correlates of Fatigue in the ASCmE Study

			MACFS fatigue presence	MACFS Fatigue severity score	RSCL-M lack of energy	RSCL-M tiredness	EORTC tired	EORTC Fatigue
Spearman's rho	MACFS fatigue presence	Correlation Coefficient	1.000	.693**	.440**	.444**	.454**	.483**
		Sig. (2-tailed)	.	.000	.000	.000	.000	.000
		N	89	89	89	89	87	89
	MACFS fatigue severity score	Correlation Coefficient		1.000	.430**	.495**	.427**	.421**
		Sig. (2-tailed)		.	.000	.000	.000	.000
		N		89	89	89	87	89
	RSCL-M lack of energy	Correlation Coefficient			1.000	.774**	.681**	.716**
		Sig. (2-tailed)			.	.000	.000	.000
		N			89	89	87	89
	RSCL-M tiredness	Correlation Coefficient				1.000	.728**	.715**
		Sig. (2-tailed)				.	.000	.000
		N				89	87	89
	EORTC tired	Correlation Coefficient					1.000	.853**
		Sig. (2-tailed)					.	.000
		N					87	87
	EORTC Fatigue	Correlation Coefficient						1.000
		Sig. (2-tailed)						.
		N						89

**. Correlation is significant at the 0.01 level (2-tailed).

Relationships Among Measures of Sleep

The correlations for sleep were conducted using the MACFS sleep items and sleep items on the RSCL-M and the EORTC QLQ C30. A positive correlation was noted between the MACFS difficulty sleeping symptom score and both the RSCL-M difficulty sleeping item (ϱ =0.650, p<0.0001) and the EORTC trouble sleeping item (ϱ =0.647, p<0.0001). Stronger correlations were noted to exist between the MACFS individual item for difficulty sleeping with

each of the comparison instruments, than the MACFS difficulty sleeping score (which measures both presence of an item and relative severity).

Table 4.6 Correlates of Difficulty sleeping in the ASCmE Study.

			MACFS difficulty sleeping	MACFS sleep Severity score	RSCL-M difficulty sleeping	EORTC trouble sleeping
Spearman's rho	MACFS difficulty sleeping	Correlation Coefficient	1.000	.738**	.794**	.826**
		Sig. (2-tailed)	.	.000	.000	.000
		N	89	89	89	89
	MACFS sleep severity score	Correlation Coefficient		1.000	.650**	.647**
		Sig. (2-tailed)		.	.000	.000
		N		89	89	89
	RSCL-M difficulty sleeping	Correlation Coefficient			1.000	.929**
		Sig. (2-tailed)			.	.000
		N			89	89
	EORTC trouble sleeping	Correlation Coefficient				1.000
		Sig. (2-tailed)				.
		N				89

**. Correlation is significant at the 0.01 level (2-tailed).

Relationships Among Measures of Shortness of Breath

The correlations for shortness of breath were conducted using the MACFS shortness of breath items, and the shortness of breath items in the RSCL-M and the EORTC QLQ C-30. A positive correlation was noted between the MACFS shortness of breath score and both the RSCL-M shortness of breath score (ϱ =0.562, p<0.0001) and the EORTC individual item short of breath (ϱ =0.603, p<0.0001). Once again, this correlation is higher than when the correlation was conducted using the shortness of breath severity score.

Table 4.7 Correlates of Shortness of Breath in the ASCmE Study.

			MACFS short of breath presence	MACFS short of breath severity score	RSCL-M shortness of breath	EORTC short of breath	EORTC Dyspnea
Spearman's rho	MACFS short of breath presence	Correlation Coefficient	1.000	.806**	.579**	.685**	.685**
		Sig. (2-tailed)	.	.000	.000	.000	.000
		N	89	89	89	89	89
	MACFS short of breath severity score	Correlation Coefficient		1.000	.562**	.603**	.603**
		Sig. (2-tailed)		.	.000	.000	.000
		N		89	89	89	89
	RSCL-M shortness of breath	Correlation Coefficient			1.000	.701**	.701**
		Sig. (2-tailed)			.	.000	.000
		N			89	89	89
	EORTC short of breath	Correlation Coefficient				1.000	1.000**
		Sig. (2-tailed)				.	.
		N				89	89
	EORTC Dyspnea	Correlation Coefficient				1.000**	1.000
		Sig. (2-tailed)				.	.
		N				89	89

**. Correlation is significant at the 0.01 level (2-tailed).

Relationship Between Measures of Skin Irritation

The correlations for skin irritation were conducted using the MACFS skin irritation items and the skin irritation items in the RSCL-M. A positive and statistically significant correlation was noted between the MACFS skin irritation score and the RSC skin irritation item (ρ =0.571, p<0.0001). This data is presented in Table 4.8. The correlation between the MACFS skin irritation score and the RSCL-M skin irritation score was higher than the correlation of the MACFS skin irritation severity score and the RSCL-M skin irritation item.

Table 4.8 Correlates of skin irritation in the ASCmE study.

		MACFS skin presence	MACFS skin severity score	RSCL-M skin irritation
MACFS skin presence	Pearson Correlation	1	.787**	.619**
	Sig. (2-tailed)		.000	.000
	N	89	89	89
MACFS skin severity score	Pearson Correlation		1	.571**
	Sig. (2-tailed)			.000
	N		89	89
RSCL-M skin irritation	Pearson Correlation			1
	Sig. (2-tailed)			
	N			89

**. Correlation is significant at the 0.01 level (2-tailed).

Relationships Among Measures of Mouth Sores

The correlations for mouth sores were conducted using the MACFS mouth sore items and the mouth sore items in the RSCL-M. The positive correlation was noted between the ACFS mouth sores score and the RSCL-M mouth sore item (ρ =0.276, p=0.009). Once again the correlation of the mouth sore score was higher when assessing the relationship between the MACFS mouth sore score and the RSCL-M than when comparing the MACFS mouth sore severity score with the RSCL-M item. This data is presented in Table 4.9.

Table 4.9 Correlates of mouth sore measurement in the ASCmE Study.

			MACFS mouth sore presence	MACFS mouth sore severity score	RSCL-M sore mouth
Spearman's rho	MACFS mouth sore presence	Correlation Coefficient	1.000	.517**	.517**
		Sig. (2-tailed)	.	.000	.000
		N	89	89	89
	MACFS mouth sore severity score	Correlation Coefficient		1.000	.276**
		Sig. (2-tailed)		.	.009
		N		89	89
	RSCL-M sore mouth	Correlation Coefficient			1.000
		Sig. (2-tailed)			.
		N			89

**. Correlation is significant at the 0.01 level (2-tailed).

Relationships Between Measures of Lack of Appetite

The correlations for lack of appetite were conducted using the MACFS lack of appetite items and the lack of appetite items from the RSCL-M and EORTC QLQ C-30. A positive correlation was noted between the MACFS lack of appetite score and both the RSCL-M lack of appetite score (ϱ =0.471, p<0.0001) and the EORTC QLQ C-30 score (ϱ =0.419, p<0 .0001). These correlations were stronger when calculated using the symptom presence scores, than when using the symptom severity score. This data is presented in Table 4.10.

Table 4.10 Correlates of lack of appetite measures in the ASCmE Study.

			MACFS lack of appetite	MACFS appetite severity score	RSCL-M lack of appetite	EORTC lacked appetite
Spearman's rho	MACFS lack of appetite	Correlation Coefficient	1.000	.663**	.660**	.493**
		Sig. (2-tailed)	.	.000	.000	.000
		N	89	89	89	89
	MACFS appetite score	Correlation Coefficient		1.000	.472**	.419**
		Sig. (2-tailed)		.	.000	.000
		N		89	89	89
	RSCL-M lack of appetite	Correlation Coefficient			1.000	.836**
		Sig. (2-tailed)			.	.000
		N			89	89
	EORTC lacked appetite	Correlation Coefficient				1.000
		Sig. (2-tailed)				.
		N				89

**. Correlation is significant at the 0.01 level (2-tailed).

Relationships Among Measures of Nausea and Vomiting

The correlations for nausea and vomiting were conducted using nausea and vomiting items form the MACFS and EORTC QLQ C-30. The MACFS severity score was moderately correlated with the EORTC QLQ C-30 item (ϱ =0.548, p<0.0001). This data is presented in Table 4.11. The MACFS symptom presence score had a strong correlation with the EORTC QLQ C30 nausea /vomiting item.

