



E2Z02
REVISED

Revised 12/06, Addendum #1
Revised 12/06, Update #2

Eastern Cooperative Oncology Group

SOAPP (Symptom Outcomes and Practice Patterns):
A Survey of Disease and Treatment-Related
Symptoms in Patients with Invasive Cancer of the
Breast, Prostate, Lung or Colon/Rectum

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STUDY PARTICIPANTS

ACTIVATION DATE

Rev. 12/06 Limited to randomly-selected institutions/sites that agree to participate.

March 3, 2006

Rev. 12/06 Access
http://www.ecog.org/ecoginst/tools/e2z02_instlist.html
to see the list of participating sites.

Update #1 – Incorporated Prior to Activation

Addendum #1 – 12/06

Update #2 – 12/06

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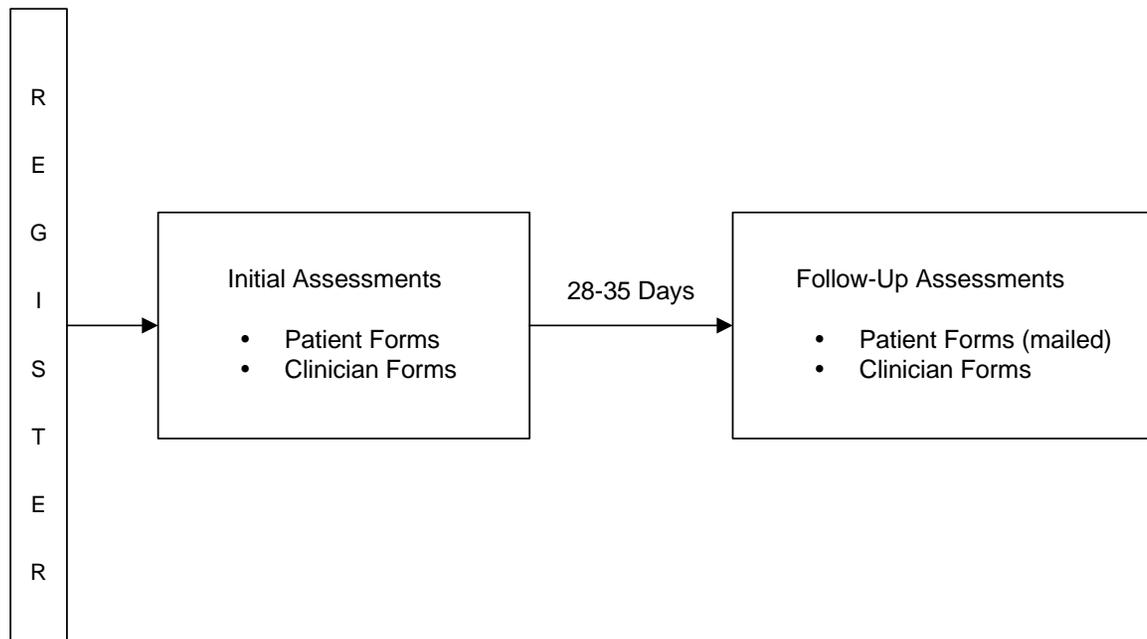
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Rev. 12/06

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Schema



Total Accrual Goal = 2310

1. Introduction

Roughly 1.3 million people per year are diagnosed with cancer in the United States, and more than half of those patients live for 5 years or more at risk for bothersome symptoms that may diminish their quality of life. With a population that is both expanding and aging, the burden of disease and suffering attributed to malignancy is expected to grow significantly (1). Although pain due to cancer is reasonably well-described, the scope and quality of scientific evidence on cancer pain epidemiology and treatment is lagging compared to what is known about the epidemiology and treatment of cancer itself (1). Likewise, there is a need for reliable data on the prevalence, severity and treatment of other common symptoms experienced by cancer patients. The National Institutes of Health State-of-the-Science statement on symptom management in cancer (July 2002) concluded that too many patients with pain, depression, and fatigue receive inadequate treatment for their symptoms, and that “research is needed on the definition, occurrence, assessment, and treatment of pain, depression, and fatigue alone and together through adequately funded prospective studies (2).”

Prospective research is needed to evaluate treatment strategies for symptom management and to better understand the role of demographic variables and comorbidity in patterns of symptom expression and change over time. However, descriptive data is needed to plan the interventional research. This clinical survey study involves an initial assessment of multiple symptoms self-reported by patients and understood by clinicians with a second assessment at the next office visit. These data on the prevalence, severity, impact and current treatment of common symptoms in the most frequently-occurring cancers will serve as a major starting point in planning and prioritizing symptom-directed interventional studies.

Patients with cancer experience multiple symptoms related to cancer, cancer treatment, and procedures involved in cancer care (3). Common symptoms include physical symptoms (pain, fatigue, shortness of breath), cognitive symptoms (memory problems, impaired concentration), and affective symptoms (especially depression and anxiety) (4-8). These symptoms may be the side effects and “toxicities” of treatment, the psychological impact of having a potentially-fatal and life-modifying disease, and/or the direct product of the disease process itself on normal physiology. Symptoms may interrupt treatment and have a negative influence on its effectiveness. Symptoms may also be associated with reduced survival (9-11). Symptom severity is related to the extent of disease, the aggressiveness of therapy, and the extent of appropriate symptom management. Because of a lack of systematic management and the reluctance of patients to report symptoms, symptoms often reach a severity that requires an emergency room visit or hospitalization, adding substantially to the cost of treatment and to the disruption of the patients’ routines and the routines of their family members.

