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SWOG CANCER RESEARCH NETWORK

A RANDOMIZED PHASE III DOUBLE-BLIND CLINICAL TRIAL EVALUATING THE EFFECT OF IMMUNE-ENHANCING NUTRITION ON RADICAL CYSTECTOMY OUTCOMES **(SIMmune)**

NCT # 03757949

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See Section 13.2b.3 for site approval requirements

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Questions related to: Oncology Patient Enrollment Network (OPEN)	See Protocol Section 13.3 or contact CTSU Help Desk: Phone: 1-888-823-5923 or Email: ctsucontact@westat.com
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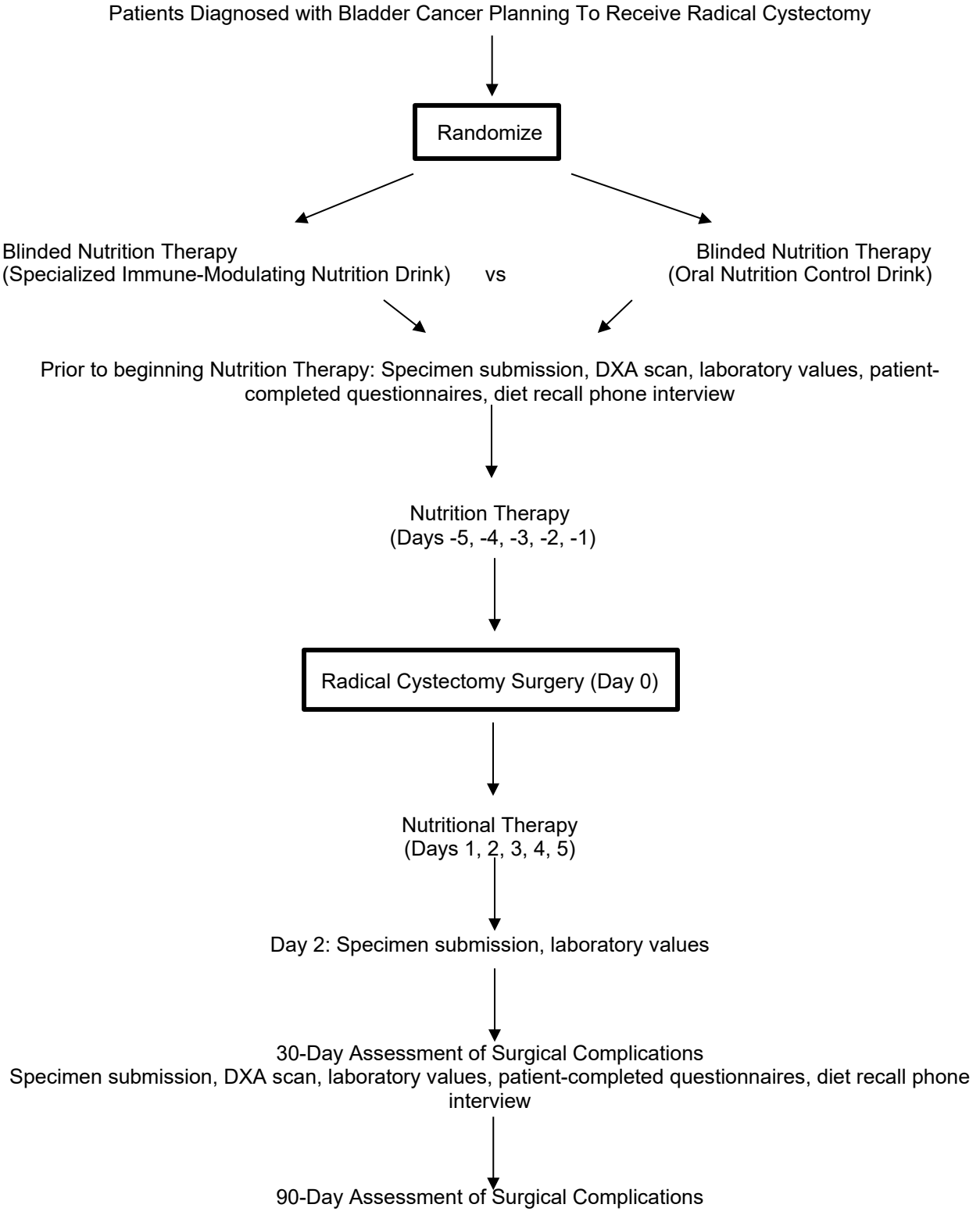
Serious Adverse Event Reporting questions:	See Protocol Section 16.1 Email: adr@swog.org

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

CONTACT INFORMATION		
For regulatory requirements:	**For patient enrollments:**	**For study data submission:**
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal. Sign in at www.ctsu.org, and select the Regulatory Submission. Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance.	Refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN). OPEN can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Refer to the data submission section of the protocol for further instructions. : Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions. Other Tools and Reports: Institutions participating through the CTSU continue to have access to other tools and reports available on the SWOG CRA Workbench. via the SWOG website (www.swog.org)
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password.		
For patient eligibility or data submission questions contact the SWOG Statistics and Data Management Center (SDMC) by phone or email: 206/652-2267 cancercontrolquestion@crab.org **For treatment or toxicity related questions** contact the Study Chairs by phone or email: Jill Hamilton-Reeves, Ph.D., R.D., C.S.O, phone: 913/588-7650 or email jhamilton-reeves@kumc.edu; or Jeffrey M. Holzbeierlein, M.D., phone 913/588-7654 or email jholzbeierlein@kumc.edu		
For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU Website is located at https://www.ctsu.org		

SCHEMA


Patients Diagnosed with Bladder Cancer Planning To Receive Radical Cystectomy
Randomize
Blinded Nutrition Therapy
(Specialized Immune-Modulating Nutrition Drink)
vs
Blinded Nutrition Therapy
(Oral Nutrition Control Drink)
Prior to beginning Nutrition Therapy: Specimen submission, DXA scan, laboratory values, patient-completed questionnaires, diet recall phone interview
Nutrition Therapy
(Days -5, -4, -3, -2, -1)
Radical Cystectomy Surgery (Day 0)
Nutritional Therapy
(Days 1, 2, 3, 4, 5)
Day 2: Specimen submission, laboratory values
30-Day Assessment of Surgical Complications
Specimen submission, DXA scan, laboratory values, patient-completed questionnaires, diet recall phone interview
90-Day Assessment of Surgical Complications

1.0 OBJECTIVES

1.1 Primary Objective

a. To compare the impact of consuming perioperative specialized immune-modulating drinks (SIM, Impact Advanced Recovery®, Nestlé) to oral nutrition supplement control drinks (ONS, Oral Nutrition Control, Nestlé) on post-operative complications (any vs. none) within 30 days after scheduled radical cystectomy (RC).

