Final SCOPE Protocol

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The SCOPE Trial
Surgery for Cancer with Option of Palliative Care Expert

A Randomized Trial of an Early Palliative Care Intervention for Patients Undergoing Surgery for Cancer

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1.0 Introduction

Cancer represents a significant burden of aging. When comparing those over 65 years to those under 65, the incidence of cancer is 10 times greater, and the cancer death rate is 16 times greater.[1] Care for older adults with surgically-treated gastrointestinal (GI) or genitourinary (GU) malignancies imposes particular burdens because the treatments are highly morbid, especially in older adults with multimorbidity. For instance, pancreatic cancer is the fourth leading cause of cancer deaths with 70% of this mortality occurring in patients over 65, and nearly three-quarters of patients die within 5 years of resection.[1,2] Surgeons face a quandary: resection is the only chance for cure, but resection potentially increases suffering.

Concurrent palliative care consultation (PCC) with oncologic care improves clinical outcomes earlier in the illness trajectory as well as at the end of life (EOL).[3] PCC reduces use of intensive life-prolonging therapy at EOL while improving quality of life (QOL) and other patient-centered outcomes.[4,5] Early PCC concurrent with chemotherapy improves survival for patients with advanced malignancies.[4,6] **PCC also has been associated with improved surgical outcomes,[7] yet surgeons frequently call for such expertise only as a last resort. There is a dearth of literature to help surgeons understand how PCC can benefit surgical patients with serious age-related conditions, such as abdominal malignancies**.

The **S**urgery for **C**ancer with **O**ption of **P**alliative Care **E**xpert (**SCOPE**) Trial is an investigation that will study the effect of a palliative care implementation during the preoperative, perioperative, and postoperative phase for older adults undergoing cancer surgery for selected (see inclusion criteria) abdominal malignancies. SCOPE will be a single-blind, single-institution randomized controlled trial of 236 patients. Intervention arm patients will receive a preoperative outpatient specialty palliative care consultation from a palliative care provider (physician or nurse practitioner) in addition to inpatient and outpatient palliative care follow-up postoperatively. Control arm patients will receive usual care with PCC available at the discretion of the primary treatment team (currently these patients rarely get PCC and usually only in the last weeks of life). **The central hypothesis of the SCOPE Trial is that preoperative, perioperative, and postoperative specialty PCC will improve patient functioning and quality of life while decreasing intensive life-prolonging therapy at EOL in patients undergoing resection of selected abdominal malignancies.**

Specific Aims

Aim 1: To determine whether preoperative, perioperative, and postoperative specialty palliative care consultation improves 90 day post-operative functional status. We hypothesize that PCC will improve physical and functional quality of life as measured by the Trial Outcome Index (TOI) of the FACT-G instrument in patients undergoing resection. The SCOPE Trial's primary end-point will be TOI at approximately 90 days postoperatively, controlling for baseline score. Secondary end-points will be QOL (FACT-G) at approximately 90 days and days alive at home during the first 90 days. Exploratory endpoints will be anxiety, and depression (PROMIS Anxiety-6 and Depression-6) and Karnofsky performance status at 90 days; satisfaction with hospital stay; and initiation of appropriate adjuvant therapy.

Aim 2: To determine whether preoperative, perioperative, and postoperative specialty palliative care consultation improves cancer survivorship. We hypothesize that PCC will improve the length and quality of life for patients undergoing resection. Secondary outcomes for

Aim 2 are overall survival at three years and post-traumatic stress disorder symptoms at 180 days. Exploratory endpoints include healthcare utilization, post-traumatic growth, and physical functioning at approximately 180 days post-operatively; long term trends in physical functioning, QOL, size of life space, employment, health care utilization, long-term facility placement, and caregiver burden.

Aim 3: To determine whether preoperative, perioperative, and postoperative specialty palliative care consultation affects quality of EOL care after resection. We hypothesize that preoperative and ongoing PCC will improve quality of EOL care. To test this hypothesis, we will analyze patients who die during the SCOPE Trial. Outcomes for this subgroup analysis will be receipt of ineffective and burdensome treatment (chemotherapy within 14 days of death) or delayed referral to hospice (length of stay in hospice less than 7 days), days at home without an ER visit in last 30 days of life, location of death, and quality of death and dying as measured by the FATE-S instrument.

To accomplish these Aims, my team will randomize 236 patients at Vanderbilt University's surgery, urology, and gynecology clinics to complete the SCOPE Trial with 118 patients in each arm. A positive effect of PCC in any of the Aims would indicate early PCC is novel strategy to improve clinical care in these surgical patients. Any negative results will be investigated using multivariate analyses on covariates to identify subpopulations (such as frail patients) in which the intervention was more effective as a basis for designing future studies of the effects of PCC on surgical patients with serious age-related conditions.