Due to the influence of managed care, cancer therapy has shifted to the ambulatory setting in recent years, while at the same time therapy has become much more aggressive with a greater burden of treatment-related symptoms. As a result, more responsibility for symptom management has moved from the healthcare professional to patients and their families. The patient and family are increasingly responsible for initial symptom assessment, initial home-based symptom management, or active contacts with care providers when symptom management is needed. Families have varying resources, abilities, and assertiveness in contacting health care professionals.

Most studies of multiple symptoms have been done in the palliative care setting (12-14). Very few epidemiological studies have examined the multiple symptoms of cancer patients who remain in active treatment. Often, within individuals, multiple symptoms (i.e. pain, fatigue, and depression), occur (15). There is a need for studies that examine the severity of multiple symptoms together, and the M D Anderson Symptom Inventory is one of the valid and reliable multidimensional scales that could be used to explore the construct of symptom clusters (16). There is also a need to examine how symptoms are managed in different types of institutions caring for cancer patients. A few single institution studies have assessed multiple symptoms in samples of cancer patients with different stages of disease. Portenoy and colleagues administered the Memorial Symptom Assessment Scale to a random sample of inpatients and outpatients with cancer (7). The most frequently reported symptoms for the sample were lack of energy, worry, feeling sad, and pain. In a recent

study of 527 patients in active treatment, more than 20% of patients reported a variety of severe symptoms, including fatigue, worry, distress, poor sleep, lack of appetite, and dry mouth (4). Multi-institutional symptom survey data in a broad mix of patients is lacking.

Many cancer specialists recognize that symptom control is often sub-optimal. Medical oncologists were surveyed about their treatment of cancer pain in a study conducted by the Eastern Cooperative Oncology Group (17). Only half of the physicians surveyed indicated that cancer pain control was good or very good in their practice setting. Seventy-five percent of the physicians indicated that the most important barrier to cancer pain management was inadequate pain assessment. Over 60% reported those physicians' reluctance to prescribe analgesics and patients' unwillingness to report pain or take opioids were barriers to adequate pain treatment. Inadequate knowledge about cancer pain management was reported by over 50% of the ECOG physicians surveyed. The survey acknowledged that a substandard level of education about cancer pain management and a reluctance to address it in practice existed at all levels of professional health care. In a recent study, Cleeland repeated the ECOG study format with physician members of the Radiation Therapy Oncology Group (18). Although there has been some improvement in the use of stronger analgesics, many barriers to good pain control remain. One possible barrier to effective pain control is opioid toxicity. Dr. Thomas Smith and colleagues recently published a clinical trial comparing the use of an intrathecal opioid delivery system to comprehensive medical management (19). One important finding of that study was the prevalence and impact of opioid toxicity on the study population. The importance of opioid toxicity and its influence on patients and prescribing physicians has not been well characterized. Interestingly, researchers in Switzerland have recently reported that direct patient estimation of overall treatment burden is feasible and potentially useable as an endpoint in clinical trials (20). These researchers asked patients to judge the overall burden of cancer treatment, but it may also be reasonable to assess patient-reported overall burden (and benefit) of symptom treatment.

Overall, cancer is a disease that is feared not only because it can be life-threatening, but also because of its association with loss and suffering. Numerous factors can interfere with adequate symptom management. A better understanding of current patterns of symptom expression and treatment, and the relationship of symptoms to disease factors, patient factors, and interactions among providers, patients, and the health care system is clearly needed. This study holds promise for expanding our knowledge base in this important area of cancer care.

Gender and Ethnicity Statement

This study will be open to both males and females of all racial and ethnic backgrounds.

2. Objectives

2.1 Primary Objective

To describe the prevalence, severity and interference due to physical and psychological symptoms experienced over a 4-5 week period by cancer patients being followed on an outpatient basis at ECOG institutions.

2.2 Secondary Objectives

2.2.1 To determine if the number of symptom-related interventions are related to the providers' perception of symptom severity.

2.2.2 To determine whether physical symptoms are more commonly prioritized and treated compared to psychological symptoms.

2.2.3 To determine the percentage of patients who experience a significant reduction in moderate-to-severe symptoms and to characterize the determinants of symptom relief.

2.2.4 To determine the focus and scope of interventions chosen by oncologists to improve the symptom control of patients seen in outpatient clinics.

3. Selection of Patients

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Each of the criteria in the checklist that follows must be met in order for a patient to be considered eligible for this study. For each patient, this checklist must be photocopied, completed and maintained in the patient's chart.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday four weeks later would be considered Day 28.

ECOG Patient No. _____

Patient's Initials (L, F, M) _____

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Physician's Signature _____ **Date:** _____

NOTE: All questions regarding eligibility should be directed to the ECOG Coordinating Center at (617) 632-3610.

NOTE: Institutions may use the eligibility checklist as source documentation if it has been reviewed, signed, and dated prior to registration/randomization by the treating physician.

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3.1 Patients must be seen in an outpatient setting at an ECOG affiliated academic institution, a CGOP site or a CCOP site.

Outpatient at ECOG affiliated academic institution? Yes _____ No _____

CCOP? Yes _____ No _____

CGOP? Yes _____ No _____

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3.2 Patients must have a clinical diagnosis of invasive cancer involving at least one of the following primary sites: breast, lung, prostate, or colon/rectum. Patients may be in pretreatment, active treatment or follow-up.