1.2 Secondary Objectives

a. To assess whether SIM use compared to ONS reduces late-phase post-operative complications within 90 days after scheduled RC.

b. To assess whether SIM use compared to ONS reduces infections.

c. To assess whether SIM use compared to ONS reduces skeletal muscle wasting.

d. To assess whether SIM use compared to ONS reduces high grade post-operative complications.

e. To assess whether SIM use compared to ONS reduces readmission rates.

f. To assess whether SIM use compared to ONS improves quality of life.

g. To assess whether SIM use compared to ONS improves disease-free survival after surgery and overall survival.

1.3 Tertiary Objectives

a. To assess the impact of SIM use on the expansion of myeloid-derived suppressor cells.

b. To assess the impact of SIM use on pro-inflammatory cytokines and neutrophil: lymphocyte ratios.

c. To assess the impact of SIM use on post-operative arginine deficiency and amino acid metabolism.

d. To explore the association of dietary intake variables (nutrition status, calories, protein, and immune-enhancing factors) and study outcomes.

1.4 Translational Medicine Objectives

a. To describe the microbiome of the gut in patients undergoing radical cystectomy and urinary diversion prior to initiation of immunonutrition or a nutrition control.

b. To define the microbiome change in patients undergoing radical cystectomy and urinary diversion after they have received blinded immunonutrition or control nutritional supplement.

c. To correlate cancer treatments, postoperative complications (specifically infections) and nutritional status with microbiome composition.

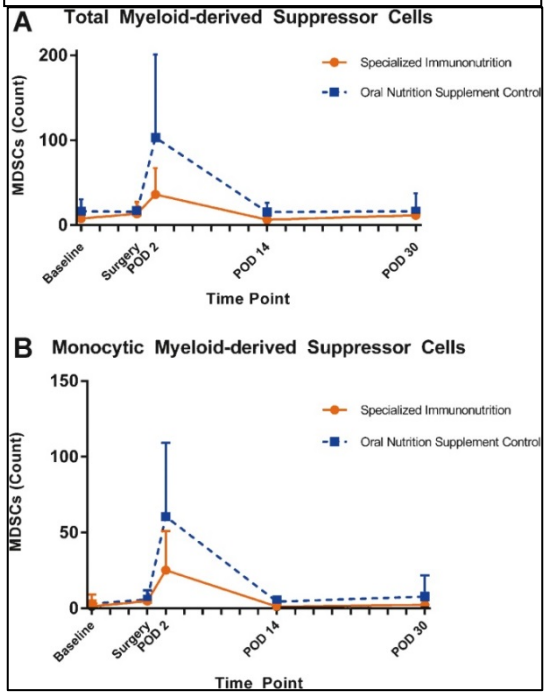
2.0 BACKGROUND

Bladder cancer (BCa) is common. The standard treatment for advanced BCa involves radical cystectomy (RC), which is plagued by very high rates of complications and mortality. *(1,2)* RC impairs gut function and metabolism in part due to reconstruction which routes urine through intestinal segments. As a result, infection, rapid skeletal muscle wasting, and other complications are common. *(3,4,5,6)* New surgical care pathways preserve gut function after RC and have opened a new potential avenue for intervention: perioperative nutrition. *(7,8)* Preliminary studies are promising; however, there is a critical need to identify the most effective forms of perioperative nutritional support, and to determine their impact on RC surgical outcomes. Without this care, RC will continue to save lives, but at a high cost in terms of downstream adverse surgical complications.

Our long-term goal is to unlock the potential of nutrition interventions to improve outcomes, survival, and quality of life in cancer patients. The objective of this project is to determine the impact of a specialized form of nutritional support on surgical outcomes and to better understand the mechanisms by which it acts.

Poor nutritional status is associated with higher complication rates after RC. *(9,10,11)* Specialized Immunonutrition (SIM) is fortified with nutrients (L-arginine, omega-3 fatty acids, dietary nucleotides, and vitamin A) that have immediate effects on immune and inflammatory responses, muscle sparing, and wound healing after surgery. In a randomized pilot trial of 29 patients, we found that giving SIM before and after RC reduced post-operative complications by 33% and most notably, reduced infections by 39% compared to an identical Oral Nutrition Support (ONS) lacking the immuno-modulators. *(12)* After RC, the SIM intervention significantly restrained the expansion of myeloid derived suppressor cells (MDSC), dampened the post-surgical inflammatory response with a reduced magnitude of IL-6 elevation, and reduced muscle wasting by 10% compared to ONS. (*13,14)* Using perioperative SIM may benefit patients undergoing RC in a way that standard nutrition supplementation cannot. While the results of our pilot study are encouraging in that they show SIM improves immune response, a larger clinical trial is needed to definitively confirm whether SIM can significantly reduce post-operative complications. *(15)* A reduced post-operative complication rate is the key surgical outcome that would influence adoption of a new intervention aimed at improving the safety of RC.