Table 4.11 Correlates of measurement of nausea and vomiting in the ASCmE Study.

			MACFS N/V presence	MACFS NV severity score	EORTC Nausea / vomiting
Spearman's rho	MACFS N/V presence	Correlation Coefficient	1.000	.716**	.721**
		Sig. (2-tailed)	.	.000	.000
		N	89	89	89
	MACFS NV severity score	Correlation Coefficient		1.000	.548**
		Sig. (2-tailed)		.	.000
		N		89	89
	EORTC Nausea / vomiting	Correlation Coefficient			1.000
		Sig. (2-tailed)			.
		N			89

**. Correlation is significant at the 0.01 level (2-tailed).

Relationship Between Measures of Difficulty with Urination

The correlation of difficulty with urination was assessed by comparing the MACFS items, and those of the RSCL-M. The MACFS severity score correlation was slightly stronger with the RSCL-M symptom item, however, the relationship of both the MACFS presence and severity score items with the RSCL-M were weak and non-significant.

Table 4.12 Correlates of urinary dysfunction in the ASCmE Study.

			MACFS GU presence	MACFS GU severity score	RSCL-M problems controlling your urine
Spearman's rho	MACFS GU symptom presence	Correlation Coefficient	1.000	.595**	.163
		Sig. (2-tailed)	.	.000	.127
		N	89	89	89
	MACFS GU severity score	Correlation Coefficient		1.000	.179
		Sig. (2-tailed)		.	.093
		N		89	89
	RSC problems controlling your urine	Correlation Coefficient			1.000
		Sig. (2-tailed)			.
		N			89

**. Correlation is significant at the 0.01 level (2-tailed).

Relationship of Measures of Sexual Dysfunction

Sexual function was a construct only assessed on the MACFS and RSCL-M tools. A positive moderate correlation was noted between both the individual items (ϱ =0.590, p<0.0001), and the ACSF sexual function score and the RSC item (ϱ =0.503, p<0.0001). The results of the correlation are presented in Table 4.13. The MACFS sexual dysfunction was more closely correlated with the RSCL-M measure of decreased sexual interest than the MACFS sexual dysfunction severity score.

Table 4.13 Correlates of Sexual dysfunction in the ASCmE study.

			MACFS sexual dysfunction presence	MACFS sexual dysfunction severity score	RSCL-M decreased sexual interest
Spearman's rho	MACFS sex dysfunction symptom presence	Correlation Coefficient	1.000	.673**	.590**
		Sig. (2-tailed)	.	.000	.000
		N	89	89	89
	MACFS sexual dysfunction severity score	Correlation Coefficient		1.000	.503**
		Sig. (2-tailed)		.	.000
		N		89	89
	RSCL-M decreased sexual interest	Correlation Coefficient			1.000
		Sig. (2-tailed)			.
		N			89

**. Correlation is significant at the 0.01 level (2-tailed).

Correlations Between Total Measures of Symptom Score and RSCL-M Total Score

The correlation of the MACFS composite symptom burden score and Rotterdam total scale score was noted to be weak (ϱ =0.183) and was not statistically significant. A score comprised by adding the number of symptoms was then constructed. The correlation of the MACFS total number of symptoms score and the RSCL-M total score was then calculated, and found to have a very strong positive correlation with the total RSCL-M score (ϱ=0.801, p<0.0001) (see Table 4.14).

In summary, the MACFS is a reasonably valid measure of pain, difficulty sleeping, shortness of breath, skin irritation, appetite, and nausea/vomiting, but not a validated measure of coping, fatigue, mouth sores, difficulty with urination, or sexual dysfunction.

Question 2: Correlations Between Symptom Measures and HRQL

The objective underpinning question 2 was to determine whether a total symptom score based on the MACFS could be considered as a valid indicator of HRQL. In order to do this, I examined the relationship between the total symptom scores on each of the assessment tools and HRQL. I began by examining the internal consistency of the MACFS measure, using symptom severity scores. Cronbach's alpha was noted to be 0.845. This measure of internal consistency indicates that the items in the MACFS measure correlate highly with each other. As a secondary check of the reliability of the MACFS, the internal consistency was calculated using the symptom presence scores and the Cronbach's alpha was 0.713. These results indicate that the measure is adequate for research purposes.

The second component of question 2 addressed the relationship between total symptom scores and HRQL. As a first step a correlation matrix comprised of the MACFS composite symptom burden score, the MACFS number of symptoms score, the RSCL-M total scale score and the global health status as measured by the EORTC QLQ C30 questionnaire was examined. The MACFS number of symptoms was found to be strongly correlated with the RSCL-M total score (ϱ =0 .801, $p<0.0001$), while still demonstrating an improved yet still weak correlation with the results of the EORTC global health rating (ϱ =-0.347, $p=0.001$), compared to the MACFS composite burden score and EORTC Global health score correlation (ϱ =-0.240, $p=0.038$).

The correlation between the ACFS composite symptom burden score and the EORTC Global health status score was statistically significant (ϱ=-0.240, $p=0.038$), but had a weak and negative correlation. The correlations between the MACFS composite burden score and the MACFS total number of symptoms score was not significant. Similarly the correlation between the MACFS composite burden score and the RSCL-M total scale score was not significant.

Table 4.14 Correlates of symptom experience and global health status in the ASCmE Study.

			MACFS composite symptom burden	MACFS number of symptoms	RSCL-M total scale score	Global health status/QOL
Spearman's rho (ρ)	MACFS composite symptom burden	Correlation Coefficient	1.000	.044	.183	-.240*
		Sig. (2-tailed)	.	.711	.117	.038
		N	75	75	75	75
	MACFS number of symptoms	Correlation Coefficient		1.000	.801**	-.347**
		Sig. (2-tailed)		.	.000	.001
		N		89	89	89
	RSCL-M total scale score	Correlation Coefficient			1.000	-.351**
		Sig. (2-tailed)			.	.001
		N			89	89
	Global health status/QOL	Correlation Coefficient				1.000
		Sig. (2-tailed)				.
		N				89

*. Correlation is significant at the 0.05 level (2-tailed).

**. Correlation is significant at the 0.01 level (2-tailed).

The inverse relationship between the MACFS composite burden scale (where a higher score indicates a higher level of impairment) and the EORTC global health status (where a higher number presents a higher level of quality of life) was an anticipated finding. After reviewing the

results of the correlations using the MACFS composite burden score, it was noted that although correlations were present, these correlations were not as strong as had been anticipated.

In summary, the work related to this question suggests that while number of symptoms on the MACFS is significantly correlated with HRQL, the correlation is weak.

Question 3: The Individual Symptom and HRQL Relationship

This question was not included in the original proposal but was added following further consideration of the work of Hassan et al. (2006) who studied HRQL outcomes in patients with advanced colorectal malignancies. They suggested, based on clinical observation that key symptoms [bowel function, fatigue, anxiety and spiritual well being] were indicators of HRQL in patients with colorectal cancer. My study provided the opportunity to examine these potential relationships. Although no measures of spiritual well being or anxiety were collected as part of this study, patient reports of fatigue, bowel function and HRQL were collected on the EORTC QLQ C-30; these data were used to calculate correlations between fatigue, bowel function and quality of

life. I then explored the correlations between other symptoms and HRQL as measured in the EORTC QLQ C-30. The most significantly correlated symptom was insomnia (ρ =-0.336, p=0.001), which was moderately negatively correlated with HRQL. All of the other significant correlations were weak [fatigue (ρ=-0.288, p=0.006), pain (ρ =-0.250, p=0.018) and nausea /vomiting (ρ =-0.213, p=0.045)].