Clinical diagnosis: _____

Treatment status: _____

3.3 Patients must be 18 years of age or older.

Age _____

3.4 Patients must be willing to complete a written survey between day 28 and day 35 following completion of the baseline assessment.

Date of baseline assessment: _____

Willing to complete survey 28-35 days later? Yes _____ No _____

Date follow-up survey to be completed: _____

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3.5 [Deleted criterion in Addendum #1]

3.6 Patients must not have significantly impaired cognitive status which, in the opinion of the screener, would hinder their ability to provide responses.

Unimpaired cognitive status? Yes _____ No _____

4. Registration

Submitting Regulatory Documents

Before an ECOG Institution may enter patients, protocol specific regulatory documents must be submitted to the CTSU Regulatory Office at the following address:

CTSU Regulatory Office
Coalition of National Cancer Cooperative Groups
1818 Market Street, Suite 1100
Philadelphia, PA 19103
FAX: (215) 569-0206

Required Protocol Specific Regulatory Documents

1. CTSU Regulatory Transmittal Form.
2. Copy of IRB Informed Consent Document.

NOTE: Any deletion or substantive modification of information concerning risks or alternative procedures contained in the sample informed consent document must be justified in writing by the investigator and approved by the IRB.

3. A. CTSU IRB Certification Form.
Or
B. HHS 310 Form.
Or
C. IRB Approval Letter

NOTE: The above submissions must include the following details:

- Indicate all sites approved for the protocol under an assurance number.
- OHRP assurance number of reviewing IRB
- Full protocol title and number
- Version Date
- Type of review (full board vs. expedited)
- Date of review
- Signature of IRB official

The CTSU encourages you to link to the following RSS2.0 webpage so that more information on RSS2.0 as well as the submission forms can be accessed http://www.ctsu.org/rss2_page.asp. If you have questions regarding regulatory document submission, please telephone the CTSU Help Desk at 1-888-823-5923 or E-mail CTSUContact@westat.com. Monday through Friday, 9:00am - 6:00pm.

Institutions may register eligible patients to this study via the ECOG webpage 24 hours a day, 7 days a week, using the Web-based Patient Registration Program (<https://webreg.ecog.org>). If you need assistance or have questions, please telephone the Central Randomization Desk at the ECOG Coordinating Center at (617) 632-2022, Monday through Friday 9:00am – 5:00pm Eastern Time. Please note that a password is required to use this program. The following information will be requested:

4.1 Protocol Number

4.2 Investigator Identification

4.2.1 Institution and affiliate name

4.2.2 Investigator's name

4.3 Patient Identification

4.3.1 Patient's initials and chart number

4.3.2 Patient's Social Security number

4.3.3 Patient demographics

4.3.3.1 Sex

4.3.3.2 Birth date (mm/yyyy)

4.3.3.3 Race

4.3.3.4 Ethnicity

4.3.3.5 Nine-digit ZIP code

4.3.3.6 Method of payment

4.4 Eligibility Verification

Patients must meet all of the eligibility requirements listed in Section 3. An eligibility worksheet has been appended to the protocol. A confirmation of registration will be forwarded by the ECOG Coordinating Center.

4.5 Additional Requirements

4.5.1 Patients must provide a signed and dated, written informed consent form.

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5. Study Methods

5.1 Patient Recruitment

Rev. 12/06 This is a survey of patient symptoms and symptom treatment in the context of outpatient oncology care for at least one of the following malignancies: breast, lung, prostate or colon/rectum. Patients will have verified invasive disease, because the likelihood of symptoms is much greater in these patients than in patients with carcinomas in situ. At enrollment, patients may be at any point in their trajectory of care for cancer.

Rev. 12/06 The enrollment scheme has been conceived on the basis of practical issues. In academic centers, patients are usually seen in disease site-specific clinics. In contrast, community oncology patients are usually seen in general oncology clinics. Two-thirds of the patients enrolled will derive from CCOP sites (patients in community oncology practices) and one-third from academic centers. In order to reduce selection bias, each site will devise a system for recruiting patients for enrollment.

Rev. 12/06 Recruitment of patients will occur when patients check in for their appointment. The recruitment process can take place over a number of days. In participating clinics, all oncology outpatients who appear to be eligible, based on the site-specific recruitment scheme, will be asked to participate in the study. Patients will either be enrolled in the study or listed on the "Patient Log" (Appendix III), which requires a reason for the patient's decision not to participate. If acceptable to your IRB, at the end of accrual, please send a copy of the Patient Log to the attention of the E2Z02 Coordinator at the ECOG Coordinating Center.

Rev. 12/06 Institutions will identify a nurse/CRA who will be responsible for all aspects of this study. The designated nurse or CRA from each institution will be available to work with physicians during the clinical session to identify and recruit patients with invasive disease. This person will also be available to answer any questions regarding the study.

5.2 Data Collection

Rev. 12/06 5.2.1 Patients will be recruited to participate in the study when they check in for their scheduled physician appointment.

5.2.2 A consent form and instructions for completing the forms will be given to each patient.

5.2.3 A signed consent form is required for participation.

Rev. 12/06 5.2.4 Patients will be asked to complete the baseline forms in the clinic prior to meeting with the clinician. However, if the clinician visit interrupts their completion, forms can be completed at the most appropriate opportunity prior to the patients' departure from the clinic on that day.