Figure 1: MDSCs after RC, *Eur Urology, 69(3), 2016*

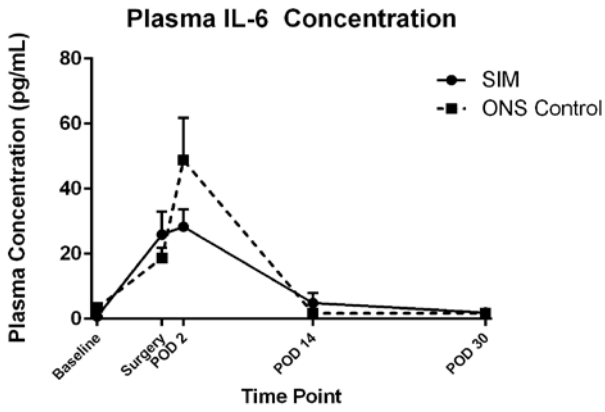


Bladder cancer is prevalent and treatable, but morbidity, recurrence, and mortality are high. BCa is the fourth leading cancer in men, the sixth most common cancer in the United States, and has the highest lifetime treatment cost of all cancers. *(16,17,18)* Furthermore, up to 30% of all newly diagnosed patients present with muscle-invasive BCa. *(19)* The American Society of Clinical Oncology recently endorsed treatment guidelines for muscle-invasive BCa to include neoadjuvant

chemotherapy followed by radical cystectomy (RC). *(20,21)* Unfortunately, RC is associated with high rates of post-operative complications (66%), infections (25%), and cancer recurrence (34%). *(22,23,24)* Ninety-day mortality rates are 7%. *(25)*

Immune suppressive factors lead to complications. It is plausible that many complications associated with RC are initiated by an exaggerated adaptive immune suppression and inflammatory response, especially infections and muscle wasting. Major surgeries disrupt T helper (Th)1-Th2 balance to a Th2 predominant response which impairs cell mediated immunity, leaving patients more susceptible to infection. *(26)* Myeloid-derived suppressor cells (MDSC) are immune cells that expand rapidly after physical injury but quickly differentiate into granulocytes, macrophages, or dendritic cells. MDSC accumulation suppresses T-cells, and lowers the resistance to infection. MDSCs express and release arginase-1, depleting plasma arginine concentrations. *(27)* Arginine deficiency imposed by surgery impairs T-cell function, contributes to protein degradation from muscle, impairs wound healing, and negatively affects blood flow and tissue oxygenation needed for healing. The pilot data show that SIM counteracts the Th1-Th2 shift (P=0.027), restrains the expansion of immune suppressive cells [MDSCs; between groups over time P=0.005 and significantly lower in SIM 2 d after RC (P<0.001); Figure 1], and lowers the neutrophil:lymphocyte ratio (P=0.039) compared to ONS. *(28,29)*

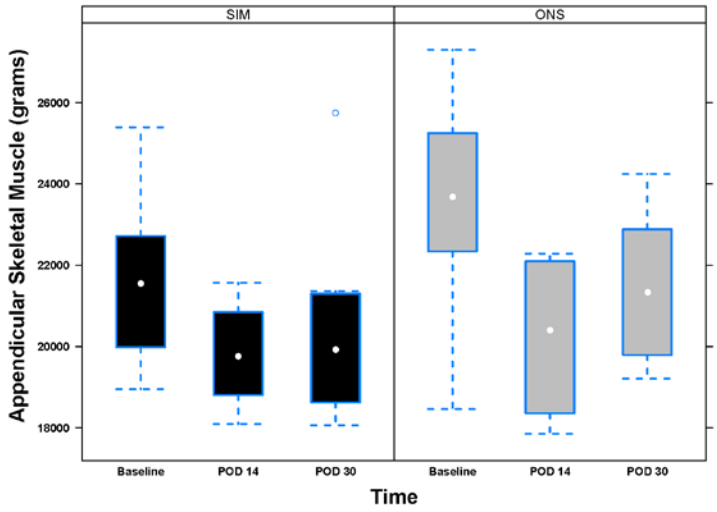
Figure 2: IL-6 after RC, *Journal of Urology (in review)*



Rapid weight loss and muscle wasting following RC are commonly observed. *(30,31)* Interleukin (IL)-6 is released in response to surgery, and the magnitude of IL-6 elevation is associated with post-operative complications and muscle wasting. *(32,33,34)* Therefore, a strategy to prevent an exaggerated post-surgical IL-6 response may be an effective way to reduce common complications. We reported lower post-operative IL-6 (P=0.020; Figure 2) and a trend of less profound appendicular muscle loss (P=0.078; Figure 3) in RC patients consuming SIM compared to ONS. *(35)*

Improving nutritional status before and after RC is a promising approach to reducing post-operative complications. Many cystectomy patients have poor nutritional status at completion of neoadjuvant chemotherapy, which is then compounded by the catabolic effects of RC. *(36,37)* Using the Nutritional Risk Screening (NRS-2002) tool, between 21-55% of patients were found to be at risk of malnutrition before cystectomy. *(38,39,40,41)* However, using a more robust, validated, malnutrition screening and assessment tool, the Patient-Generated Subjective Global Assessment (PG-SGA), we found that 27.6% of patients were moderately or severely malnourished before surgery. *(42)* Given the short lag time between diagnosis and surgery and the likely feeding issues from neoadjuvant chemotherapy, reversing malnutrition prior to surgery is not realistic. Impracticality is compounded by the disproportionate burden of this disease in smokers and the frail elderly. However, there are promising data showing that short term supplementation with L-arginine, omega-3 fatty acids, dietary nucleotides, and vitamin A before and after surgery has profound and measurable acute effects on immune and inflammatory response, muscle preservation, and blood flow/tissue oxygenation. Effective nutrition interventions are a critical unmet need given that evidence showing that complications and death after RC may be attributable to poor nutritional status. *(43,44,45,46)*

Figure 3: Loss of uscle in the arms & legs after RC, Journal of Urology (in review).



The goal of perioperative use of SIM is not merely to serve as the substrate for nutritional improvement but to influence the intensity and perhaps the duration of the systemic inflammatory response underlying the protein catabolism of cancer, major surgery, and infection. Thus, if the catabolic effect of surgery is diminished by SIM, then there will be short and long-term benefit for net anabolism. A nitrogen balance test would not be valid in this setting; therefore, we focus on body composition because lean tissue loss has severe pathologic consequences. We aim to prevent muscle degradation from amino acid deficiencies and elevated pro-inflammatory cytokines induced by surgery. The dual-energy X-ray Absorptiometry time points were chosen based on longitudinal body composition data from RC patients in our pilot and from Mathur et al. *(47)* This study reported a 7% loss in total body protein, two weeks following RC. Six months later, only 63% of the lost muscle was regained. *(48)* In our pilot, appendicular skeletal muscle Index (muscle in the arms and legs) was better preserved in the SIM group with a 7% loss compared to a 17% loss in the ONS group, two weeks following RC (P=0.078; Figure 3). *(49)* However, we found many patients felt too ill to return for a scan two weeks after surgery, but most patients felt well enough to return at 30 days for a scan. The appendicular skeletal muscle was very similar at two weeks and 30 days post-surgery. The FAACT trial outcome index and anorexia subscales were used in our pilot and the SIM showed better quality of life scores than the ONS group but the differences were not statistically significant (P=0.15 for both), but the pilot was underpowered for this outcome. Also, the anorexia and cachexia subscale asks about issues common after RC such as: taste alterations, appetite, early satiety, and pain while eating. These data are crucial for optimizing nutrition interventions to help patients.