Table 4.15 Correlations of individual symptoms and HRQL

			Fatigue	N/V	Pain	Dyspnea	Insomnia	Appetite loss	Consti-pation	Diarrhea	Global health status/QOL
Spearman's rho	Fatigue	Correlation Coefficient	1.000	.102	.295**	.253*	.302**	.143	.084	.243*	-.288**
		Sig. (2-tailed)	.	.340	.005	.017	.004	.181	.431	.023	.006
		N	89	89	89	89	89	89	89	88	89
	N/V	Correlation Coefficient		1.000	.122	.041	.167	.184	.122	.178	-.213*
		Sig. (2-tailed)		.	.253	.702	.117	.084	.253	.097	.045
		N		89	89	89	89	89	89	88	89
	Pain	Correlation Coefficient			1.000	.271*	.222*	.126	.394**	.082	-.250*
		Sig. (2-tailed)			.	.010	.036	.238	.000	.447	.018
		N			89	89	89	89	89	88	89
	Dyspnea	Correlation Coefficient				1.000	-.016	.026	.160	.115	-.090
		Sig. (2-tailed)				.	.885	.810	.134	.284	.400
		N				89	89	89	89	88	89
	Insomnia	Correlation Coefficient					1.000	-.044	.293**	.250*	-.336**
		Sig. (2-tailed)					.	.682	.005	.019	.001
		N					89	89	89	88	89
	Appetite loss	Correlation Coefficient						1.000	.176	.190	-.097
		Sig. (2-tailed)						.	.099	.076	.366
		N						89	89	88	89
	Constipation	Correlation Coefficient							1.000	.099	-.177
		Sig. (2-tailed)							.	.360	.097
		N							89	88	89
	Diarrhea	Correlation Coefficient								1.000	-.114
		Sig. (2-tailed)								.	.289
		N								88	88
	Global health status/ QOL	Correlation Coefficient									1.000
		N									89

CHAPTER 5: DISCUSSION

The discussion of results from the ASCmE study will be broken down in to four main points: the review of missing data, the selection of measures and related issues, the measurement of severity of symptoms and the use of total symptom scores as opposed to individual symptom scores as correlates of QOL.

Missing Data

At completion of the study period 101 patients were enrolled in the Ambulatory Symptom Checklist evaluation study. Of these patients, 3 did not submit completed forms, 2 patients withdrew from the study due to the perceived burden of completion of forms and 2 patients submitted duplicate forms. A further 5 patients had significant quantities of missing data, as they failed to complete one or more of the study questionnaires, and the MACFS form (the main questionnaire for the study) was one of the questionnaires not completed. Thus analysis was completed on results from 89 patients. Although the quantity of missing and incomplete questionnaires was concerning, the study was designed at a level requiring complete data from 88 patients, and this benchmark was achieved.

In considering the missing or incomplete questionnaires which were excluded from the study (5/94 or 5.3%), several possible contributing factors were reviewed. One possible reason so many of the MACFS forms were not completed may have been that many patients enrolled in the study and completed the forms on the same day as a clinic appointment. Patients being assessed in the clinic complete the MACFS and may have omitted the study version as they had completed one form for clinic. Patients reviewed complete study packages and questionnaires with the researcher prior to enrolment in the study and returned completed forms to the researcher in a sealed envelope. Patients were instructed to complete all forms in the study package and to return the package to the researcher; however no checklist for study completion was given to patients.

The completed questionnaires (n=89) were then reviewed for missing data prior to analysis. To establish the level of missing data acceptable by other tool developers, both the FACIT and EORTC scoring manuals were reviewed to examine the levels of acceptable missing data for analysis of quality of life measures. Both of these organizations have established that for analysis of questionnaires, 80% of individual items was the required level, below which analysis could not be completed with accuracy (Fayers, Aaronson, Bjordal et al. 2001, Cella et al., 1993). Moinpour et al. (2000) in the review of QOL studies with missing data discussed the level of 70% questionnaire submission rate as the lowest acceptable. If individual subscales were missing 20% or less data, subscales could be calculated using mean substitution for missing values. The FACIT QOL measure developers (Cella et al., 1993) suggest a prorating method for calculating subscales if up to 50% of the data is available, but requires that overall 80% response rate is required for analysis. Based on this standard, the level of acceptable missing data for this study was set at no greater than 20% missing data.

Missing data was assessed through SPSS 17, with each tool measured independently. The EORTC-QLQ C30 measure had the best response rate with 6 missing items throughout the completed questionnaires, representing 0.22% of the data (6/2670 items). The RSCL-M questionnaire had 7/2670 missing items or 0.22% missing data. The MACFS data was assessed for symptom presence and rating of symptom. Symptom presence was well responded with 17 missing responses, or 1.6% missing (17/1068). The greatest numbers of missing responses in the MACSF questionnaire were those in response to questions about fatigue (7.9%) and diarrhea/constipation (5.6%): other symptoms ranged between 2.2 and 4.5% missing data. No single item had greater than 7.9% missing data (See Appendix I for missing data in the MACSF questionnaire). The cumulative missing data was also calculated. Total missing data for the cumulative measure was calculated using SPSS 17 as comprising 4.1% (44/1068 items), which was within the pre-established acceptable limit for missing data. Of the 89 sets of questionnaires, 13 questionnaires (14.7%) were missing one item response, and 11 questionnaires (12.5%) were missing 2 items. Of all the 89 sets of participant data that underwent analysis, no questionnaire series was missing 3 or more items.

When looking at the specifics of the missing data, 9 of the 13 single missing items were on the MACFS questionnaire. The complexity of response options on the MACFS may have increased the difficulty of choosing the correct response. In the questionnaire patients were asked to note the presence or absence of symptoms, and rate the symptom for severity. Seven of the 9 questionnaires with missing items had noted the presence of a symptom but did not rate it. Choosing to rate the symptom as "not present" does not require a further rating of the symptom, however, scoring the symptom as "present" does require a severity rating. Indicating that the symptom was new was not an option, and patients may have experienced difficulty in determining how to rate a new symptom. In addition, the use of two checkboxes to capture information about symptoms may have created confusion for many study participants. For patients who rated symptom severity, but did not indicate symptom presence, a substitution rule was generated. Prior to the use of substitution rules for symptom presence based on patent rating of severity, 19 patients (21%) rated symptom severity , but did not indicate the symptom presence (for 74 items). No pattern of missingness was observed as patients would indicate both symptom and severity for one symptom and on other items would not indicate either one or both of these two indicators.

The number of missing individual items and questionnaires was unanticipated, and alternative theories are considered for the cause. Some of the study participants wrote "not applicable" in the border of the checklist adjacent to specific questions. Specifically, several patients wrote "too old" on the questionnaire adjacent to the questions about sexual function, and left these responses blank. Between the MACFS and RSCL-M, 5 patients left the questions about sexual function or interest blank on both instruments. The questions about sexual function or sexual interest had the most missing data

on one topic throughout the study (7 missing items, across 5 study participants. An alternative wording or an alternative response option (not applicable, or prefer not to respond) might have eliminated some of the missing data related to the questions about sexual function or sexuality.

Understanding how Patient's Interpret and Complete Forms

One challenge identified in conducting this research study was in the accuracy of the questionnaire completion. The study participants reviewed each of the study forms with the PI prior to completion, yet significant numbers of patients (25/89 or 28%) had some missing data in completion of the MACFS form. Contributing factors may include text size of the forms, or issues of English fluency. During the pilot study, participants identified that the text size of the questions and response boxes could be larger. For the purpose of the study text size was required at the current formatting used to fit the questions on a single page. All patients participating in the study indicated that they were comfortable to complete the forms in English, no patient identified that written literacy was an issue at any point during the study.

Although numerous instruments have been developed to assess the readability of cancer information (Friedman & Hoffman-Goetz 2006), no assessment has been made of measures of this nature, which consist of a single list of symptoms. The educational level of study participants was not captured, however Beckman & Lueger (1997) suggest that using a measure with an eighth or ninth grade education level can be useful. The authors cautioned against the use of self reported measures with clients who have had limited reading ability or disrupted education. They further suggested the impact of reading competence may be moderated by motivation, interest in completing the form, and time permitted. Other researchers interested in the relationship between functional literacy and health outcomes have hypothesized that there may be a relationship between health literacy and disease state control, recommending further study of this relationship on patient outcomes (Keller, Wright & Pace, 2008). Doak, Doak and Pace (1996), in reviewing the factors that adversely impact readability point out that numerous factors beyond readability levels should be considered. The format of the measure, lack of explanations, and too much information can also impair comprehension of patient materials. The authors emphasized that English language literacy and health literacy are not the same issue: the ability to recognize words on the form does not indicate comprehension of the word in that context (Doak, Doak and Pace, 1996).

In considering the factors that may limit the patient comprehension of the MACFS measure, several of the above issues have been identified. The space allocated on the current forms is small (restricted to 30 % of one page), and current page format limits the font size, with dense text distribution. The use of a series of box columns for responses to symptom questions is of necessity small to fit in the available space. Increased size of boxes or the addition of separation lines between symptoms might improve the item readability and improve the response for individual items.