Rev. 12/06 5.2.5 The designated nurse or CRA from each institution will be available to answer questions and assist with the completion of baseline form(s), as necessary. A CRA or nurse must review form(s) for completeness as soon as the patient finishes them, to ensure all items have been marked appropriately.

Rev. 12/06 5.2.6 The CRA or nurse will collect completed form(s) prior to patients seeing the clinician, if possible, and before the clinician completes the clinician form(s).

5.2.7 The clinician forms must be completed within 48 hours of the patients' completion of the baseline forms.

Rev. 12/06 5.2.8 Completed clinician and patient form(s) will be sent to the ECOG Coordinating Center within 7 days of collection. The follow-up clinician form(s) will be completed between days 28-35 from the baseline clinician's form(s) and sent to the ECOG Coordinating Center within 72 hours of completion.

- Rev. 12/06 5.3 Administration Instructions
- Survey measures will be completed when the patient is enrolled (baseline) and repeated sometime between day 28 and day 35 *after* baseline date. The purpose of the 'follow-up survey' is to address the objectives directed at changes in symptom intensity and changes in patient management.
- Rev. 12/06 5.3.1 The forms must be administered at the time points noted above. At the time the baseline forms are completed, the study nurse will identify the 28-35 day interval within which the follow-up survey should be completed and returned.
- 5.3.2 The patient should be asked to read the instructions at the beginning of each questionnaire and complete all the items. The patient should be instructed to respond to questions in terms of his/her experience during the time frame specified on the form. It is permissible to assist the patient with completion of the forms, as long as the staff person does not influence the patient's responses.
- 5.3.3 The baseline forms must be reviewed by the designated nurse or CRA, as soon as the patient completes them, to ensure all items were marked appropriately. If more than one answer was marked, the patient should be asked to choose the answer which best reflects how s/he is feeling. If a question was not answered, the patient should be asked if s/he would like to answer it. The patient should always have the option to refuse. If the patient refuses, it should be indicated on the form that s/he declined to answer the item.
- 5.3.4 If the patient cannot complete the baseline form properly, the reason should be noted on the Assessment Compliance Form.
- 5.3.5 If a patient cannot complete the follow-up questionnaire because s/he is too sick AND the nurse/CRA learns of it via the scheduled telephone call, it will be documented on the Assessment Compliance Form. The patient will be informed of the option to complete the forms, if the patient recovers and is able to mail the forms by day 42. Forms received on or prior to day 42 will be accepted.
- Rev. 12/06 5.3.6 The clinician responsible for filling out the forms may be the treating physician, the nurse or physician assistant or the resident/fellow involved in the clinical care of the patient. The same clinician must complete both baseline and follow-up forms.
- 5.4 Provision of Appropriate Care for Patients
- The clinical management of all patients (regardless of symptom severity) will be determined by the treating physician.

6. Measures

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6.1 MD Anderson Symptom Inventory (MDASI-ECOG)

We will use the M D Anderson Symptom Assessment Inventory (MDASI), a validated measure that has patients rate the symptoms most frequently found in this group of patients (21). The MDASI also asks the patients to rate how much their symptoms have interfered with mood and activity-related domains. The MDASI is very similar in structure and in patient burden to the Brief Pain Inventory that was successfully used in the ECOG pain needs assessment study. In the NIH state-of-the-science conference on symptom management in cancer held in 2002, the MDASI was noted to be one of the reliable and valid multidimensional instruments that is well-suited for measurement of symptom clusters (16). The MDASI has been used in Phase I through Phase IV trials in the U.S. and in Europe.

Based on our pilot study experience, as well as feedback from patient advocates with Gilda's Club, we determined that there was a need to explore a small set of additional key symptoms (outside the core MDASI items) that are commonly encountered in cancer patients receiving treatment (including skin symptoms, hair loss, mucositis, diarrhea, etc.). The developers of this instrument intended it to be flexible for the addition of specific items that have been validated on an item-specific basis. For this reason, we will collect 6 additional validated items and the combined instrument with 25 items overall will be referred to as the MDASI-ECOG.

6.2 The Revised Edmonton Staging System for Cancer Pain (rESS)

Also included in the clinician questionnaire at baseline and follow up are the 4 items that comprise the revised version of the Edmonton Staging System for cancer pain. The original Edmonton Staging System (ESS) was initially developed as a prognostic indicator for cancer pain management (22). Using the principles of the TNM classification system as a guide, the ESS attempted to classify cancer pain on the basis of seven characteristics that were thought to have a clinical prognostic value for achieving good pain control. The characteristics were: mechanism of pain (visceral, bone or soft tissue, neuropathic, mixed, unknown); incidental pain (presence or absence); amount of daily opioid use on admission; cognitive function (impaired or normal); psychological distress (present or absent); tolerance (present, according to an average daily increase in opioid consumption of more than 5% over the first three weeks of follow-up); and a past history of alcoholism or drug addiction (positive or negative). Depending on the combination of these features, patients were defined as having a good, intermediate, or poor prognosis for pain control. Through further modification, two features, cognitive function and opioid consumption, were excluded from the ESS, as they were not found to be independently associated with the probability of obtaining good pain control.