2.0 Background

End-of-life (EOL) care in the United States is extremely expensive and often fails to deliver comfort and dignity. Care in the last year of life consumes over 25% of Medicare expenditures.[8] Most people desire to die at home, but only about a third do so, and a quarter die as inpatients in hospitals.[9,10] Hospice care, in which patients with terminal illnesses forego life-prolonging care and instead receive intensive comfort focused care with an aim of remaining at home as long as possible, is one means to address these shortcomings in EOL care.[11] However, fewer than half of patients receive hospice care at the time of death, and almost 30% of patients who enroll in hospice do so within three days of death and so have very little time to benefit from hospice.[10]

One strategy to address these issues is involvement of palliative care specialists earlier in the course of life-limiting illnesses. Palliative care providers specialize in helping patients articulate the goals for their care and in determining when medical interventions are consistent with these goals. When involved early in the course of treatment, palliative care specialists guide patients through their treatment and allow patients and providers to recognize the point when aggressive life-prolonging care no longer meets the patient's goals. Early palliative care interventions accordingly have both decreased intensity of EOL care and increased hospice enrollment and the duration of time under hospice care.[4,13]

Palliative care providers also specialize in alleviating physical symptoms and psychosocial distress brought by life-threatening illnesses. Thus, the early initiation of palliative care has been shown to bring benefits beyond improving EOL care: interventions involving early initiation of palliative care have improved patient-centered outcomes including physical functioning, quality of life, satisfaction, and symptom burden.[4,5,12-15] Moreover, in patients with

advanced cancer, randomized controlled trials have shown a survival advantage in patients who receive palliative care interventions early in the course of their treatment.[4,6]

Early palliative care consultation has the potential to lengthen life, improve patient-centered outcomes, increase quality of EOL care, and reduce unnecessary expenses associated with inappropriately aggressive EOL care. Patients with incurable metastatic cancer are one population where palliative care has been shown to have such positive effects, but there are likely other populations for whom palliative care could provide similar benefits, including surgical patients with serious age-related conditions, like cancer.

There is a driving, unmet need to determine what surgical patients with age-related conditions would benefit from early palliative care. A recent expert panel convened by the National Institutes of Health and the National Palliative Care Research Center identified a need to develop clinical trials to test the effectiveness of early specialist palliative care consultation in surgery patients.[16] The SCOPE Trial will address this research priority and determine whether patients undergoing resection for **poor-prognosis abdominal malignancies** constitute another group for whom early palliative care will yield improvements in care.

3.0 Preliminary Studies

Previous research on early initiation of palliative care has occurred mostly in the setting of incurable diseases—typically metastatic cancer or end-stage heart failure. Only one trial has examined the initiation of early palliative care in surgical patients, and this trial examined only outcomes related to quality of life and symptom burden without looking at effects on surgical or oncologic outcomes or EOL care.[17] Moreover, the patients involved in that study were patients with advanced malignancy undergoing any surgical procedure, not necessarily the potentially curative resections to be examined in the SCOPE Trial. The only trial to examine the impact of early palliative care along with potentially curative therapy was a recently reported trial in bone marrow transplant patients.[18] The SCOPE Trial is novel as the population is both a surgical population and a population undergoing potentially curative therapy.

Another burgeoning area of research is the pre-operative optimization of surgical patients to improve outcomes and reduce complications, especially in surgical patients with age-related conditions. Most research has focused on encouraging physical prehabilitation to improve patient functional status before the operation, eliminating modifiable risk factors (such as smoking), or controlling comorbidities (such as diabetes).[19-21] Preoperative palliative care is thus a novel preoperative intervention that may alleviate symptom burden and psychosocial distress, both of which could impair the resilience of patients to withstand the stresses of an operation.[22,23]

A third important growing area of research is cancer survivorship, especially in older patients. A recent expert conference convened by the National Institute on Aging and the National Cancer Institute identified a research priority of investigating interventions to improve health and functioning of older patients undergoing treatment for cancer.[24] The SCOPE Trial offers the opportunity to address this recently identified research priority by examining the effect of early palliative care on survivorship after surgery for cancer.

Studying the benefits of preoperatively initiated palliative care for patients undergoing resection of GI and GU malignancies thus would ride the crest of three waves of research—research into early palliative care interventions, research into preoperative interventions to improve surgical outcomes, and research on interventions to improve cancer survivorship. At the same time as it fits into these young but robust areas of research, the SCOPE Trial also fills voids in these bodies of investigation by using a novel intervention with a novel population.

The SCOPE Trial will investigate a new strategy of preoperative, perioperative, and postoperative PCC, which can improve patient reported and clinical outcomes while promoting patient-centered care. This investigation could offer hope for patients by reducing suffering and improving their clinical recovery. Preoperative PCC could then be applied to different surgical populations with serious age-related conditions, such as frailty and organ failure.

4.0 Study Objectives and Endpoints

4.1 Study Objectives. The primary objective of the **SCOPE** trial is to determine whether a palliative care intervention improves recovery and quality of life after major abdominal operations for cancer. Secondary objectives are to determine whether the palliative care intervention improves long-term functioning and quality of life for these patients and whether the palliative care intervention improves EOL care for the subset of patients who die during the study.

4.2 Efficacy Endpoints

4.2.1 Primary Endpoint. The **trial's primary endpoint** will be score on the FACT-G TOI at 90 days post-operatively (controlling for baseline score).