Selection of Measures and Related Issues

The measures used in this study were selected for their ability to accurately record patient data about symptoms (MACFS, RSCL-M and NRS scales) and HRQL (EORTC QLQ C-30). Although the symptom measures did measure symptoms differently the measures were very strongly correlated. The creation of a composite symptom burden score based on the MACFS tool was intended to create an over-all score that reflected symptom incidence and severity. I thought that if the MACFS composite burden score correlated well with the RSCL-M, it could be used by providers to identify patients at increased risk of decreased HRQL. This score, however, did not correlate with the RSCL-M measure, indicating that further reflection on the use of the tool was warranted.

The MACFS tool was originally developed to facilitate the communication of symptoms and patient information from the patient to the health care team. Nurses who use the tool on a daily basis state that what they need from the symptom portion of the measure was an understanding of the patient experience. The nurses wanted to know whether the symptoms were present and whether they were adequately managed. (S. Bell, outpatient nurse coordinator, Cross Cancer Institute, personal communication, March 15, 2009).

An evaluation of the MACFS using the criteria developed by Kirkova for symptom assessment tools (P. 11) and the results of the study show that the MACFS is a reasonably reliable and valid tool for assessing individual symptoms. Although the composite burden score was weakly correlated with HRQL, the total number of symptoms was moderately correlated with HRQL. This is good news for busy nurses in ambulatory care settings. The complex calculations required to calculate a composite burden score are unnecessary. They may infer risk for decreased HRQL as the number of symptoms on the MACFS goes up.

The lower than anticipated correlations between the MACFS and other measures may have resulted not from the choice of comparator (RSCL-M), but the way the MACFS measures symptoms. The choice to use a response option which assesses not only the presence of symptoms, but the severity is a novel concept, and perhaps more challenging to analyze. The comparison measures (the RSCL-M and the EORTC QLQ C30) both ask about questions in a very similar way and with identical response options. The MACFS collects information through a series of questions which require patients to note symptom presence and severity. In addition the MACFS asks patients to indicate whether a symptom is worse, about the same or better it was at their previous visit. The indication of symptom presence is of value in determining potentially necessary interventions, while noting severity of the symptom allows the clinician to have a more complete understanding of the experience, and whether symptoms are being appropriately managed. Patients who rate the symptom severity as increasing can be tagged for interventions, while those who demonstrate improvements in severity can be further monitored and provided with ongoing support in the management of symptoms. The capacity for patients to rate the

symptoms as improving or deteriorating also allows the patient to visually see the pattern of symptom incidence, and to learn to recognize symptom stability or change with different interventions. The ability to obtain this type of information is clinically useful when communicating with patients and other healthcare providers, although it is difficult to manage statistically, it is of value to the therapeutic relationship.

The modified RSCL-M was scored using the procedures developed for the original measure, since no scoring manual for the modified version was available. This may have affected the validity of the scores obtained.

All patients were accrued and interviewed by the same researcher, providing consistency in the presentation of the material. The study was conducted using a single tumour group population, and within a short time period. The single data collection time allows for a snapshot view of symptom experience, but does not allow analysis of how patients use the questionnaire over time, or to determine if familiarity with the questionnaire allows patients to become more confident in rating symptom severity. The format of the questionnaire was noted by several patients to be difficult to read due to text size, and due to size limitations of the original document, it may be difficult to make the print format larger. If a larger font and print area could be used, some of the technical difficulties patients reported with the use and completion of the form could have been minimized. The sample size of the study (n=89) was relatively small, and conducted in a relatively homogenous population: a larger size study, in a broader range of patients with different cancers would provide data that would be more generalizable to a greater population of cancer patients.

Concept Definition

One of the key issues in measure development is the operationalization of variables. Terwee et al. (2002) , in assessing guidelines for assessing quality of life instruments suggest that assessing responsiveness of instruments is best accomplished when the concepts of interest are clearly specified, when the tools for measurement are validated, the measure(s) can actually measure these concepts, and when the interpretation of results is well understood. For the ASCmE study, the 12 concepts measured and evaluated were symptoms previously identified by clinic staff and patients as difficult to control during treatment. The symptoms measured on the MACFS are not defined; rather, it is assumed that the terms are self explanatory. For some of the items (lack of appetite, nausea/vomiting, diarrhea/constipation) the symptoms are very objective and clearly understood. Other items are, more subjective (coping, sexual function).

The lack of a clear definition for sexual function or sexuality changes on the MACFS may have contributed to difficulty in choosing appropriate response. For participants who were elderly, widowed or without a partner, the discussion of sexual function or sexuality may have been inappropriate from their perspective. Others may have felt that this aspect of their life is a private matter which is unrelated

to cancer treatment, or which they declined to discuss. Gujral et al. (2007) commented on the amount of missing data in the assessment of sexual function or sexual interest of patients undergoing colorectal cancer treatment, and noted that the response rate to these questions was generally lower in female participants (82%) than in males, and more female participants reported being upset by the question (78%) than male participants (3%). Health care professionals need to respect the wishes of patients, but still provide education and support to patients who wish to address this area.

Quality of Life

The purpose of this study was to examine the relationship between symptoms and quality of life. In reviewing the literature on quality of life, it can be seen that the concept of quality of life continues to mean different things to different people. For the purposes of exploring variations in the conceptualization of quality of life, I used the conceptual framework of Moons et al. (2006), who stated that quality of life was best defined as life satisfaction. As the analysis was conducted, it became apparent that a comparison of findings to those studies in which other tools were used was difficult because the developers of the EORTC measure never specified how they conceptualized quality of life. The concept of quality of life in the EORTC QLQ C30 was one in which quality of life is essentially defined as normal functional status (Bruley, 1999). This idea is supported by Boehmer & Luszczynska (2006) who in a study of individuals with colorectal cancer used confirmatory factor analysis to show that the items assessing various types of functional status (physical, role, cognitive, social and emotional) in the EORTC QLQ C30 measured the level of HRQL.

It is important to distinguish between health status and quality of life. This distinction has been emphasized by many authors (Aaronson et al 1991, 1993, Moons et al. 2006, Smith, Avis & Assman 1999). Smith, Avis and Assman (1999) conducted a meta-analysis that examined the differences between quality of life and health status. In this review of 12 studies examining the differences between healthy status and QOL, both items were seen to represent the impact of physical and mental well-being. Health status was seen to be more reflective of physical function, and QOL was seen as placing a greater emphasis on mental well-being, although both of these items represented a combination of physical and mental function. Although authors distinguish between health status and quality of life, in this study a high correlation was noted between health status and quality of life as assessed in the EORTC QLQ C30 data ($\alpha = 0.709$, $p < 0.0001$).

In an effort to better understand the relationship between health status and quality of life as separate items, further analysis was conducted to examine how these two items differed in their relationship with individual symptoms. Insomnia, fatigue and pain were statistically significantly correlated with both health status and QOL, while nausea and vomiting was statistically significant only with quality of life. Correlations were all weak ($\varrho = -0.0216$ to -0.292), with the exception being the relationship between insomnia and quality of life which was moderately correlated ($\varrho =$ -

0.309, p=0.003). These findings indicate that once again, researchers need to think carefully about what is being measured, and how each concept may be interpreted differently by both care providers, and recipients. Quality of life is about more than symptoms, and using a mechanistic approach prevents a full understanding of quality of life from the patient perspective (Fitzsimmons et al 1999).

In this study, once more the complex nature of "quality of life" has been emphasized. Although I found a relationship between symptoms and quality of life, it was not as strong as expected. Several possible factors which may influence the nature of the relationship include the processes of coping and adaptation (Fitzsimmons et al., 1999; Lazarus & Folkman 1984), the understanding of exactly how quality of life is defined (Moons et al, 2006; Bruley, 1999), and the communication of these ideas with care providers and patients. Recognizing that quality of life is a more abstract and fluid construct makes it challenging to assess and intervene. Other aspects of quality of life exist which may not be assessed on a particular questionnaire, but which never the less, have great impact. Based on clinical observations, Hassan et al. (2006) stated that spirituality was of great importance in the quality of life of advanced colorectal cancer patients.

For example, Bruley (1999) noted that spirituality has been identified by a number of researchers as an important element of quality of life, and that while it is included in other HRQL measures such as the Quality of Life Index, the McGill Quality of Life Questionnaire and the Missoula-Vitas Quality of Life Index, it is not included in the EORTC QLQ C30.