The ESS has been used in a number of reports where it was found useful in describing an underlying cancer pain syndrome. Difficulties with interpretations and definitions, however, have limited the use and international acceptance of the ESS. In the original ESS validation studies, a good prognosis for pain control had a high positive predictive value. Approximately 50% of the patients with a poor prognosis, however, would still achieve good pain control. To overcome these limitations and improve the clinical and research validity of the ESS, a revised version, the Revised Edmonton Staging System (rESS), was developed. An expert panel, consisting of physicians and researchers working in the Edmonton Regional Palliative Care Program, developed the rESS to improve upon the noted areas of deficiency. Since the initial development of the rESS, a multicentre validation study involving advanced cancer patients has recently been completed and the instrument demonstrated good reliability and validity (23).

Overall, the rESS is a simple, comprehensive classification system for meaningfully assessing cancer pain for clinical prognosis and treatment, as well as for research. While many factors have been proposed as prognostic for pain control, the rESS is the first pain classification system to simultaneously integrate these factors within a cohesive framework. In the context of this study, it also provides an explicit clinician assessment of the presence or absence of cognitive dysfunction and addiction behaviors with definitions of these entities that have been carefully developed and validated.

7. Study Parameters

	Initial Assessment	Follow-up Assessment ¹
Rev. 12/06		
	X	X
	X	
		X
	X	
		X
Rev. 12/06	X	X

¹ To be completed (mailed) between days 28-35 following initial assessment

8. Statistical Considerations

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8.1 Overview

This is primarily a descriptive study aimed at assessing prevalence, severity and interference due to physical and psychological symptoms in patients with cancer being treated on an outpatient basis at ECOG institutions. It is also of interest to determine the relation between the number of symptom related interventions and the providers' perception of symptom severity. Other objectives include an evaluation of the commonly treated symptoms, a count of the number of patients who experience symptom reduction from their moderate to severe symptoms and a characterization of the determinants of symptom relief. Since this survey will accrue patients with cancer of the colon/rectum, breast, lung and prostate, a secondary analysis of the previously stated objectives will also be conducted to study the differences and similarities among these patients with respect to their disease sites.

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The anticipated accrual goal will be 2310 patients and their physicians. This estimate is based on a pain survey study that was activated in February, 1989 with 119 patients accrued. The survey had the following levels of participation; 80% (4/5) of the main members, 100% (5/5) of the CCOP institutions and 60% (3/5) of the CGOP institutions participated.

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8.2 Selection of Participating Clinics

Two-thirds of patients (n=1,540) will be recruited from ECOG primary CCOPs. The principal investigator of each CCOP will designate which affiliated members will participate and the projected number of patients to be accrued per member. In the first round of recruitment, up to 100 patients per CCOP may be accrued. Patients may be approached if they are being evaluated for possible treatment or symptom management, if they are currently being treated or if they are in active follow-up for breast, lung, colorectal, or prostate cancer. Sites will be encouraged to use a patient selection strategy that is feasible and somewhat systematic, to avoid introducing bias. Some examples might be to approach every third patient arriving for a previously scheduled visit on consecutive weekdays until all of the site's patients are accrued, or to approach the first 5 patients scheduled for afternoon appointments. After data are received for approximately 80% of the total patients targeted in the first round of CCOP recruitment, remaining patients will be recruited from CCOPs who indicated an interest in enrolling additional patients and whose data submission is in good standing. First priority for additional patients will be given to the 5 minority-based CCOPs to assure adequate representation of minority patients.

One-third of patients (n=770) will be recruited from disease site-specific clinics in the 20 ECOG main institutions. Invitations to participate will be issued randomly to ten clinics in each target malignancy (breast, lung, colorectal, and prostate cancer). Each clinic will be expected to enroll 19 patients if they accept the invitation. If clinics decline the invitation to participate, additional clinics in that disease site selected at random will be issued invitations. If patients remain to be recruited after all main institution site-specific clinics have been offered the invitation to participate, main institutions will be given the opportunity to recruit patients with the target malignancies from their community affiliates (CGOPs).

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8.3 Sample Size Justification and Plan for Analysis

Since this is a descriptive study, no adjustments will be made for multiple comparisons however statistically significant results will be interpreted with caution. It is assumed that 70% (approximately 1620) of the patients enrolled will complete forms at baseline and follow-up. After 25% of the patients (577) have been enrolled, the compliance rate will be verified and the sample size adjusted if the projected rate is not met.

Following are the specific objectives and hypotheses of the study:

1. To describe the prevalence, severity and interference due to physical and psychological symptoms experienced over a 4-5 week period in cancer patients being treated on an outpatient basis at ECOG institutions.

Hypothesis 1: The symptoms rated as most severe at baseline and follow-up will include pain, fatigue and emotional distress.

Hypothesis 2: Greater than 30% of patients with advanced disease will have at least 3 moderate-to-severe symptoms despite the current symptom management efforts.

Rev. 12/06 Patients will be administered the M D Anderson Symptom Assessment Inventory (MDASI-ECOG) at baseline and follow-up in which symptoms are rated on a 0-10 scale. The presence of symptoms will be categorized as moderate (ratings of 5-6 in a 0-10 scale) and severe (ratings ≥ 7). The severe symptoms at both time points will be recorded for each patient. The analysis for this objective will primarily be descriptive.