Feeding the gut before and after RC surgery is a new opportunity. Few nutrition intervention studies in the cystectomy population have been published. Before enhanced recovery after surgery (ERAS) pathways were widely adopted, only parenteral nutrition (TPN) studies or pre-surgery oral supplements had been used for nutritional support. *(50,51,52)* A recent study in RC showed that following a regular healthy diet decreased the length of stay compared to TPN post-operative feeding. *(53)* Similar to other surgical nutrition support literature, TPN in RC has led to higher infection rates when compared to consuming a regular diet (32% vs 11%; p = 0.001). *(54)* These data are not surprising since the guidelines from the Society of Critical Care Medicine/American Society of Parenteral and Enteral Nutrition (SCCM/ASPEN) suggest that enteric feeding is best to maintain gut integrity and modulate the immune response. *(55)*

Specialized immunonutrition (SIM) before and after surgery has strong potential for reducing post-operative complications. The SCCM/ASPEN Critical Care guidelines recommend that surgical patients consume ***perioperative*** immune modulating formulas that include arginine and nutrient combinations along with arginine, regardless of baseline nutrition status. *(56)* The quality of evidence for this recommendation was determined to be ***moderate to low*** revealing that we do not have the most robust scientific evidence. Although the notion of SIM to improve surgical outcomes has been studied since 1992, there is a surprising gap in the understanding of how SIM works. *(57)* Moreover, the literature is riddled with underpowered studies. Other issues that weaken the evidence are studies that lack a calorie and protein matched control, use non-uniform dosing, and use self-report rather than nutrient biomarkers as objective measures of compliance. *(58,59,60,61,62,63,64)* Additionally, meta-analyses of SIM draw mixed or conflicting conclusions, adding to the confusion. *(65,66,67)* In addition, in over two decades, this very simple formula has only undergone one minor reformulation (the sugar content was lowered). Thus, a large, well-designed, adequately powered, clinical trial in this area is needed to help RC patients, drive knowledge discovery, and generate hypotheses for ways to improve nutrition strategies for even better surgical outcomes. Although randomized controlled trials (RCTs) with iso-caloric and iso-nitrogenous controls have provided clues as to how SIM might improve surgical outcomes or offer no benefits, key knowledge gaps remain. *(68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84)*

Our scientific premise is that SIM has high potential as an effective, low-risk, and ground-breaking strategy to improve surgical outcomes *and* quality of life for patients with bladder cancer who undergo RC. Published data show that this is a promising strategy, but these studies lack scientific rigor which has manifested and enabled ambiguity and thus no change in the standard of care. Our study is designed to provide conclusive evidence about the efficacy of this approach. A negative study would be highly informative and go far towards putting this concept to rest; a positive study would change practice. However, even a negative study has the potential to provide important information about disease mechanisms and biology. The carefully selected mechanistic work will be conducted in experienced laboratories that are either CLIA-certified or have published data for their endpoints demonstrating their capabilities. The key correlative aims were chosen to drive discovery.

- Cystectomy has been overlooked and understudied. To change practice, it is important to study the effect of the intervention in the surgical context in which it is used, especially given the uniqueness of, and high rate of morbidity in, RC. To date, there are only two published studies in this area. In a small (n=60), case-controlled, pilot study in the RC population, Bertrand and colleagues reported that SIM taken before surgery resulted in a reduction of 30 day post-operative complications (40% vs. 77% in the historical control) (*P* = 0.008) and infection rates (23% vs. 60% in the historical control) (*P* = 0.008). *(85)* However, this study is limited by the use of historical controls. Our group has previously published the only blinded RCT of immunonutrition in RC. *(86)*

- How does immunonutrition work? Studies of how the SIM works and correlative mechanisms are limited, usually with very small subsets of patients within larger studies. *(87,88,89)* Our preliminary data on a possible mechanism is promising. The studies

proposed will provide insight into mechanisms and will inform what can be done to optimize nutrition interventions. For knowledge discovery, it is critical to know how the nutrition intervention is changing both biology and clinical outcome.

- Only two large trials in the United States. Large double-blind randomized controlled trials of SIM are very limited in the US with only two published studies across all malignancies, both published in the 1990s: a post-operative feeding only trial in upper GI (n = 85; 2 arms) and peri-and postoperative in head/neck (n = 136; 4 arms). *(90)* Undoubtedly, our knowledge base has grown since these studies were conducted with further insight about immunology and better surgical practice. Since the 1990's most of the work in this field has taken place outside of the US. Importantly, there are other unmeasured differences between the healthcare system in the US and other countries where this work has been conducted. The surgical approach, the market in cystectomy care, and the peri-operative pathways and inpatient stays are drastically different. For example, a recent well-designed large (n = 264) multi-center trial conducted in Spain found that colorectal patients administered perioperative immunonutrition had fewer 30-day complications than the control group (23% vs. 35%, P=0.035). *(91)* These data are encouraging and would suggest that our results will be positive, but the same gaps remain: correlative translational science, data from RC which is a more morbid surgery than colorectal surgery, and data from US practices.