The understanding of health status and quality of life as two separate concerns is challenged by the findings of this study. The results showed that, in this population, patient perceptions of their health were strongly correlated to how they perceived quality of life, although the relationships between these two concepts were not as strong as one might expect.

Unidirectional vs. Bidirectional Measures of Severity

The results of correlations with MACFS severity items with other measures reflect the differences in the structure of the response options. The response options for the MACFS tool are quite unlike those used in other measures, allowing patients to indicate the presence of a symptom, and then rate the severity by reflecting improvement, no change or deterioration since the last assessment. The ability to rate severity of a symptom in this way is not included in the other measures used, and while practical, may be difficult to analyze. The higher correlation between the scores for MACFS for symptom presence scores and the other individual symptom measures, when compared to the MACFS symptom severity scores likely reflects this difference in the structure of the response options.

Total Symptom Scores or Individual Symptoms

This study has added to our understanding of the relationship between symptoms as measured in the MACFS and quality of life. It was thought that the MACFS composite symptom score would be helpful in identifying patients at risk of decreased quality of life but I found that individual symptom

scores were more strongly correlated with HRQL than the composite symptom burden score. This indicates we need to reframe how we think about the symptom and HRQL relationship. All but one of the correlations between symptoms and HRQL were weak. This finding suggests that even when HRQL measures are used quality of life is about more than symptoms. Aaronson et al. (1991) suggests assessment instruments that use a checklist approach (Fitzsimmons et al.1999), may not be as informative as a single global question about quality of life.

Hassan et al. (2006) indicated that clinically specific symptoms of bowel function, fatigue, anxiety, and spiritual well-being have the most impact on quality of life in patients with colorectal malignancies. The results of this study did not support his observation. I found that symptoms related to bowel function were not significantly correlated with HRQL. Fatigue, nausea/vomiting, pain and insomnia on the other hand had weak to moderate significant correlations with HRQL. The correlations between these key symptoms and a global health status question were noted to be weakly negative, indicating that as symptoms increase, quality of life as measured by the global health question decreases.

CHAPTER6: IMPLICATIONS FOR PRACTICE, EDUCATION, RESEARCH, AND POLICY

Health care providers make treatment decisions based on the information available to them. Sometimes this information is obtained through the use of patient completed questionnaires. Understanding how patients report symptoms, and how this information relates to quality of life facilitates the decision making process. In this study the goal was to examine more closely the relationship between symptoms and quality of life. This study has shown a relationship among some symptoms and quality of life as measured on the EORTC QLQ C30. Problems arose when comparing questionnaires that were not similar in the wording of root questions, that described the symptoms differently or that varied in conceptual definitions. In this study I showed that as the number of symptoms increased patients reported decreased health related quality of life.

The intent of this study was to examine the relationship between symptoms and quality of life for the purpose of helping nurses and other health care providers understand that when they successfully manage symptoms they have an important impact on quality of life. Patients who are currently receiving cancer treatment fill out many documents during the course of their care. The purpose of those documents is to facilitate interventions that are timely and appropriate. If clinicians can appropriately identify patients who are at risk of, or currently suffering from, impaired quality of life without requiring any additional paperwork burden for patients, it may be possible to provide more timely interventions, improved access to support services and improved patient satisfaction with care.

Implications for Nursing Practice

Patients experience numerous symptoms during cancer therapy, related to both the disease process and the treatment chosen. Appropriate interventions are determined based on the assessment and information available about the patient experience. It is critical that nurses recognize the importance of using instruments that are reliable and valid when collecting assessment information. Tools which are used without this examination may be presumed to be accurate, when in fact they may be poorly constructed, poorly completed or misinterpreted by health care providers. The findings of this study suggest that the use of the MACFS should be continued as it is a reasonably valid symptom assessment instrument.

A further concern is that patients may feel that the assessment tool is the only place to comment on problems or symptoms. It must be recognized and appreciated that these tools are just that— they are but one component of the thorough patient assessment required at each appointment. Appropriate nursing care involves discussion of the information on the assessment tool. Assessment tools can play a valuable role in ensuring the continuity of information, and in promoting a discussion of symptom management, but by themselves, and without the correct interpretation, they are only one part of the picture.

During the course of this study, many patients had difficulties completing the paperwork portion of the symptom assessment, and experienced the most difficulty with the MACFS. Although the symptom lists were familiar, many patients have difficulty in following the directions written on the questionnaire, to note the presence/absence of each of the symptoms, and then to rate the symptom. During the course of active treatment, patients complete many forms, and do not have a person available to review how to complete the form ahead of time. If motivated research participants, who had an opportunity to review an assessment tool with a researcher and ask questions for clarification, still had significant difficulty in completing the questionnaire, one must consider how patients routinely interpret and complete forms. Adequate instructions, both verbal and written must be provided to patients. The format of the questionnaire must be one that meets the needs of not only the clinician, but also those of the patient. Text size, question wording and page layout must be supportive to ease of comprehension and completion. Forms which are poorly planned, printed or worded may provide poor quality of information on which to make medical treatment.

Implications for Education

This study has further emphasized the importance of teaching new nursing students and practitioners the importance and value of regular symptom assessments, regardless of the setting. The information garnered through complete assessments is vital to ensure appropriate interventions, and monitoring during the treatment trajectory. Additionally, although tools may be practical, it is important that they are proven to be valid and reliable. Tools that have not been adequately tested may provide poor quality information for decision making, or be misinterpreted by health care providers. It is only through the process of instrument testing and validation that we can be confident that symptom measurement tools actually ask and gather the information for which they have been designed.

Implications for Further Research and Theory Development

This study provided and initial evaluation of a clinical tool which is used to track changes in patient information during cancer treatment. The purpose of this evaluation was specifically to review a tool which was practical in tracking information changes, and which incorporated patient symptom reports in a clear and concise manner to clinicians. Although this study was small in size, patient feedback indicated that completing a form which is proven helpful to their care was not burdensome. Future research regarding the reliability of the MACFS is warranted This would be difficult as symptoms do change over time. Larger validation studies throughout the ambulatory care department should be conducted to show that the tool measures symptoms in a reliable and valid manner in a larger populace. Identifying which patient will experience difficulty in the management of symptoms is not always possible. If key symptoms of concern within a group of patients undergoing cancer treatment can be identified, patient assessments can become more focused, and interventions more timely and specific. Patients could be assessed by using tools which are specific to tumor group or treatment type,

and a more accurate picture of the treatment experience could be recorded. Being able to track changes over time, may enable us to predict which patients may be at risk of inadequate symptom management without intervention, and this could be studied through a longitudinal assessment of key symptoms throughout the course of treatment, in an effort to identify the time periods when patients are most at risk of developing symptom control issues. If an identifiable time-period could be established, which could predict uncontrolled symptom issues within the next cycle/weeks, thought could be given to the development of "treatment survival" classes, access to extra support programs or refractory symptom clinics.

Further research in this area would involve a revised version of the ACFS that is more user friendly, using current adult health literacy standards, to create better more useful form layouts that are legible, with adequate instructions for completion. The advent of new information technology makes it reasonable to suggest that future research on this type of project might be centered on the use of web-based or computer-based patient-completed assessment forms. By transitioning this form to a secure web-browser or fire walled computer system within the institution, patients could complete individualized questionnaires which would be based on the symptoms that they, personally, experience. These computer based forms would allow the patient to provide more information about symptoms they experienced, and provide a greater degree of independence and self empowerment to the patient. Computer based programs could easily calculate and present a composite score, as well as a graphical representation of symptom control over time. This tracking of symptoms over time would be beneficial for members of the healthcare team and patients alike, in recording symptoms and evaluating interventions over time. Using a computer-based interface would further facilitate updating and adjusting forms over time, as questionnaires could be individualized to assess specific toxicities of chemo- or radiation specific regimens, or to address other issues identified by patients (biologic therapies, hormones, alternative therapies). Computer adaptive programming would facilitate the transition of the current measure into a highly adaptable and useful tool.

Implications for Policy

In the review of health care policy, health care agencies need to ensure that thorough nursing assessment is an institutional standard. Orientations to health care agencies need to review both standards for- and documentation of the assessment, to ensure that the information is current, accurate and appropriately documented. Standards for quality assurance should routinely evaluate these standards and their implementation at the institutional level, and develop programs for ongoing improvement.