4.2.2 Secondary Endpoints

[1] FACT-G score at 90 days
[2] Days alive at home during first 90 days
[3] PTSD Checklist-Civilian Version score at 180 days
[4] Overall survival at 1 year

4.2.3 Exploratory Endpoints

[1] FACT-G TOI score [180 days, trend over study period]
[2] FACT-G score [180 days, trend over study period]
[3] PROMIS Anxiety-6 score [90 days, 180 days]
[4] PROMIS Depression-6 score [90 days, 180 days]
[5] Satisfaction with hospital stay [30 days]
[6] Time from surgery to adjuvant therapy
[7] Overall Survival [3 years]
[8] Post-traumatic Growth Inventory score [180 days]
[9] Karnofsky Performance Status [90 days, 180 days, trend over study period]
[10] Employment [trend over study period]
[11] Number of hospital admissions over study period
[12] Number of ER visits over study period
[13] Long-term care residence [trend over study period]
[14] Life Space Assessment Questionnaire score [trend over study period]
[15] Zarit Burden Interview [90 days, 180 days, trend over study period]

4.2.4 Planned Subgroup Analysis: Patients who die during the course of the study will be included in a subgroup analysis with the following outcomes.

[1] Receipt of chemotherapy within 14 days of death
[2] Hospice enrollment of less than 7 days before death
[3] Days at home without ER visit or hospital stay in last 30 days of life
[4] Location of death (home vs. facility)
[5] Quality of end-of-life care (FATE-S score)

5.0 Inclusion/Exclusion Criteria

5.1 Inclusion Criteria. Consecutive patients will be eligible for inclusion in the SCOPE trial if they are:adult patients (≥18 years old) scheduled for one of the following abdominal operations with intent to provide cure or durable oncologic control of malignancy:

1) Total or partial gastrectomy requiring anastomosis
2) Total or partial pancreatectomy
3) Partial hepatectomy
4) Colectomy or proctactomy if one of the following 3 conditions is also met:
    i) patient age is 65 years or older
    ii) disease is metastatic
    iii) disease is locally invasive requiring extensive resection
5) Radical cystectomy
6) Pelvic exenteration
7) Abdominal debulking for ovarian or endometrial carcinoma
8) Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy

5.2 Exclusion Criteria. Patients will be excluded (i.e., not consented) for any of the following reasons:

[1] Non-English speaking patient
[2] Residence >150 miles away from Vanderbilt and do not visit the Nashville area regularly
[3] No telephone or otherwise unwilling/unable to complete follow-ups
[4] Prisoner
[5] Current enrollment in a study that does not allow co-enrollment or that uses a non-pharmacologic, non-procedural intervention directed at surgical or cancer care.
[6] Deaf
[7] Severe prior cognitive or neurodegenerative disorder that prevents a patient from living independently at baseline
[8] Inability to obtain informed consent from patient meeting all inclusion criteria for the following reasons:
    (a) Attending surgeon refusal
    (b) Patient refusal
    (c) Period of time between screening patient and time of operation does not allow preoperative outpatient palliative care visit.
[9] Currently participating in palliative care or seeing a palliative care provider.

6.0 Enrollment/Randomization

6.1. Screening and Obtaining Informed Consent. Patients will be identified at their clinic visits to a surgeon to schedule a resection of an eligible malignancy. Study staff will determine eligibility. When an eligible patient is identified (i.e., inclusion criteria are met and no exclusion criteria are present), informed consent will be pursued. Additionally, the patient will identify a caregiver who will be the subject for caregiver evaluation and will be the contact person in later phases of the study if the patient is unable to respond for him or herself. In some cases, the main caregiver may change due to various circumstances and a new caregiver will be contacted. Patient will be randomized and assigned via randomization to the Intervention Group or the Control Group.

To maintain group balance among types of malignancy, a critical determinant of outcome, the treatment group allocation will be specified by stratified randomization. We will randomize patients meeting all eligibility requirements in a 1:1 ratio to early PCC or standard of care using a computer-generated randomization scheme using a permuted block design, stratified by type of cancer. The randomization scheme will be created by the trial's primary biostatistician and be directly uploaded into REDCap's randomization module. In rare cases some patients may be enrolled into trial but not randomized for uncontrollable reasons such as a surgery date is talked about with patient with the expectation that surgery may not occur due to lack of response to a therapy. Some surgeons have tight windows of time scheduling the patient a few days after a scan which gives little room to meet with patient to consent and complete pre-surgery interventions. It will be rare (<10% of patients enrolled) that a patient is consented without randomization but the study team wants the option to connect with these patients when it is most convenient for them. The goal is to have 236 randomized patients with the expectation that more than 236 patients may be enrolled/consented to get to a total of 236 patients randomized.

6.2 Blinding. The post-op assessments of patients will be completed by a masked outcome assessor who is not aware of randomization assignments of patients. The assessors will be trained to avoid discussing assignment during their interactions with subjects.

7.0 Study Procedures

7.1 Enrollment. After informed consent is obtained, on the day of enrollment baseline demographic, clinical, and psychometric data will be collected on all consented subjects if feasible. If baseline information is not obtained on consent day, it will be completed as soon as possible and always before scheduled operation date.
The following procedure will be conducted:

> A **baseline function assessment** form will ascertain important information about the patient's baseline functional status, including history of depression and anxiety. Quality of life will be measured.