Rev. 12/06 Means, medians, and ranges of severity of symptoms measured with the MDASI-ECOG and percentages of patients with symptoms at severe (ratings ≥ 7) levels will be reported. The proportion of patients with severe pain, fatigue and emotional distress by disease type will be estimated using proportions and adjusting for variability between patients, institutions and type of institutions. PROC Mixed procedure in SAS will be used to fit multi-level or hierarchical models to account for the different sources of variability and where the dependent variable is a binary outcome, i.e., presence or absence of the symptom. Such models will be four-levels that refer to situations in which the data are at four levels of hierarchy, i.e., patients within disease site, disease site within institutions, institutions within institution type, i.e., CCOP, CGOP or main and within institution type. In order to get a symptom prevalence overall similar models will be fitted to the data except that the model will have three-levels. In addition to stratification by disease type, prevalence according to gender, race/ethnicity, age and type of treatment will be reported using analogous methods.

Rev. 12/06 Similar procedures will be used to estimate the number of patients reporting moderate-severe symptoms at the two time points. Assuming that about 70% (1620) of the patients enrolled will complete questionnaires at baseline and follow-up, and assuming that prevalences of severe symptoms are 50% (most conservative estimate for common symptoms of pain, fatigue and emotional distress), the maximum length of the 90% confidence interval will be 4.2% using the exact binomial distribution. The paired t-test or the Wilcoxon signed rank test will be used to assess changes at baseline and follow-up for continuous variables. Table 1 presents the power to detect a specified effect (in terms of standardized means) to be detected using a paired t-test with a 0.05 two-sided significance level assuming different values for the correlation between the measures at baseline and follow-up. The different sample sizes represent various subgroups, i.e., overall, by disease site, by gender and by race/ethnicity. The standard deviations for the MDASI in patients treated with chemotherapy were assumed to be 2.8 for the global interference score and 1.92 for the global severity score (Cleeland et al, Cancer 2000; 89:1634-46.). The correlation between the measures at baseline and follow-up is assumed to be 0.5.

Table 1
Power to Detect a Specified Effect according to Sample Size

Sample size	Size of the effect to be detected (in standard deviations), assuming correlation = 0	Size of the effect to be detected (in standard deviations), assuming correlation = 0.3	Size of the effect to be detected (in standard deviations), assuming correlation = 0.5	Size of the effect to be detected (in standard deviations), assuming correlation = 0.7	Change to be detected in the MDASI scores in a 0-10 scale		Power (%)
					Interference	Severity	
1295	0.11	0.09	0.08	0.06	0.22	0.15	80
863	0.14	0.11	0.096	0.07	0.27	0.18	80
432	0.19	0.16	0.136	0.10	0.38	0.26	80
216	0.27	0.22	0.193	0.15	0.54	0.37	80

We will also use individual growth models, designed for exploring longitudinal data (on patients) over time. Therefore, categorical variables that assess the burden of the treatment will be dichotomized and PROC Mixed procedure in SAS will be used to fit an individual growth model to assess the significance of changes between baseline and the follow-up visit. For patients who have symptoms, type of symptom management offered, response to symptom-directed treatment, and patient compliance with symptom treatment recommendations will be described using percentages and confidence intervals.

2. To determine if the number of symptom-related interventions are related to the providers' perceptions of symptom severity.

Hypothesis 3: The number of provider interventions for symptom management is more associated with the provider's perception of moderate or severe symptoms than the patient's self-report of symptoms.

Hypothesis 4: Patients seen in NCI-designated minority-based practices will have fewer interventions directed at managing symptoms compared to the majority-based practices.

For each commonly reported symptom, i.e., pain, fatigue, emotional distress, multi-level models will be used to examine the association between the number of provider interventions and the provider's perception and the patients' self-report of severity of that symptom while adjusting for clinical and demographic factors. Discrepancies between patient and physician estimates of adequacy of symptom control will also be assessed. Fisher's exact test (or a test for concordance using Kendall's coefficient of concordance) and the t-test or the Wilcoxon rank sum test will be used to identify and select potential predictors that will be entered in a multi-level model. Goodness of fit statistics will be used to evaluate the multi-level models and to compare the goodness of fit between models (possibly nested).

3. To determine whether physical symptoms are more commonly prioritized and treated compared to psychological symptoms.

Hypothesis 5: There will be a greater discrepancy between provider and patient estimates of psychological symptoms compared to physical symptoms.

Hypothesis 6: There will be more frequent provider interventions directed at physical symptoms as compared to psychological symptoms self-reported by patients.

To assess symptom burden, total symptom severity (mean of the MDASI severity scores) will be used for both the 7 physical items and the 6 non-physical items of the 13 core items of the MDASI. In addition, as an exploratory analysis, symptom burden will be assessed by counting the number of MDASI symptom items with a score 7 or greater, both for severity and interference. This alternative way of scoring the symptom burden will be used as a sensitivity analysis. If either way of evaluating symptom burden produces a similar set of predictors, the conclusions will be stronger.

Adequacy of pain treatment will be assessed using the Pain Management Index (PMI) (Cleeland et al, NEJM 1994). The PMI is based upon the patient's level of worst pain intensity categorized as 0 (no pain), 1 (1 to 3, mild pain), 2 (4 to 7, moderate pain), or 3 (8 to 10, severe pain). The pain level is subtracted from the most potent level of analgesic drug therapies as prescribed by clinicians. scored as 0 (no analgesic drug), 1 (non-opioids), 2 (a weak opioid), or 3 (a strong opioid). The PMI index can range from -3 (a patient receiving no analgesic drug who is in severe pain) to +3 (a patient receiving strong opioids who is pain-free). These scores will be dichotomized: negative scores indicate inadequate orders for analgesic drugs, and scores of 0 or higher indicate acceptable treatment. Determining whether the item score improved by 2 or more points compared to the previous item score will assess adequacy of management of other symptoms.