SIM nutrients (L-arginine, omega-3 fatty acids, and dietary nucleotides) have immediate biological effects that set the stage for improved surgical outcomes later. Most of the SIM studies mentioned above use a short-term feeding strategy before and after surgery. A short intervention works because the nutrients act on acute mechanisms that occur perioperatively. Arginine supply is vital to the immune response as T-cells need it for healthy immune function (for lymphocyte proliferation and T-cell receptor integrity). *(92)* Surgery depletes the arginine supply. A group of immune cells, MDSCs, expand due to the predominant Th2 response following surgery. MDSCs contain Arginase-1 which rapidly depletes arginine by metabolizing it to ornithine and urea. In turn, the arginine necessary for the proliferation of lymphocytes and the formation of nitric oxide for tissue oxygenation is insufficient, resulting in an increased risk of infection and poor wound healing. Mechanistic work by Fletcher et al. showed that L-arginine deprivation induces MDSC expansion; we discovered that the reverse is also true, supplementing L-arginine as part of SIM suppresses MDSC expansion. *(93,94)* Emerging data suggest cancer-induced cachexia (muscle wasting) may also be partly driven by the expansion of MDSCs. Arginine deficiency triggered by surgery impairs protein synthesis and healing because arginine is a conditionally indispensable amino acid in states of tissue injury and repair. Therefore, inadequate arginine even in the absence of a dramatic change in MDSC counts will lead to muscle degradation.

Omega-3 fatty acids, specifically docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), modulate immune cell function and inflammation through a variety of pathways. *(95)* Resolvins and protectins, derived from EPA and DHA, speed up the resolution of inflammation and improve healing after surgery. *(96)* Clinical data also show that EPA and DHA improve wound healing. *(97)* EPA also inhibits muscle degradation relevant to the muscle-wasting process. (*98*) Vitamin A, as all-trans retinoic acid, promotes the maturation of MDSCs. Mature myeloid cells lose the capacity to suppress T cell function. *(99)* Under conditions of surgical stress, dietary nucleotides become essential—they stimulate lymphocyte differentiation and contribute to T cell homeostasis to the Th1-dominated response. (*100*)

The **S1600** trial prepares for and corrects the nutrient (arginine) deficiency known to be triggered by surgery in a very brief (10 day) intervention.

Arginine deprivation has detrimental effects on patient outcomes after surgery. Data from Bobak et al. *(101)* demonstrate that arginine deprivation using ADI-PEG induces endoplasmic reticulum stress in human solid tumor cell lines. Arginine deprivation increases tumor resistance to immune editing by the immune suppressive effects of MDSC expansion and reduced T cell proliferation. Arginine deficiency may also lead to wound breakdown, muscle wasting, thrombosis, and infection susceptibility. In summary, our objective is to support the patients' overall acute nutritional needs for a healthy surgical recovery without imposing any long-term harm.

Arginine deprivation using the ADI-PEG drug is being tested as a therapy against various cancers. *(102,103)* The JCO Phase I trial by Beddowes et. al. *(104)* shows that in a biomarker-selected subset of patients with ASS1-deficient cancers, ADI-PEG, which is a drug that converts arginine to citrulline and ammonia, shows activity worthy of further study in the medical oncology setting. These authors make no suggestion that arginine supplementation in patients with established cancer prior to surgery could carry any clinical risk. Likewise, no preclinical data exist to suggest that arginine supplementation prior to surgery unfavorably influences cancer recurrence or new cancer development. Since ASS1 is decreased or lost in 40% of bladder cancers *(105)* and can be reversed with ADI-PEG, then arginine supplementation would not impose any long-term risk. (*106*) ASS1 loss has been identified in bladder cancer, and in studies of cell lines ASS1 deficient cells were sensitive to ADI-PEG. (*107*)

The pre-clinical ADI-PEG data have several limitations. The data available do not account for the clinical context of arginine demand and requirements to support the immune system in the surgical setting. The pre-clinical data do not take into account the necessity of adequate arginine to prevent wound breakdown, muscle wasting, thrombosis, and infection susceptibility in surgical patients. Lastly, the preclinical data also do not take into account the immune contribution to staving off tumors. In summary, the hypotheses from ADI-PEG studies have not yet been tested in models translatable to the acute surgical oncology context.

In contrast, published clinical data show improved tumor-free and overall survival in patients with head and neck cancer taking extra arginine or Impact Advanced Recovery supplementation around the time of cancer treatment. Buijs reported an increase in tumor-free survival in patients consuming perioperative arginine for their head and neck surgery. *(108,109,110)* Similarly, Senesse (Phase II trial) reported a decrease in tumor recurrences in patients receiving arginine replacement therapy (Impact Advanced Recovery) during chemotherapy for head and neck cancer. *(111,112)* These patients have been followed for more than 12 years. Of note, the majority of these cancers demonstrate high arginase/MDSC infiltration. Our pilot data show arginine supplementation leads to MDSC restraint and T cell support, which may protect against the spread of cancer.

The totality of evidence does not support tumorigenic effects of supplemental arginine.

Standard ONS is high in protein and micronutrient content, but lacks the immunomodulating ingredients. Some data suggest ONS intake will provide benefit to surgical patients and a significant difference will not be detected between complication rates and postoperative muscle mass when compared to SIM. *(113)* Therefore, it is critical to use standard ONS as a control and test it against SIM in a blinded study design. ONS and SIM will be packaged identically and flavored the same. Although both drinks will be vanilla flavor, a taste test will not be provided before the randomization because participants with great taste sensitivity may detect a slight variation in flavor from the fish oil in the SIM. Regarding the taste and acceptability of the drinks, our pilot study found no striking differences in the adherence to the drinks. 100% consumed the SIM intervention drink and 93% consumed ONS the control drink.

The 30 day time point is preferable as the primary endpoint, given our data on the biologic mechanisms of the intervention showing that SIM counteracts the Th1-Th2 shift, restrains the expansion of immune suppressive cells, blunts the magnitude of IL-6 elevation, and lowers the neutrophil:lymphocyte ratio within days of the operation. These data suggest that the biology shifts quickly, but there are insufficient data to know how long the latency lasts from these biological effects to a clinically meaningful impact on overall complications. The majority of published immunonutrition trials with post-operative complications as the primary outcome do not list the timeframe in which the outcomes are collected. In addition, most trials did not use the Clavien-Dindo scheme for standardized complication reporting. Therefore, we think it is important to retain both time points, including the 30 and 90 day complication rates as measured outcomes, in case there is latency between surgery and a clinically significant effect of SIM on complication rates.