7.2 Intervention Trial. The Intervention Trial Phase will comprise of the Pre-operative Phase, In-Patient Phase, and the Long-Term Follow-up Treatment Phase. Patients in the control group will receive routine care for their malignancy and can receive palliative care consultation at the discretion of their providers. Patients assigned to the intervention group will be immediately scheduled for a preoperative outpatient palliative care consultation by a physician or

nurse practitioner on the Vanderbilt palliative care team. This encounter will focus on advance care planning, helping the patient articulate goals of care, and addressing any symptoms the patient is experiencing. If the patient is unable to come for the scheduled in-person consultation, a provider will contact them by phone to provide a phone consultation. Intervention patients will be compensated with a $50 gift card or check for coming to the pre-operative in person palliative care visit. Patients in the intervention group will also receive an inpatient palliative care consultation at least twice weekly during post-op hospitalization focusing on pain and symptom management and addressing any psychosocial distress around the operation. While inpatients, the palliative care team will follow these patients at the discretion of the palliative care provider.

After discharge the intervention group patients will have three outpatient follow-up contacts (in person visit or phone call) with a palliative care provider in the first 90 days post-operatively to address any symptoms and to continue addressing goals of care and any psychosocial distress. Patients will be compensated with a $50 gift card or check if they come to at least one in person post-operative palliative care clinic visit. From that point, the patient will have continued follow-up appointments in the outpatient palliative care clinic at a frequency at the discretion of the palliative care provider, with recommended appointment frequency of at least every 3 months. A palliative care visit is planned on every subsequent inpatient admission at Vanderbilt during the three-year study period. If an intervention patient is not able to come to a scheduled outpatient palliative care clinic visit, a phone call between the provider and the patient will be scheduled instead.

Data Timeline

Construct	Scale	Baseline	30 Days	60 Days	90 Days	180 Days	Biannually up to the end of 3 years	Post-Mortem (Final)
Demographics								
Cancer Type								
Operation								
Comorbidities	Charlson Comorbidity Index							
Frailty	Risk Analysis Index							
Cognitive Impairment	AD-8							
ASA Class								
Employment								
Religiosity/Spirituality	DUREL							
Functional Status	FACT-G TOI							
Functional Status	Karnofsky PS							
Quality of Life	FACT-G							
Anxiety	PROMIS Anxiety 6							
Depression	PROMIS Depression 6							
Fatigue	PROMIS Fatigue-Short Form 6a							
Hospital Satisfaction	HCAHPS Question 21							
PTSD	PTSD Checklist-Civilian Version							
Post-traumatic growth	Post-traumatic Growth Inventory							
Initiation of Adjuvant Rx								
ER Visits w/o admission								
Unplanned hospital admissions								
Hospital/Facility LOS								

Caregiver Burden	Zarit Burden Interview							
Size of Lifespan	Life Space Assessment Questionnaire							
Long term care residence								
Date of Death								
Date of Last Chemo								
Hospice Admission Date								
Hospice LOS								
Quality of Death	FATE-S							
Location of Death								

*<u>*Abbreviations (alphabetical)*</u>: **AD8**- Alzheimer Disease, **ASA-**American Society of Anesthesiologists, **DUREL**-Duke University Religion Index , **ER** – Emergency Room, **FACT-G**-Functional Assessment of Cancer Therapy - General, **TOI**-Trial Outcome Index, **FATE-S**-Family Assessment of Treatment at End of Life Short Form, **HCAHPS-**Hospital Consumer Assessment of Healthcare Providers and Systems , **LOS**-Length of Stay, **PROMIS-**Patient-Reported Outcomes Measurement Information System , **PS-**Performance Status , **PTSD**- Post Traumatic Stress Disorder, **Rx**- Prescription

7.2.2 Interventional Trial: Follow-up Phase. We will evaluate outcomes among survivors, approximately **90 days** after operation. The follow-up team will be blinded to patient assignment and will be instructed to avoid having patients reveal treatment group. Under the direction of the Vanderbilt Coordinating Center's lead neuropsychologist, trained study personnel will assess patients using the following validated telephone assessments:

[1] Functional Assessment of Cancer Therapy-General (FACT-G) Trial Outcome Index (TOI) assessing functional status.

[2] Karnofsky performance status assessing functional status.

[3] FACT-G assessing Quality of Life

[4] PROMIS Anxiety-6 assessment

[5] PROMIS Depression-6 assessment

[6] HCAHPS Question 21 assessment of satisfaction with hospital stay.