Multi-level models will be fitted to the data to examine the relationship between the number of interventions and the type of symptom, i.e., physical or psychological.

4. To determine the percentage of patients who experience a significant reduction in moderate-to-severe symptoms and to characterize the determinants of symptom relief.

Hypothesis 7: The greater the agreement between provider and patient in symptom reporting, the greater the likelihood that moderate-severe symptoms will be improved at follow-up.

Hypothesis 8: NCI-designated minority-based practices will have less evidence for improvement between the baseline and follow-up visit.

Multi-level models will be used to identify clinical, demographic, and/or discrepancy factors predictive of symptom improvement. The Fisher's exact test and the t-test or the Wilcoxon rank sum test will also be used to identify and select potential predictors that will be entered in the model. Goodness of fit statistics will be used to evaluate the multi-level models and to compare the goodness of fit between models (possibly nested).

5. To determine the focus and scope of interventions chosen by oncologists to improve the symptom control of patients seen in their outpatient clinics.

The interventions chosen by oncologists used to improve the symptom control of patients will be described using descriptive statistics. We will study the association between the interventions used and the symptoms reported by patients using multi-level models.

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8.4 Handling Missing Data

If more than 20% of the cases have missing data in some of the variables, a Bayesian approach to assess predictor factors will be used. This analysis will allow us to include in the model all the subjects that participate in the survey. The regression coefficients will be given 'non-informative' Normal priors. Prior distributions for the covariates will be assumed to be Normal or Binomial ($p, 1$) with p distributed as Uniform (0,1). The BUGS program (Bayesian inference using the Gibbs sampling algorithm) will be used to estimate the coefficients and obtain 95% credible confidence intervals. Results obtained using this modeling strategy will be compared with the complete case analysis. In case of discrepancies, possible explanations will be discussed.

9. Records to Be Kept

Please refer to the E2Z02 Forms Packet for the forms submission schedule and copies of all forms. The E2Z02 Forms Packet may be downloaded by accessing the ECOG World Wide Web Home Page (<http://www.ecog.org>). Forms must be submitted to the ECOG Coordinating Center, FSTRF, 900 Commonwealth Avenue, Boston, MA 02215 (ATTN: DATA).

This study will be monitored by the CTEP Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly from the ECOG Coordinating Center to CTEP by electronic means.

10. Patient Consent and Peer Judgment

Current FDA, NCI, state, federal and institutional regulations concerning informed consent will be followed.

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SOAPP (Symptom Outcomes and Practice Patterns): A Survey of Disease and Treatment-Related Symptoms in Patients with Invasive Cancer of the Breast, Prostate, Lung or Colon/Rectum

Version Date: December 7, 2006

**Appendix I
Informed Consent Template**

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You are being asked to take part in this study because you have cancer of the breast, lung, prostate, or colon/rectum.

This is a questionnaire study (a type of research study). Like clinical trials, this descriptive study is a type of research that includes only patients who choose to take part.

WHY IS THIS STUDY BEING DONE?

This research is being done because there is a need for better understanding of common symptoms experienced by cancer patients and how they are treated. This study holds promise for expanding our knowledge base in this important area of cancer care.

The National Institute of Health has stated that too many patients with pain, depression, and fatigue receive inadequate treatment for these symptoms, and that more information is needed about what is bothersome to patients and what treatments are already being used for symptom management. This kind of research does not change how a patient is treated, but it provides information to researchers that helps them plan future studies of new treatments directed at relieving symptoms and improving quality of life.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

About 2310 people will take part in this study.

WHAT IS INVOLVED IN THIS STUDY?

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There are 2 sets of questionnaires which will be used to document symptoms you are experiencing. You will be asked to complete one set of questionnaires today and return the second set either by mail or at your next visit to this clinic. Completion of the forms should take about 30 minutes each.

WHAT WILL HAPPEN IF I TAKE PART IN THIS RESEARCH STUDY?

If you take part in this study, you will be asked to complete forms that will assess your cancer symptoms. These forms will be completed at the beginning of the study and again 28-35 days later.

HOW LONG WILL I BE IN THE STUDY?

We think you will be in the study for 4-6 weeks.

You may stop participating at any time. However, we encourage you to talk to your doctor before you decide to stop participating in the study.

WHAT SIDE EFFECTS OR RISKS CAN I EXPECT FROM BEING IN THE STUDY?

This is a survey study that is not expected to produce any serious adverse events or risks. If the survey is the cause of any unexpected adverse event, that event will be reported.

Completing the questionnaires which are part of the study may remind you of unpleasant aspects of your condition and treatment, which may be upsetting.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you agree to take part in this study, there may or may not be direct medical benefits to you.

Possible benefits are increased awareness of your cancer treatment symptoms, your physician gaining more insight into your cancer symptoms and their severity, and possible reduction of your moderate-to-severe symptoms because of this increased awareness.

We hope the information learned from this study will benefit other patients experiencing cancer-related symptoms in the future.

WHAT OTHER OPTIONS ARE THERE?

Instead of being in this study, you have the option:

- Not to participate and simply continue with the symptom assessment methods available through your physician and treatment center.