To develop the strongest study design to answer our research questions, we examined the evidence and design of larger and more contemporary immunonutrition trials. The strongest immunonutrition trial published to date is the SONVI study. *(114)* This recent, well-designed, large multi-center trial (n=264) conducted in Spain was designed and powered to examine the overall post-operative 30 day complication rate. The study found that colorectal patients administered perioperative immunonutrition had fewer 30-day complications than the control group. *(115)* However, we could not use complication rates from a colorectal population for our power calculation estimates; therefore, we used the 30 day complication rates from a cystectomy population for our power calculations. *(116)* We assumed a relative reduction of 35% (on the somewhat conservative end of the estimate of 37% indicated in the Bertrand paper), from 65% down to 42% (a 23% absolute reduction). *(117)*

In summary, nutrients in SIM work synergistically and immediately to improve immune response, dampen inflammatory response, preserve muscle, and enhance wound healing in surgical patients.

Inclusion of Women and Minorities and Planned Enrollment Report

This study was designed to include women and minorities, but was not designed to measure differences of intervention effects. The anticipated accrual in the ethnicity/race and sex categories is shown in the table below.

DOMESTIC PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	0	1	0	0	1
Asian	2	6	0	0	8
Native Hawaiian or Other Pacific Islander	0	1	0	0	1
Black or African American	4	8	0	0	12
White	39	126	3	10	178
More Than One Race	0	0	0	0	0
Total	45	142	3	10	200

3.0 PRODUCT INFORMATION

3.1 Impact Advanced Recovery® / Oral Nutrition Control

a. DESCRIPTION

Test product: Impact Advanced Recovery® (Nestlé) is a complete nutritional source or may be served as a supplemental source of balanced nutrition. The supplement is specifically designed to support the body's immune system by addition of omega-3 fatty acids, arginine, and dietary nucleotides.

Control product: An Oral Nutrition Control (Nestlé) will be used in isocaloric amounts in the control group. Nestlé is specifically manufacturing the control oral supplement for this study.

The products used in this study are considered medical foods by the U.S. Food and Drug administration with documented safety in multiple clinical trials.

The term medical food, as defined in Section 5(b) of the Orphan Drug Act (21 U.S.C. 360ee (b) (3)) is "a food which is formulated to be consumed or administered enterally under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation."

Medical foods are not drugs and, therefore, are not subject to any regulatory requirements that specifically apply to drugs. IND regulations do not apply to the product due to the product being regulated as a food.

Nestlé (and Nestlé Health Science) has a strict process that assures minimal variability, excellent standardization, quality control, and stability. Both intervention and control products undergo the same testing before and after manufacturing. Product manufacturing, composition, release, and stability are carefully monitored as per the FDA compliance program (7321.002) and are subject to FDA review for manufacture and distribution of medical foods and infant formula. Prior to release, each batch is inspected and verified to be in compliance with FDA's CFR Title 21, Part 110, Part 113, and Part 101.

The tables below compare the two products in terms of energy and macronutrient content as well as immune-modulating ingredients. An additional table demonstrating the similarity of the products is located in Appendix 18.1.

Table 1: Energy and macronutrient content Impact Advanced Recovery ®/Oral Nutrition Control

Test & Control Product	**FDA Category & Indication**	**One serving**					**Three servings (daily amount)**	
		Fluid	Energy	Total protein	Fat[B]	Carbo-hydrates[C]	Fluid	Energy
*Test (*Nestlé*):* **ORAL IMPACT Advanced Recovery**	**Formula food**	178 ml	200 kcal	18 g[A]	8 g	15 g	534 ml	600 kcal
*Control (*Nestlé*):*	**Formula food**	178 ml	185 kcal	14 g	8 g	15 g	534 ml	555 kcal

[A] Protein content starts out the same in the intervention and control. In order to fortify l-arginine in the intervention, there is a 4 g protein difference per 6 fl. oz. serving between products.
[B] Both products contain 1.3 g MCT per 178 mL serving.
[C] Both products contain approximately 13 g sugar per 178 mL serving.

Table 2: Differences in immune-modulating ingredients

Test & Control Product	**FDA Category & Indication**	**One serving**			**Three servings (daily amount)**		
		Supplemental L-Arginine g/d	EPA + DHA g/d	Dietary Nucleotides g/d	Supplemental L-arginine g/d	EPA+DHA g/d	Dietary Nucleotides g/d
*Test (*Nestlé*):* **ORAL IMPACT Advanced Recovery**	**Formula food**	4.2	1.1	0.43	12.6	3.3	1.29
*Control (*Nestlé*):*	**Formula food**	0	0	0	0	0	0

Both products contain 2.8 g glutamine per 178 mL serving inherent to the casein protein source. Both products contain 575 mcg of beta-carotene and 290 mcg of retinol per 178 mL serving. Both products contain 5 mg of zinc per 178 mL serving.

b. DOSING AND ADMINISTRATION

Both products will be provided in liquid format for oral intake. See Section 7.0 for additional details.

c. HOW SUPPLIED

Study products are supplied free of charge by Nestle for distribution by McKesson Specialty Pharmacy.

Patient-specific supplies will be sent to the registering investigator at the time of registration/randomization.

Upon randomization to the study, the SWOG Statistics and Data Management Center will provide McKesson Specialty Pharmacy with randomization information via secure data transmission.

Upon receipt of patient registration and randomization, McKesson will place a call to the study site confirming the order was received and provide the estimated day and time of arrival for the study drink. McKesson will prepare shipment of patient specific study product. Each shipment will include sufficient study product for the two 5-day treatment periods. It will be packaged in one box with all 30 drink bottles. Each shipment also includes a patient label with the following information:

- Study Number
- Lot identification
- Expiration date
- Storage conditions
- Detailed dosing instructions
- Patient ID number, initials, and date dispensed

In addition, each individual drink bottle will be labeled with the SWOG patient ID number and patient initials.

Packaging will be labeled “Complete Nutrition Product. For Clinical Trial Use Only. This product has been specifically provided for use in a clinical trial. It is to be used only under the supervision of the study physician. If you have any questions regarding the use of this product, please contact your study personnel.”