[7] Days alive at home without an Emergency Room (ER) visit

[8] Initiation of appropriate adjuvant therapy

At approximately 30, 60, and 90 days after the operation, study subjects will be contacted by the research personnel who will inquire about hospitalizations and ER visits and whether patients have initiated chemotherapy or radiotherapy since the operation; these data will be supplemented and corroborated by searches of the VUMC electronic medical record. Because adjuvant therapy is not the optimal therapeutic approach in all patients with these malignancies (some for instance, may require neo-adjuvant therapy that obviates adjuvant therapy), the medical records of all subjects will be examined by an oncologist to determine whether adjuvant therapy would be recommended based on any preoperative treatment and the results of the operation, assuming that the patient's functional status would allow it. The initiation of adjuvant therapy would then

be an outcome for this subgroup of patients. There is also one small subgroup of patients that will have fatigue examined closer at baseline and 30 days after the operation.

At the 90 day assessment the assessors will administer the psychometric instruments listed above to access the 90 day outcomes. Patients who cannot be reached by phone will have hard copy assessments mailed to them and/or electronic versions sent by e-mail with links to the instruments in REDCap.

We will evaluate long-term outcomes among survivors, approximately **180 days** after operation.

[1] PTSD Checklist-Civilian Version

[2] FACT G TOI and Karnofsky Performance Status

[3] Life Space Assessment Questionnaire

[4] FACT-G

[5] Trend in employment

[6] Zarit Burden Interview

[7] Trend in long-term care residence

[8] Overall Survival

[9] Trend in hospital admissions and in ER visits

At approximately 180 days after the operation, the outcomes assessor will again contact the subjects and will inquire about hospital admissions, ER visits, the patient's employment status (full-time, part-time, none) and whether the patient still lives at home or in a long-term care facility. At this time point, instruments to evaluate PTSD, post-traumatic growth, functional status, and quality of life will be administered. Additionally, the assessor will administer the Zarit Burden instrument to the caregiver. At approximately every 6-months thereafter patients and/or caregivers will be contacted, and functional status, life-space, quality of life, employment, long-term facility residence, hospital admissions, and ER visits along with caregiver burden will be assessed. Follow-up will continue for three years. Information about survival will be monitored by periodic surveillance of the medical record for indication of patient deaths as well as by newspaper searches of obituaries. If a scheduled 6-month contact occurs for a patient of whose death the study personnel were unaware, information about date of death will be obtained from the patient's caregiver.

When it is determined that a subject has died, the study personnel will contact the subject's designated caregiver to determine the end of life care utilization: whether and when the patient enrolled in hospice, when the patient's last dose of chemotherapy occurred, hospital admissions

and ER visits in the last month of life, and where the patient died. Additionally, a quality of death and dying survey will be administered to the caregiver

7.3.1 Long-term Follow-Up Patient Retention Plan. In order to maximize full participation of the randomized patients, the Long-Term Follow-Up Committee will rely on strategies refined over the past 15 years to produce a Follow-Up assessment rate of >85%. Study personnel will be instructed to obtain as much contact information as possible at time of enrollment (e.g. multiple phone numbers, mailing addresses, discharge destination etc.). The Neuropsychology Coordinator will perform the following interventions to maintain >85% Follow-Up assessment rates:

[1] A periodic phone call or letter will serve as an additional reminder of study participation.

[2] Weekly meetings will be conducted with study staff to evaluate the status of follow-up evaluations, with a particular focus on devising and implementing effective strategies to reach patients who may be difficult to contact. In rare situations, home visits may be conducted to help complete assessments.

[3] Participants will be compensated a $50 gift card or check after they complete the 90 day phone assessment.

[4] Participants may be contacted by SMS text messaging to arrange times to perform assessments or to remind participants to complete electronic versions of assessments. When contacting participants by text, study staff will identify themselves in a message with no PHI and then ask participants to confirm their identity before communicating any potentially identifiable information.

7.4 Data Collection/Case Report Form Details. During all study phases, all data will be entered into electronic case report forms (eCRFs) in a secured password-protected database. Copyrighted forms will be used when required. This study will utilize REDCap for data collection, transmission and storage. REDCap (Research Electronic Data Capture) is a secure, web-based application for building and managing online databases. Vanderbilt University, with collaboration from a consortium of institutional partners, including the Vanderbilt Institute for Clinical and Translation Research (VICTR) Informatics Core, developed and manages a software toolset and workflow methodology for electronic collection and management of research and clinical trial data. All study data will be entered via a password protected, study unique REDCap database website. REDCap servers are housed in a local data center at Vanderbilt and all web-based information transmission is encrypted. REDCap was developed specifically around HIPAA-Security guidelines and is recommended by both the Vanderbilt University Privacy Office and Institutional Review Board. REDCap has been disseminated for use locally at other institutions and currently supports > 140 academic/non-profit consortium partners and 11,000 research end-users (www.project-redcap.org)

7.5 Schedule of Events

Action	Enrollment	Interventional: Pre-operative Phase	Interventional: In-Patient Phase	Interventional: Long-Term Follow-up Phase
Consent	X			
Demographics	X			

Baseline Function Assessment	X			
Palliative Care Visit/Consult		X	X	X
Post-op phone call				X (~30, ~60, ~90 days after operation)
90 Day Post-op Assessment				X
180 Day Post-Op Assessment				X
Zarit Burden Interview				X
Biannual Assessments				X (~Every 6 months after 180 days evaluation)
Final Assessment				X

7.6 The Vanderbilt Coordinating Center (VCC). The VCC has extensive experience in the conduct of large, phase III clinical trials over the past decade. The VCC will perform (among other functions) the following: design the database and data collection tool, conduct site-training regarding protocol implementation and delirium monitoring to standardize all research activities during the trial, monitor enrollment pace and quality to ensure patients meet the inclusion/exclusion criteria, maintain blinding, track adverse events and ensure safety reporting, ensure protocol compliance, conduct follow-up phone testing of neuropsychological function and quality of life via neuropsychology technicians, and work with local study personnel using multiple proven patient retention techniques that have consistently achieved over 80% follow-up during previous studies.