Summary

This study was developed to address two identified gaps in the literature about symptoms and quality of life. The first gap was the lack of information about the degree and extent of the relationship between HRQL and symptom burden. The development of a new symptom assessment instrument at

the Cross Cancer Institute, the MACFS, provided an opportunity to address this gap. I established that the MACFS was a reasonably valid and internally consistent measure. The number of symptoms was significantly and weakly correlated with HRQL as measured on the EORTC QLQ C-30. Symptom burden as measured by the composite symptom burden score on the MACFS was also significantly and weakly correlated with HRQL.

The second identified gap in the literature was the lack of information about the relationships between individual symptoms and HRQL. Hassan et al. (2006) suggested that bowel function, fatigue, anxiety and spiritual well-being were related to quality of life in patients with colorectal cancer. My available data made it possible to examine the relationships among bowel function, fatigue and quality of life more closely. I found that while bowel function was not correlated with quality of life, fatigue and other symptoms including insomnia, pain and nausea/vomiting were significantly correlated with quality of life.

In the process of addressing these questions, much has been learned about the process of symptom assessment, documentation development and the role of nursing research within the clinical care setting. The process of completing this study has affirmed the importance of assessing the literature, and identifying the current research trends and gaps. It is through recognizing and addressing these gaps in the current literature that nursing-driven research can identify areas of research which are relevant and impact practice. As nurses undertake to establish these lines of inquiry based in clinical practice, the multidisciplinary healthcare team is strengthened, and research initiatives can be established which will benefit both care providers and recipients.

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Appendix A: List of Symptoms assessed in measures of Symptom Experience

Rotterdam Symptom Checklist Modified	Memorial Symptom Assessment Scale
Lack of appetite	Difficulty concentrating
Sore mouth/pain when swallowing	Pain
Dry mouth	Lack of energy
Heartburn/belching	Cough
Weight loss	Feeling nervous
Weight gain	Dry mouth
Lack of energy	Nausea
Tiredness	Feeling drowsy
Difficulty sleeping	Numbness/tingling in hands/feet
Sore muscles	Difficulty sleeping
Low back pain	Feeling bloated
Dizziness	Problems with urination
Nausea	Vomiting
Vomiting	Shortness of breath
Decreased sexual interest	Diarrhea
Problems controlling your urine	Feeling sad
Abdominal aches	Sweats
Problems controlling your bowels	Worrying
Constipation	Problems with sexual interest or activity
Diarrhea	Itching
Skin irritation	Lack of appetite
Tingling hands or feet	Dizziness
Shivering	Difficulty swallowing
Loss of hair	Feeling irritable
Burning/sore eyes	Mouth sores
Shortness of breath	Change in the way food tastes
Headaches	Weight loss
Cough	Hair loss
	Constipation
	Swelling of arms or legs
	"I don't look like myself"
	Changes in skin

M.D. Anderson Symptom Inventory

- Pain
- Fatigue (tiredness)
- Nausea
- Disturbed sleep
- Distress
- Shortness of breath
- Remembering things
- Lack of appetite
- Drowsiness
- Dry mouth
- Sadness
- Vomiting
- Numbness or tingling
- Headaches
- Sore/scratchy/dry eyes
- Feeling angry/aggressive
- Nausea before treatment
- Weight gain or loss
- Changes in your vision
- Dry mouth/lips
- Indigestion
- Feeling irritable
- Bleeding/spotting (female patients only)
- Hot flushes
- A change in your appetite
- Mood swings
- Dry/itchy/inflamed skin
- Difficulty concentrating/remembering
- Sore or aching joints
- A change in you sense of taste
- Irregular periods (female patients only)
- Watery eyes
- Sore or aching muscles
- A change in the sensitivity of your skin
- Feeling restless
- Needing to urinate more frequently
- Decreased sexual interest
- Feeling bloated
- A change in your sense of smell

Worthington Chemotherapy Questionnaire

- Vomiting
- Nausea
- A sore/sensitive mouth or throat
- hair loss feeling tired feeling low/depressed diarrhea
- Pain (patient specifies where)
- Constipation
- Feeling generally anxious/worried
- Vomiting before treatment
- Feeling anxious before treatment
- Feeling weak
- Pins and needles/numbness of your hands and feet
- Shortness of breath
- Feeling fearful
- Nose bleeds
- Difficulty sleeping

Chemotherapy Symptom Assessment Scale
List not available from tool developer, list comprised of items derived from WCQ

Edmonton Symptom Assessment Scale
- Pain
- Tired
- Nauseated
- Depressed
- Anxious
- Drowsy
- Appetite
- Feeling of wellbeing
- Shortness of breath
- Other

Appendix B: Information sheet and consent form

INFORMATION SHEET

Title of Research Study **The ASC-mE Study- the Ambulatory Symptom Checklist Evaluation**

Principal Investigator(s): Susan Horsman, MN student, University of Alberta

Sub-Investigator(s):Dr. Karin Olson, Faculty of Nursing, University of Alberta
Dr. Karen Kelly, Faculty of Nursing, University of Alberta
Dr. Heather Au, Medical Oncologist, Cross Cancer Institute

Background: *You are being invited to participate in a research study conducted by Susan Horsman, a Master's of Nursing student at the University of Alberta because you have colorectal cancer.*

This form gives information about this research study. This study will be discussed with you. Please ask questions if you wish to do so.
Once you understand the study, you will be asked to sign this form if you wish to participate. Please take your time to make your decision. Feel free to discuss it with your friends, or your family physician.

Purpose: *This study is part of a Master's of Nursing thesis. This study will explore the relationship between symptoms patients may experience during cancer treatment and how satisfied they are with their quality of life. This goal to this study is to determine whether knowing about symptoms a person experiences can help nurses and doctors learn about a patients' quality of life.*

Procedures:

No additional visits to the hospital/clinic are anticipated. This information for the study will be collected on the same day as you are seen by the doctor, prior to the second cycle of treatment. The forms you will complete should take 20-30 minutes.

You will be asked to complete several questionnaires that ask you to describe symptoms you are currently experiencing, and about your quality of life.

Possible Benefits: The possible benefits to you for participating in this study are that you may better understand how to monitor and report symptoms to the clinic staff. You may also be better able to identify concerns about quality of life issues, which you can discuss with the clinic staff.

Possible Risks: No risks are anticipated from this study. If you become distressed during participating in this study, an appointment will be made for you to speak with a psychologist at the Cross Cancer Institute.

CONFIDENTIALITY: *YOUR INFORMATION RELATING TO THIS STUDY WILL BE KEPT CONFIDENTIAL. ANY INFORMATION COLLECTED ABOUT YOU WILL NOT IDENTIFY YOU BY NAME. ONLY A STUDY NUMBER WILL BE USED TO LABEL YOUR INFORMATION. YOUR NAME WILL NOT BE DISCLOSED OUTSIDE THE RESEARCH TEAM. ANY REPORT PUBLISHED AS A RESULT OF THIS STUDY WILL NOT IDENTIFY YOU BY NAME.*

ASC-mE Study

IN ADDITION TO THE INVESTIGATORS(S) AND THE SPONSOR REPRESENTATIVES, THE HEALTH RESEARCH ETHICS BOARD, AND/OR OTHER FOREIGN REGULATORY AGENCIES MAY HAVE ACCESS TO YOUR PERSONAL HEALTH RECORDS TO MONITOR THE RESEARCH AND VERIFY THE ACCURACY OF STUDY DATA.

BY SIGNING THE CONSENT FORM YOU GIVE PERMISSION TO THE STUDY STAFF TO ACCESS ANY PERSONALLY IDENTIFIABLE HEALTH INFORMATION WHICH IS UNDER THE CUSTODY OF OTHER HEALTH CARE PROFESSIONALS AS DEEMED NECESSARY FOR THE CONDUCT OF THE RESEARCH.

BY SIGNING THE CONSENT FORM YOU GIVE PERMISSION FOR THE COLLECTION, USE AND DISCLOSURE OF YOUR MEDICAL RECORDS. IN CANADA, STUDY INFORMATION IS REQUIRED TO BE KEPT FOR 25 YEARS. EVEN IF YOU WTITHDRAW FROM THE STUDY, THE MEDICAL INFORMATION WHICH IS OBTAINED FROM YOU FOR STUDY PURPOSES WILL NOT BE DESTROYED. YOU HAVE A RIGHT TO CHECK YOUR HEALTH RECORDS AND REQUEST CHANGES IF YOUR PERSONAL INFORMATION IS INCORRECT.