Orders will be generated by McKesson Specialty Pharmacy using the randomization information provided by the SWOG Statistics and Data Management Center, on the next business day following patient registration. Orders will be processed and shipped Monday through Friday for next business day delivery. All shipments will be sent via FedEx for Priority Overnight delivery. McKesson Specialty Pharmacy will be closed the following holidays: New Year’s Eve, New Year’s Day, Memorial Day, Independence Day, Labor Day, Thanksgiving, Thanksgiving Friday, Christmas Eve, and Christmas Day.

Packages are tracked until confirmed delivered and delivery exceptions are managed with the highest level of urgency to ensure therapy start date adherence. Packing slips with the shipment tracking number will be faxed to the designated site coordinator for all shipments.

d. STORAGE AND STABILITY

At each clinical trial site, the study products will be maintained in a dry environment, at temperatures between 5 ºC (41 ºF) and 25 ºC (77 ºF). Investigators and site staff

are reminded to check and record temperatures and ensure that thermometers (as applicable) are working correctly as required for proper storage of study product.

Store unopened. Once opened, unused portion should be tightly covered, kept refrigerated, and used within 24 hours. NOTE: For this study, one bottle should be consumed between meals and any bottle not wholly consumed per protocol requirements should be discarded and a new bottle opened for the next expected time point. The patient should record the amount consumed from the bottle on the Patient Intake Calendar (see Section 18.4).

e. PRODUCT ACCOUNTABILITY

Each trial site will inventory and acknowledge receipt of all shipments of study products. All study products must be stored in accordance with the manufacturer's instructions.

Product transfer: **MAY NOT** be transferred from one patient to another patient or from one protocol to another protocol. All other transfers (e.g., a patient moves from one participating institution to another participating institution) must be approved **in advance** by emailing protocols@swog.org.

Product Returns**:** All unused product must be destroyed on-site in accordance with institutional policy. Opened bottles with remaining products should be documented in the patient-specific accountability record (i.e., logged in as "# of bottles returned") and destroyed on-site in accordance with institutional policy.

Product accountability**:** The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing, and destruction of all study drinks received from the distributor using the **NCI Oral Drug Accountability Record Form,** available on the NCI home page (http://ctep.cancer.gov). A separate record should be maintained for each patient on this protocol.

4.0 STAGING CRITERIA

4.1 Staging Criteria **(AJCC Eighth Edition, 2010)**

Patients will be staged according to standard of care methods. All patients will undergo cystoscopy with transurethral resection of the tumor, adequate for staging as muscle invasive.

Consistent with World Health Organization/International Society of Urologic Pathology (WHO/ISUP) – tumors will be classified as either low or high-grade. Tumor will also be classified for TIS (CIS): Carcinoma in situ (non-invasive flat carcinoma) in addition to the primary tumor stage since TIS (CIS) is an independent predictor of recurrence.

Primary Tumor (T)

TIS (CIS)	Carcinoma in situ (non-invasive flat carcinoma)
Ta	Non-invasive papillary carcinoma
T1	Tumor invades the submucosa or lamina propria
T2	Tumor invades muscularis propria
pT2a	Tumor invades superficial muscularis propria (inner half)
pT2b	Tumor invades deep muscularis propria (outer half)
T3	Tumor invades perivesical tissue

pT3a	Microscopically
pT3b	Macroscopically (extravesical mass)
T4	Tumor invades any of the following: prostatic stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall
T4a	Tumor invades prostatic stroma, uterus, vagina
T4b	Tumor invades pelvic wall, abdominal wall

Regional Lymph Nodes (N)
Regional lymph nodes include both primary and secondary drainage regions. All other nodes above the aortic bifurcation are considered distant lymph nodes.

NX	Lymph nodes cannot be assessed
N0	No lymph node metastasis
N1	Single regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac, or presacral lymph node)
N2	Multiple regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac, or presacral lymph node metastasis)
N3	Lymph node metastasis to the common iliac lymph nodes

Distant metastasis (M)

M0	No distant metastasis

5.0 ELIGIBILITY CRITERIA

Each of the criteria in the following section must be met in order for a patient to be considered eligible for registration in OPEN. Section 5 may be printed and used by the site, but is not to be uploaded in RAVE (unless specially stated). For each criterion requiring test results and dates, please record this information on the Onstudy Form and submit via Medidata Rave® (see Section 14.0). Any potential eligibility issues should be addressed to the SWOG SDMC in Seattle at 206/652-2267 or cancercontrolquestion@crab.org prior to registration. **NCI policy does not allow for waiver of any eligibility criterion (http://ctep.cancer.gov/protocolDevelopment/policies_deviations.htm).**

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 4 weeks later would be considered Day 28. This allows for efficient patient scheduling without exceeding the guidelines. **If any of the days mentioned in Section 5 falls on a weekend or holiday, the limit may be extended to the next working day.**

5.1 Disease Related Criteria

a. Patients must have a tissue diagnosis of primary urothelial cell carcinoma of the bladder by TURBT or partial cystectomy. Patients may not have any evidence of unresectable disease or metastatic disease as assessed by exam under anesthesia or imaging (CT, MRI, PET).

b. There must be plans for the cystectomy to be performed within 28 days after registration.

c. Surgery must be planned to be performed under pre-approved, study-specific surgical guidelines (see Section 7.3).

5.2 Prior/Concurrent Therapy Criteria

a. Patients must have completed any neoadjuvant chemotherapy or immunotherapy (intravesical or systemic) ≥ 14 days prior to registration and any toxicities resolved to at least Grade 2.

b. Patients may have a history of radiation therapy. Radiation therapy must have been completed ≥ 180 days prior to registration.

c. Patients may have a history of prior partial cystectomy. Prior partial cystectomy must have been completed at least 180 days prior to registration.

d. Patients with planned adjuvant chemotherapy within 90 days after radical cystectomy are not eligible.