8.0 Risks and Benefits of Mitigating Risks. Risks are minimal in this study. Some questions that are asked may be emotionally upsetting when noting that for example quality of life has declined or caregiver may be sad talking about their loved one that has died. The benefits of this study may have a great impact on patient outcomes, quality of life, and may have an impact on patients' likelihood to survive a life-threatening illness. During the consenting process and assessments, the research staff along with palliative care team will be mindful of patient's and caregiver's feelings and provide resources for them if appropriate such as counseling with a trained professional.

8.1 Data and Safety Monitoring Plan. To ensure data is accurately and completely collected during the SCOPE trial, the VCC will follow a specific Data Monitoring Plan. A VCC member will assure that the study protocol is being followed and that changes to the protocol have been approved by the local IRB. Also, the VCC will oversee that subject records are reviewed to determine whether data collected is accurate, complete, and current. Not only will the VCC be part of the Data and Safety Monitoring plan but it is also follows monitoring expectations set by the Vanderbilt-Ingram Cancer Center (VICC).

Purpose

VICC oversees patient safety and data monitoring for its investigator-initiated and NIH-NCI funded clinical trials through its Data and Safety Monitoring Committee (DSMC). The purpose of the DSMC is to ensure the efficient implementation and management of the VICC Data and Safety Monitoring Plan (DSMP). The Committee maintains authority to intervene in the conduct of studies as necessary to ensure clinical research performed at VICC achieves the highest quality standards.

Data and Safety Monitoring Plan
The VICC DSMP which is approved by the NCI Data and Safety Monitoring Review Panel, is accessible to all VICC investigators through the VICC website: https://intranet.vicc.org/vu/dsmc/

The plan addresses the following:
- Proper monitoring of trial progress and the safety of clinical trial participants
- Compliance with requirements regarding the reporting of adverse events as per institutional and federal guidelines
- Scope of temporary or permanent suspension of an NCI-funded trial
- Data accuracy and protocol compliance

Data and Safety Monitoring Committee
The VICC DSMC membership is listed on the VICC website: https://intranet.vicc.org/vu/dsmc/

Primary responsibilities of the VICC DSMC include the following:
- Review of serious adverse event reports for investigator-initiated and NCI funded studies and ensuring appropriate actions have occurred in response to these documents
- Audit institutional trials to ensure that the conduct and integrity of the trials are of the highest quality and that all trials adhere to the regulatory requirements
- Review of audit results with regards to safety, toxicity, protocol compliance and data integrity
- Review of safety issues of clinical trials participants
- Oversight and maintenance of the DSMP

The VICC DSMC convenes on a quarterly basis and additional ad-hoc meetings may be conducted to address urgent patient safety and data integrity issues which may be noted by the investigational team, internal auditors, or the DSMC. A quarterly summary of the DSMC's review of the serious adverse events is sent to the study PI and Vanderbilt IRB.

The DSMC also provides oversight of the internal audit function as part of the DSMP. This is a Vanderbilt Sponsored Investigator-Initiated Study that meets the VICC DSMP criteria as a Low Risk study. A Low Risk study will be audited annually. During each audit, 10% of the accrued patients since the previous audit with a minimum of 4 patients will be reviewed by the QA auditor.

During the scheduled audits, the QA auditor will review the patients selected for audit for the following:
- properly signed and dated informed consent
- patient eligibility
- correct treatment and treatment sequence
- evaluation of disease outcome/tumor response
- adverse event reporting
- drug accountability and proper storage/security
- general quality of data collected

A regulatory and pharmacy audit will also be conducted as needed. The outcome of the audit is first reviewed by a member of the VICC DSMC. If the DSMC member finds that the audit findings are problematic then the audit report is sent to the DSMC for a full committee review. The DSMC will then determine if the findings in the audit report require a response from the Principal Investigator. Upon review of submitted corrective action plans, the committee maintains the authority to approve the continuation of the study, increase the frequency of auditing, suspend accrual or terminate a protocol.

9.0 Study Withdrawal / Discontinuation. Subjects may be withdrawn from study participation at the discretion of the investigator or if the patient/family or attending physician requests that the subject be withdrawn. The reason and date of every withdrawal will be recorded. The Informed Consent Document will notify participants that their participation is voluntary, and they can tell the study staff at any time if they decide to stop participating. In addition, if they choose to withdraw their authorization for study staff to access protected health information (PHI) in the medical record, they may do so by notifying study staff in writing (the address is provided). If a participant chooses to no longer participate but does not notify study staff that they withdraw authorization for access to PHI, their medical record may be accessed to obtain outcomes and safety data. Data destruction will be over seen by the VCC for patients that withdraw from the study and want to have their data destroyed.