Voluntary Participation: You are free to withdraw from the research study at any time, and your continuing medical care will not be affected in any way

Compensation for Injury: By signing this consent form you are not releasing the investigator(s), institution(s) and/or sponsor(s) from their legal and professional responsibilities.

Contact Names and Telephone Numbers:
If you have concerns about your rights as a study participant, you may contact the Patient Advocate Office of the Cross Cancer Institute, at 432-8585.This office has no affiliation with the study investigators.

Please contact any of the individuals identified below if you have any questions or concerns*:*

Dr Karin Olson_____ *Name and title* 780-242-1186 *Telephone Number*

Dr Heather Au_____ *Name and title* 780-445-5990 *Telephone Number*

Investigators must provide a phone number which can access an investigator or co-investigator 24 hours per day.

CONSENT FORM

Part 1 (to be completed by the Principal Investigator):

Title of Project: ASC-mE Study

Principal Investigator(s): Susan Horsman Phone Number(s): 780-2293-7326

Co-Investigator(s): Contact names phone numbers
Dr Karin Olson 780-242-1186
Dr Karen Kelly 780-492-2697
Dr Heather Au 780-445-5990

Part 2 (to be completed by the research subject):

	Yes	No
Do you understand that you have been asked to be in a research study?	☐	☐
Have you read and received a copy of the attached Information Sheet?	☐	☐
Do you understand the benefits and risks involved in taking part in this research study?	☐	☐
Have you had an opportunity to ask questions and discuss this study?	☐	☐
Do you understand that you are free to withdraw from the study at any time, without having to give a reason and without affecting your future medical care?	☐	☐
Has the issue of confidentiality been explained to you?	☐	☐
Do you understand who will have access to your records, including personally identifiable health information?	☐	☐
Do you want the investigator(s) to inform your family doctor that you are participating in this research study? If so, give his/her name _____	☐	☐

Who explained this study to you? _____

I agree to take part in this study: YES ☐ NO ☐

Signature of Research Subject _____

(Printed Name) _____

Date: _____

I believe that the person signing this form understands what is involved in the study and voluntarily agrees to participate.

Signature of Investigator or Designee _____ Date _____

THE INFORMATION SHEET MUST BE ATTACHED TO THIS CONSENT FORM AND A COPY GIVEN TO THE RESEARCH SUBJECT

Appendix C Demographic Information Sheet

Initials:

Age:

Gender: male, female

Marital Status: single, common-law, married, widowed, divorced

Diagnosis: colon adenocarcinoma, rectal adenocarcinoma

Stage: Stage 3, stage 4

Treatment regimen: single agent treatment: capecitabine, irinotecan, tomudex

Combination chemotherapy: Folfox, Capox, Folfiri, Folfox+ Bevacizumab, Capox + Bevacizumab, Folfiri + Bevacizumab, chemotherapy + radiation therapy

Karnofsky performance status as assigned by the clinician

Appendix D Modified Ambulatory Care Flow Sheet

(MACFS)

Alberta CANCER BOARD

Ambulatory Care Patient Visit

Location: Outpatient Department **Clinic:** _____

ALL SECTIONS ON THIS PAGE TO BE COMPLETED BY PATIENTS

THE FOLLOWING PROBLEMS WERE NOTED ON YOUR LAST VISIT. PLEASE (√) IF THEY ARE RESOLVED (NO LONGER A PROBLEM) OR STILL PRESENT:

1. _____ ☐ Resolved ☐ Present
2. _____ ☐ Resolved ☐ Present
3. _____ ☐ Resolved ☐ Present
4. _____ ☐ Resolved ☐ Present
5. _____ ☐ Resolved ☐ Present
6. _____ ☐ Resolved ☐ Present
7. ☐ No problems/concerns on last visit

CONCERNS YOU NEED ADDRESSED TODAY?

1. _____
2. _____
3. _____
4. _____
5. _____

DO YOU NEED ANY PRESCRIPTIONS RENEWED?

☐No ☐Yes (specify) _____

SINCE YOUR LAST VISIT, HAVE YOU:

1. Been hospitalized? ☐ No ☐ Yes If yes, please specify _____
2. Been diagnosed with an infectious disease? ☐ No ☐ Yes If yes, please specify _____
   (TB/Shingles, a "super bug" - also known as antibiotic resistant organism)
3. Started any new medications? ☐ No ☐ Yes If yes, please specify _____
4. Started any alternative therapies? ☐ No ☐ Yes If yes, please specify _____
5. Developed any new allergies? ☐ No ☐ Yes If yes, please specify _____

SINCE YOUR LAST VISIT, HAVE YOU EXPERIENCED ANY OF THE FOLLOWING **RELATED TO YOUR CANCER?**

	No	Yes	Please rate: Much Better	Better	Same	Worse	Much Worse
Difficulty sleeping	☐	☐	☐	☐	☐	☐	☐
Pain	☐	☐	☐	☐	☐	☐	☐
Tiredness/fatigue	☐	☐	☐	☐	☐	☐	☐
Shortness of breath	☐	☐	☐	☐	☐	☐	☐
Changes to skin	☐	☐	☐	☐	☐	☐	☐
Mouth Sore	☐	☐	☐	☐	☐	☐	☐
Changes to appetite	☐	☐	☐	☐	☐	☐	☐
Nausea/vomiting	☐	☐	☐	☐	☐	☐	☐
Diarrhea/constipation	☐	☐	☐	☐	☐	☐	☐
Difficulty urinating	☐	☐	☐	☐	☐	☐	☐
Difficulty coping	☐	☐	☐	☐	☐	☐	☐
Changes in sexuality/ Sexual function	☐	☐	☐	☐	☐	☐	☐

INFORMATION PROVIDED BY: ☐ Patient Signature: _____
☐ Other Signature: _____
Date: _____ Relationship to Patient: _____

THIS SECTION TO BE COMPLETED BY RN ONLY

Reason for Visit: ☐ NP ☐ Treatment ☐ Monitoring
☐ MD + RN ☐ APN Only ☐ APN + RN ☐ MD Only ☐ RN Only Visit

Height: ____ **Weight:** _____ **In Optx:** ☐ Yes ☐ No **Previous Weight:** _____ **Provider:** _____

ASSESSMENT, INTERVENTIONS AND PATIENT RESPONSE:
☐ See Patient Education Sheet ☐ Toxicity Assessment Done ☐ In Paper Chart ☐ In Computer

Referrals Initiated:
☐ Home Care ☐ Community Liaison ☐ Pain & Symptom ☐ Psychology ☐ Social Work
☐ Other (specify: _____)

Date: _____

Time	
	☐ No Problems Identified. No Actions Required.

Appendix E: Rotterdam Checklist-Modified

Rotterdam Symptom Checklist-Modified

For each symptom listed below, indicate to what extent you have been bothered by it during the past week by darkening the appropriate oval.

	Not at all	A little	Quite a bit	Very much
a) Lack of appetite	0	0	0	0
b) Sore mouth/pain when swallowing	0	0	0	0
c) Dry mouth	0	0	0	0
d) Heartburn/belching	0	0	0	0
e) Weight loss	0	0	0	0
f) Weight gain	0	0	0	0
g) Lack of energy	0	0	0	0
h) Tiredness	0	0	0	0
i) Difficulty sleeping	0	0	0	0
j) Sore muscles	0	0	0	0
k) Low back pain	0	0	0	0
l) Dizziness	0	0	0	0
m) Nausea	0	0	0	0
n) Vomiting	0	0	0	0
o) Decreased sexual interest	0	0	0	0
p) Problems controlling your urine	0	0	0	0
q) Abdominal aches	0	0	0	0
r) Problems controlling your bowels	0	0	0	0
s) Constipation	0	0	0	0
t) Diarrhea	0	0	0	0
u) Skin irritation	0	0	0	0
v) Tingling hands or feet	0	0	0	0
w) Shivering	0	0	0	0
x) Loss of hair	0	0	0	0
y) Burning/sore eyes	0	0	0	0
z) Shortness of breath	0	0	0	0
aa) Headaches	0	0	0	0
bb) Cough	0	0	0	0

Study number _____ Date_____

Appendix F: Numerical Response Scales- Pain and Coping

Please complete the following questions to tell us more about symptoms you may have experienced this week.