You may receive **treatment** at this medical center and at other medical centers, even if you do not take part in this study.

WILL MY MEDICAL INFORMATION BE KEPT PRIVATE?

The Eastern Cooperative Oncology Group (ECOG) is conducting this study. ECOG is a cancer research group that conducts studies for the National Cancer Institute. Your doctor is a member of ECOG or another group that is participating in this study. To help protect your privacy, ECOG has obtained a Confidentiality Certificate from the Department of Health and Human Services (DHHS).

With this Certificate, ECOG cannot be forced (for example, by court subpoena) to disclose information that may identify you in any federal, state or local civil, criminal, administrative, legislative or other proceeding. Disclosure will be necessary, however, upon request of DHHS for audit or program evaluation purposes.

You should know that a Confidentiality Certificate does not prevent you or a member of your family from voluntarily releasing information about you or your involvement in this research. If an insurer or employer learns about your participation and obtains your consent to receive research information, then ECOG may not use the Certificate of Confidentiality to withhold this information. This means that you and your family must also actively protect your privacy.

You should also understand that your doctor and ECOG may take steps, including reporting to authorities, to prevent you from seriously harming yourself or others.

Finally, the Certificate does not prevent the review of your research records under some circumstances by certain organizations for an internal program audit or evaluation. Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as:

- Eastern Cooperative Oncology Group (ECOG)
- National Cancer Institute (NCI)
- Food and Drug Administration (FDA)
- Other regulatory agencies and/or their designated representatives
- Drug manufacturers and/or their representatives
- Central laboratories, banks and/or reviewers

WHAT ARE THE COSTS OF TAKING PART IN THIS STUDY?

Taking part in this study is unlikely to lead to added costs to you or your insurance company. If you have any questions or concerns, please ask your cancer care providers.

You or your insurance company will be charged for any continuing medical care and/or hospitalization.

You will receive no payment for taking part in this study.

WHAT ARE MY RIGHTS IF I TAKE PART IN THIS STUDY?

Taking part in this study is voluntary. You may choose not to take part, or you may leave the study at any time. Leaving the study or choosing not to take part will not result in any penalty or loss of benefits to which you are entitled.

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study.

A Data Safety and Monitoring Board, which is an independent group of experts, will be reviewing the data from this research throughout the study.

WHO CAN ANSWER MY QUESTIONS ABOUT THE STUDY?

You can talk to your doctor about any questions or concerns you have about this study. Contact your doctor _____ [name(s)] at _____ [telephone number].

For questions about your rights while taking part in this study, call the _____ [name of center] Institutional Review Board (a group of people who review the research to protect your rights) at _____ (telephone number). [Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.]

WHERE CAN I GET MORE INFORMATION?

You may call the National Cancer Institute's Cancer Information Service at:

1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

You may also visit the NCI Web site at <http://cancer.gov/>

For NCI's clinical trials information, go to: <http://cancer.gov/clinicaltrials/>

For NCI's general information about cancer, go to <http://cancer.gov/cancerinfo/>

You will get a copy of this form. If you want more information about this study, ask your doctor.

SIGNATURE

I have been given a copy of all _____ *[insert total of number of pages]* pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Participant _____

Date _____

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Appendix II

Patient Thank You Letter

We ask that the physician use the template contained in this appendix to prepare a letter thanking the patient for enrolling in this trial. The template is intended as a guide and can be downloaded from the ECOG web site at <http://www.ecog.org>. As this is a personal letter, physicians may elect to further tailor the text to their situation.

This small gesture is a part of a broader program being undertaken by ECOG and the NCI to increase awareness of the importance of clinical trials and improve accrual and follow-through. We appreciate your help in this effort.

[PATIENT NAME]

[DATE]

[PATIENT ADDRESS]

Dear [PATIENT SALUTATION],

Thank you for agreeing to take part in this important research study. Many questions remain unanswered in cancer. With the help of people like you who participate in clinical trials, we will achieve our goal of effectively treating and ultimately curing cancer.

We believe you will receive high quality, complete care. Your physician and research staff will maintain very close contact with you. This is important so as to allow your physician to provide you with the best care while learning as much as possible to help you and other patients.

On behalf of **[INSTITUTION]** and the Eastern Cooperative Oncology Group, we thank you again and look forward to helping you.

Sincerely,

[PHYSICIAN NAME]

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**SOAPP (Symptom Outcomes and Practice Patterns): A Survey of Disease and Treatment-Related Symptoms in
Patients with Invasive Cancer of the Breast, Prostate, Lung or Colon/Rectum**

Appendix III

Patient Log

INSTITUTION: Use this form to record the oncology out-patients who have been asked and elected **not** to participate in this study.

Institution: _____

CRA: _____

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Patient Initials (L, F)	Date Approached (M/D/Y)	Reason Given for Not Participating
1. _____	____/____/____	_____
2. _____	____/____/____	_____
3. _____	____/____/____	_____
4. _____	____/____/____	_____
5. _____	____/____/____	_____
6. _____	____/____/____	_____
7. _____	____/____/____	_____
8. _____	____/____/____	_____
9. _____	____/____/____	_____
10. _____	____/____/____	_____
11. _____	____/____/____	_____
12. _____	____/____/____	_____
13. _____	____/____/____	_____
14. _____	____/____/____	_____
15. _____	____/____/____	_____

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Page _____ of _____'s Patient Log
Institution/site name