10.0 Statistical Considerations

10.1 Power analyses and sample size calculations. Precious studies have demonstrated a moderate effect (effect size ~0.4) of early palliative care on TOI, which is the primary outcome of the SCOPE trial. Assuming a type I error rate of 5% and a common standard deviation of 18.1 in the FACT-G TOI score in each group, 98 subjects in each group at 90 days (total N=196) would provide the study with at least 80% power to detect a change of 7.28 points (an effect size of 0.4) for TOI, the primary outcome of the SCOPE trial. Assuming 15% loss to follow-up at 90 days, enrolling 118 patients per group (total N=236) would provide this level of power. The study will not be powered to meet the secondary and exploratory outcomes.

The demographic and clinical characteristics of patients will be described using descriptive statistics. For continuous variables, median and interquartile range will be used while categorical variables will be described using frequency (percentage).
To examine the unadjusted effect of treatment on the primary end-point for the SCOPE trial, 90-day functional status as measured by the FACT-G TOI, we will use the Wilcoxon rank-sum test. In addition to unadjusted analyses, we will also perform multivariable regression to adjust for a priori-selected risk factors for outcomes, including age, frailty, cancer type, insurance status, education level, and degree of religious involvement. We will choose the type of multiple regression by carefully examining the distribution of the data. In the case of non-normally distributed outcomes, we will use a multivariable proportional odds regression model. To determine the unadjusted effect of early PCC on hospital length of stay, survival, and other time-to event outcomes, the cumulative incidence probability of these outcomes will be estimated via the Kaplan-Meier product limit method, and the log-rank test will be used to compare groups. Cox proportional hazards regression will be used to analyze the adjusted effect of PCC on time-to-event outcomes, with censoring as appropriate. To evaluate the unadjusted association between early PCC and receipt of intensive life-prolonging therapy in the last two weeks of life,

chi-squared tests will be used. A logistic regression model will be used for adjusted analysis to estimate the odds of receiving intensive life-prolonging therapy due to early PCC. Missing data will be imputed using a model-based imputation process. Non-linear effects of continuous variables will be fit using restricted cubic splines, and modern regression model building techniques will be used. All covariates included in the adjusted models will be selected a priori and the model complexity will be based on the general rule that a model must fit no more than m/10 parameters to allow for proper multivariable analysis and to be generalizable to future patients, where m is the effective sample size. Graphical techniques will be used to perform model diagnostics and evaluate assumptions. Multicollinearity will be assessed using variance inflation factors and in the event of highly collinear variables, principal component analysis will be used.

10.2 Missing Data. When data cannot be collected, we will impute missing variables via multiple imputation methods. Missing data are common due to deaths and loss to follow-up. While our team has a proven track record of achieving high follow-up we will carefully analyze whether particular baseline demographics are associated with missing evaluations of long-term testing.

10.3 Statistical Meetings. The VCC will work regularly with our statisticians at the ongoing weekly biostatistics meetings. Final analyses will occur during the last 6 months of the study period, when monitoring, quality checks, data lock, archiving and manuscript preparation will take place.

11.0 Privacy/Confidentiality Issues. Protected Health Information (PHI) will be kept confidential and shared with other investigators or regulatory bodies only when in accordance with relevant governmental and institutional policies. At no time will we reveal subject identities in any manner, whether in presentation, description or publication of the research for scientific purposes. All data obtained with subject or provider identifiers will be kept in locked file cabinets to ensure confidentiality, and all paper file contents will be shredded before disposal. All subjects will be assigned a unique study number for use in the computer database, and all electronic data will be kept in password-protected computer files to ensure confidentiality.
Most data will be collected from medical records or direct assessments and entered directly into the study database via electronic case report forms (eCRFs). Paper CRFs will be used for baseline cognitive impairment, quality of life, and follow-up neuropsychological battery (some may require copyrighted forms). Once collected on paper, data will be directly entered into the database. The study will utilize a centralized database located on Vanderbilt's secure REDCap database system.

12.0 Record Retention

12.1 Duration of Record Retention. Information stored in the database will be stored for an indefinite period of time for future reference, including for use in subsequent data analyses. Throughout the study, all collected data will be entered directly in to the secure password-protected web-based database.

12.2. Timeline and Duration of Study.

Based on annual operative volumes for the eligible malignancies at VUMC there will be about 470 eligible patients undergoing operations annually at Vanderbilt. Enrolling 21% of the eligible patients would allow the study to accrue to the desired sample size in 2 years. A review of administrative data from the Vanderbilt electronic medical record for the past five years has shown that fewer than 10% of patients who have undergone resection of the malignancies included in the SCOPE trial receive PCC at any point in their disease process. Thus, there will be very few patients in the control group who will receive PCC, and almost none as early as the intervention group.

During recruitment, VCC will diligently monitor data collection, conduct data cleaning, conference calls, in-person meetings with study personnel to ensure compliance, and overall efficiency of study implementation. We will also work regularly with our statisticians to execute the planned analyses. The final analyses will occur during the last 6 months of the study period, when monitoring, quality checks, archiving and manuscript preparation will take place.