Please use the following measure to tell us about your pain:

No pain **Worst possible pain**

0 1 2 3 4 5 6 7 8 9 10

Please use the following measure to tell us about coping

No problems coping **Worst possible coping**

0 1 2 3 4 5 6 7 8 9 10

Study number_____ Date _____

Appendix G EORTC QLQ C-30

ENGLISH

EORTC QLQ-C30 (version 3)

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

Please fill in your initials: ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

Your birthdate (Day, Month, Year): ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

Today's date (Day, Month, Year): 31 ⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋⌊ ⌋

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

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

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

1	2	3	4	5	6	7
Very poor						Excellent

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

1	2	3	4	5	6	7
Very poor						Excellent

Appendix H: MACFS Scoring Manual

To score the MACFS questionnaire, each question is first tabulated individually. Individual symptoms are scored first for absence (0) or presence (1). Individual symptom severity scores are calculated through assigning a value of 0 for 'no symptom', 1 for 'much better', 2 for 'better', 3 for 'same', 4 for 'worse ' and 5 for 'much worse'. Each patient will thus have 2 scores for each question on the MACFS, a symptom presence score and a symptom severity score. After this information has been gathered, a symptom experience score can be calculated as the total number of symptoms experienced. To calculate the Composite Symptom burden Score, the following formula is used:

$$\sum \frac{(symptom\ \ presence \times individual\ \ symptom\ score\ severity)}{symptom\ experience\ score}.$$

Example: 3 symptoms, each rated at a score of 4

$$\sum \frac{[(1\times 4)+(1\times 4)+1\times 4)]}{3} = \frac{12}{3} = 4$$

3 symptoms, 2 rated at 2, 1 rated at 3

$$\sum \frac{[(1\times 2)+(1\times 2)+(1\times 3)]}{3} = \frac{7}{3} = 2.33\bar{3}$$

Complete symptom burden score calculation rules:

1. Substitution rules for missing data on individual MACFS items.

a. If missing incidence of symptom, but rated as 4 or 5 on severity, symptom presence score of 1 (yes) may be assigned.

b. If missing incidence of symptom, but rated as 1 or 2 on severity, symptom presence score of 2 (no) may be assigned.

c. If missing incidence of symptom, but rated as 3 (same), symptom presence score must be assumed as missing (as cannot presume to know if symptom present or absent.

d. If missing data is symptom rating, and symptom is graded as 0 (no), total symptom score is 0.

e. If missing data is symptom rating, and symptom is graded as 1 (yes), symptom rating is regarded as missing, and no total symptom score can be assigned for the item.

2. To calculate the Composite Symptom Burden Score, a minimum of 80% of individual item scores must be available. The higher the number of available individual item

scores, the more likely an accurate reflection of symptom experience. To determine the cut-off point for missing data within the MACFS tool, established missing data limits were examined for other QOL and symptom measurement tools. Different strategies have been developed by the creators of quality of life measures to deal with the problem of missing data. Establishing a cut-off point below which no substitution of response can be instituted seems to be a general consensus amongst tool developers. The level of acceptable missing data varies between 70% (Moinpour et al, 2000) and 80% (Cella et al. 1993, Fayers et al. 2001). This is for individual items.

3. The MACFS thus is measured through several calculations.
   a. MACFS individual symptom presence: (raw score)
   b. MACFS individual symptom burden: $(presence \times severity)$
   c. MACFS total symptom incidence: $(\sum symptom\ presence)$
   d. MACFS composite symptom burden:

$$\sum \frac{(symptom\ \ presence \times individual\ \ score\ severity)}{individual\ \ symptom\ \ presence}$$

Appendix I Rotterdam Symptom Checklist-Modified Scoring Manual

In preparing for the analysis of the RSC-M, no scoring manual for interpretation of results was available from the American validation study. The Scoring of the RSC-M was completed using the scoring manual provided with the original RSCL. The method of calculating the physical distress score and of calculating the individual item scores was derived from this manual. In the calculation of individual item scores, a value of 1 was assigned to "not at all ", a value of 2 assigned to " a little bit", a value of 3 to " quite a bit" and 4 assigned to the response of "very much".

Individual items were studied in the RSCL manual and grouped to create scale scores, obtained by the summation of scores for individual items. Although the RSC-M does not contain the same exact items, using the format of the original document, a physical distress score can be calculated. This score was calculated using the symptoms from the RSC-M which directly correlated with the original RSCL: lack of appetite, tiredness, sore muscles, lack of energy, low back pain, nausea, difficulty sleeping, headaches, vomiting, dizziness, decreased sexual interest, abdominal aches, constipation, diarrhea, heartburn, shivering, tingling hands or feet, sore mouth, loss of hair, burning sore eyes, shortness of breath and dry mouth.

The computation of the physical distress score can be made more easily interpretable through transforming the raw scores into a 100-point scale. This facilitates comparison of the score to other measures. In a 100 point scale, a score of 0 implies no impairment. This transformation of score is calculated using the following formula:

$$\left(\frac{raw\ scale\ score - min\ raw\ score}{max - min\ score}\right) \text{X } 100 = \text{transformed score.}$$

For example: if someone has a raw score of 37. Since the score is totalled using 21 symptoms, the range is 21-84. This would imply that the transformed score of this person would be:

$$\frac{(37-21)}{84-21} \times 100 = 25.39$$

The raw score of the total RSC-M could be converted to a score out of 100, for the ease of comparison, using the same transformation formula:

$$\left(\frac{raw\ scale\ score - min\ raw\ score}{max - min\ score}\right) \text{X } 100 = \text{transformed score.}$$

Appendix J: Missing data in the MACFS questionnaire.

Missing Data on MACFS questionnaire

Data from the MACFS severity ratings which was missing was calculated where patients reported the presence of a symptom, but did not report the severity. Data is coded as: 1 or yes= data missing, 2 or no = data not missing.

Individual symptom severity data

MACFS difficulty sleeping missing

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1.00	4	4.5	4.5	4.5
	2.00	85	95.5	95.5	100.0
	Total	89	100.0	100.0	

MACFS pain missing

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1.00	4	4.5	4.5	4.5
	2.00	85	95.5	95.5	100.0
	Total	89	100.0	100.0	

MACFS fatigue missing

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1.00	7	7.9	7.9	7.9
	2.00	82	92.1	92.1	100.0
	Total	89	100.0	100.0	

MACFS shortness of breath missing

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1.00	2	2.2	2.2	2.2
	2.00	87	97.8	97.8	100.0
	Total	89	100.0	100.0	

MACFS skin irritation missing

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1.00	3	3.4	3.4	3.4
	2.00	86	96.6	96.6	100.0
	Total	89	100.0	100.0	

MACFS mouth sore missing

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1.00	3	3.4	3.4	3.4
	2.00	86	96.6	96.6	100.0
	Total	89	100.0	100.0	

MACFS appetite missing

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1.00	3	3.4	3.4	3.4
	2.00	86	96.6	96.6	100.0
	Total	89	100.0	100.0	

MACFS NV missing

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1.00	3	3.4	3.4	3.4
	2.00	86	96.6	96.6	100.0
	Total	89	100.0	100.0	

MACFS diarrhea constipation missing

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1.00	5	5.6	5.6	5.6
	2.00	84	94.4	94.4	100.0
	Total	89	100.0	100.0	

MACFS GU missing

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1.00	2	2.2	2.2	2.2
	2.00	87	97.8	97.8	100.0
	Total	89	100.0	100.0	

MACFS cope missing

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1.00	4	4.5	4.5	4.5
	2.00	85	95.5	95.5	100.0
	Total	89	100.0	100.0	

MACFS sex missing

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1.00	4	4.5	4.5	4.5
	2.00	85	95.5	95.5	100.0
	Total	89	100.0	100.0	

Missing data throughout MACFS measure

Total missing data in MACFS measure

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	yes	44	4.1	4.1	4.1
	no	1024	95.9	95.9	100.0
	Total	1068	100.0	100.0	

Missing data: Presence of symptom MACFS measure

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	yes	17	1.6	1.6	1.6
	no	1051	98.4	98.4	100.0
	Total	1068	100.0	100.0	

Missing data: Rating of symptom severity MACFS measure

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	yes	628	58.8	58.8	58.8
	no	440	41.2	41.2	100.0
	Total	1068	100.0	100.0	