13.0 Qualitative Subgroup Assessment

13.1 Description: This subgroup assessment will involve in-depth, semi-structured interviews to explore patients' perceptions of, and experiences with, palliative or standard care prior to and following surgery. To achieve this objective, we will conduct up to 48 in-depth interviews with a subset of SCOPE patients. With the qualitative interviews, we intend to investigate how the patients are experiencing their recovery from surgery and their interactions with palliative care as these processes are occurring. We will therefore conduct the interviews around 30-days after their operations to capture these ongoing experiences. This qualitative data of the ongoing experience could then be compared with the primary and secondary quantitative outcomes collected at 90 days and later.

13.2 Sample and Sample Size Justification: During the 30-day follow-up phone call, the quantitative outcomes assessor will describe to SCOPE patients the qualitative interview opportunity and invite those who are interested to provide contact information. Among those who do, we will use a purposive sampling strategy to interview 48 subjects stratified by three binary categories (for a total of 2^3=8 strata, with 6 patients per stratum): age (65 & older vs. under 65), sex, and study group (control vs. intervention). We will interview 6 patients per group—the minimum number of interviews expected to achieve saturation.[25] We will stratify by age and sex as we suspect that men and women and older and younger patients may have different experiences with care, and we want to ensure that we sample across this diversity. Within each group, we will strive to maximize diversity by other demographic characteristics.

13.3 Instrument Development and Content: We have developed an interview guide using open- and close-ended questions and standard probes to explore perceptions of the care experience. The guide was developed to elicit patient perspectives regarding their healthcare and treatment experience

13.4 Procedures: For patients who would like to participate, we will schedule an interview at their convenience, and within four weeks of the 30-day follow-up. Interviews will be conducted by telephone. We will offer $50 compensation for the hour-long interview which, with participants' permission, will be audio-recorded.

13.5 Data Analysis: Audio recordings will be professionally transcribed and any identifying information mentioned by the patient redacted. We will upload transcripts into qualitative research software NVivo 12 and develop a detailed codebook via a standard iterative process, using Holsti's method to compare inter-code agreement. We will use an applied thematic analysis approach, including running queries, generating code reports, and developing summary tables to explore the range of responses within and between groups.

14.0 Content Analysis of Psychosocial Stressors

14.1 Description: To better understand the psychosocial stressors patients experience pre-operatively, the investigators will perform a content analysis of notes on the first 50 patients enrolled in the intervention arm with a preoperative palliative care consultation. The investigators will extract the text of the palliative care consultation notes relating to psychosocial distress along with basic demographic information on these patients, including, age, sex, race, ethnicity, and surgery type to create a deidentified Microsoft Excel document with these elements. Two investigators will read the extracts on this document and jointly develop a code book of themes for analysis. The two investigators will then independently code the deidentified note texts and then assess intercoder reliability. If intercoder concordance is less than 80%, they will discuss and recode until 80% concordance is reached. Once this concordance rate is reached, the investigators will perform a qualitative content analysis of the coded text to explore common themes.

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Summary of Protocol Changes

Version	Protocol Date	Main Changes
1.0	1/30/2018	Original Version
1.01	4/11/2018	1. Section 5.2 Exclusion criteria [9] was added "Currently participating in palliative care or seeing a palliative care provider." 2. Section 6.1 Enrolled but not randomized language was added. 3. Section 7.2 Data timeline was updated to reflect when chemotherapy and radiation therapy questions are addressed with patient. 4. Section 7.3.1 Added gift card payment language. 5. Section 12 header "Record Retention" edited to match Table of Contents Footer updated.
1.02	7/5/2018	1. Under Section 7.2 of the SCOPE protocol an insertion describing the time frame that outpatient palliative care visits occur was added. In the same section it was clarified what happens if an intervention patient is not able to come to a scheduled outpatient palliative care clinic visit. In this situation a phone call between provider and patient will be scheduled.
1.03	3/18/2019	1. Updated inclusion criteria to include more specific abdominal operations that a potential participant may undergo. 2. Revised our procedures to allow for phone consultations, and are providing compensation if participants attend the pre-op and at least one post-op visit in person.
1.04	5/30/2019	1. A qualitive subgroup assessment has been added to study. Involves an interview.
1.05	3/16/2020	1. Section 14.0 "Content Analysis of Psychosocial stressors" was added to better understand the psychosocial stressors patients experience pre-operatively, the investigators will perform a content analysis of notes on the first 50 patients enrolled in the intervention arm with a preoperative palliative care consultation. 2. Formatting was done to match recent amendments to original format. 3. Section 11 had one sentence reflecting what is found in the consent and built upon what was already described in protocol.
1.06	2/1/2021	1. Clarification that compensation can be in the form of a check or gift card. 2. Added additional VICC Data and Safety Monitoring information.

		3. Addition of studying fatigue in a subgroup of patients (6 questions at baseline and 30 days after surgery).
1.07	11/2/2021	1. Participants may be contacted by SMS text messaging to coordinate long-term follow-up assessments.