5.3 Clinical/Laboratory Criteria

a. Patients must be ≥18 years of age.

b. Patients must be able to swallow liquid and have no refractory nausea, vomiting, malabsorption, or significant small bowel resection that would preclude adequate absorption. Patients on tube feeding are not eligible.

c. Patients must have their baseline nutrition status assessed using the Scored Patient-Generated Subjective Global Assessment (PG-SGA) by a clinician or licensed healthcare practitioner (trained physician, nurse, or dietitian) within 14 days prior to registration and must not have a global category rating of Stage C (severely malnourished).

d. Patients must not have galactosemia.

e. Patients must not have known active viral infections such as human immunodeficiency virus (HIV) or hepatitis, as these chronic viral infections may cause cachexia and immunodeficiency and thus alter the biology regarding the study endpoints.

f. No other prior malignancy is allowed except for the following: adequately treated basal cell or squamous cell skin cancer, *in situ* cervical cancer, adequately treated Stage I or II cancer from which the patient is currently in complete remission, or any other cancer from which the patient has been disease free for two years. Prostate cancer found at cystectomy would not be considered a prior malignancy.

g. Patients must not be pregnant or nursing as the conditions preclude candidacy for radical cystectomy.

5.4 Specimen Submission Criteria

a. Patients must consent and be willing to have specimens collected and submitted as described in Section 15.1.

b. Patients must be offered the opportunity to participate in additional specimen banking as outlined in Section 15.2.

5.5 Regulatory Criteria

a. Patients or their legally authorized representative ***must*** be informed of the investigational nature of this study and must sign and give informed consent in accordance with institutional and federal guidelines.

b. As a part of the OPEN registration process (see Section 13.3 for OPEN access instructions) the treating institution's identity is provided in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered in the system.

c. Patients must consent and provide their telephone contact information for four 24-hour dietary recall phone interviews to be conducted by staff at the Exercise, Diet, Genitourinary, & Endocrinology Laboratory (EDGE) Research Laboratory (see Sections 7.1c, 7.7e, and 15.3).

d. Patients must be able to understand and speak English and/or Spanish because the dietary recall phone interviews will only be conducted in English or Spanish.

6.0 STRATIFICATION FACTORS

Randomization will be balanced on the following stratification factors using a maximal allocation procedure:

1. Planned diversion type (neobladder vs. other); and

2. Prior neoadjuvant therapy (any vs. none); and

3. Baseline nutrition status (well-nourished [Stage A] vs. moderate malnutrition [Stage B], as assessed by the PG-SGA [see Section 7.1a]).

7.0 TREATMENT PLAN

For nutrition dose modification questions, please contact Jill Hamilton-Reeves, Ph.D., R.D., C.S.O., phone: 913/588-7650 or email jhamilton-reeves@kumc.edu. For surgical-related questions, please contact Jeffrey M. Holzbeierlein, M.D., phone 913/588-7654 or email jholzbeierlein@kumc.edu. For dosing principles or questions, please consult the SWOG Policy #38 "Dosing Principles for Patients on Clinical Trials" at http://swog.org.

7.1 Pre-Treatment

a. Initial assessment of nutrition status

Prior to registration/randomization, the Scored Patient-Generated Subjective Global Assessment (PG-SGA) must be completed to identify and categorize patients at risk for malnutrition. If the patient scores as severely malnourished, do not enroll the patient.

Patient-generated component (PG): The patient will complete items one through four on the first page of the questionnaire (weight, food intake, symptoms, activities, and function). If the patient has a severe visual deficit or cannot read, the clinician may interview the patient.

Do not allow patients to see the second page of the questionnaire as this might influence their response.

Clinician component (SGA and scoring): The clinician (trained physician, nurse, or dietitian) completes the remainder of the form. The clinician completes the worksheets to score weight loss, the disease/stages, metabolic demand, and physical exam and totals the PG-SGA score. The physical components evaluate subcutaneous fat, muscle, and fluid states (edema or ascites). (Scores will be reported on the **S1600** Nutrition Status form.) An optional training video for consistency in grading mild, moderate, and severe is available on the **S1600** protocol abstract page on the SWOG and CTSU websites. The estimated time to complete the scoring and the form is 1-5 minutes. The site will complete the **S1600** Nutrition Status form to report PG-SGA scores and upload the PG-SGA form to Rave® per Section 14.4.

A PG-SGA form is located on the abstract page of the CTSU website. A sample PG-SGA with scoring tips is also located in Section 18.5.

At any time before or during the study, treatment teams are encouraged to help patients obtain nutritional education or counseling from a registered dietitian or registered nurse as deemed necessary.

For questions about the PG-SGA, please contact S1600question@swog.org .

b. Baseline study visit – do not schedule for a Friday

Note: Baseline is after registration and before beginning preoperative nutrition drinks

After registration/randomization, the patient will have a baseline study visit consisting of the following. This visit is anticipated to take 40-45 minutes.

- Laboratory tests: complete blood count (CBC) with differential, and (if clinically indicated) albumin and prealbumin
- Blood draw for submission (see Section 15.1). NOTE: The blood for submission and for laboratory tests must be from the same blood draw.
- DXA scan (see Section 18.3)
- **S1600** Functional Assessment of Anorexia Cachexia (FAACT) Questionnaire and the **S1600** Wong-Baker FACES® Pain Rating Scale (FACES). See Section 15.3 for instructions for administration of patient questionnaires.

In addition, study staff will do the following:

- Dispense the patient-specific blinded study product (15 drink bottles) to the patient for him/her to take home.
- Instruct the patient on the administration of the study drink per Section 7.2a.
- Provide the patient with a copy of the “Patient Intake Calendar – Before Surgery” located in Section 18.4.
- Instruct the patient to discontinue any supplements containing fish oil until after completion of study.
- Provide the patient with a copy of the “Food Amounts Booklet” and “Patient Instructions for Food Amounts Booklet” and explain that the patient may refer to it during the phone interviews described in Section 15.4.
- If the patient is unable to pick up the study product from the clinic, study staff are responsible for shipping 15 drink bottles to the patient in time to begin consumption five days before the surgery date.

- If patient consented to participating in specimen banking, provide the patient with 2 kits for stool sample collection to cover timepoints per Section 15.2.:
    - After registration, but before beginning nutritional drink
    - After nutrition/before surgery (at least 4 days of drinks completed

- Call the patient at home six days before the surgery date to remind the patient to begin taking the study drinks the following morning. If patient consented, to participating in specimen banking remind the patient to collect the stool sample and record collection date on the Intake Calendar.

For questions about study visit procedures, please contact S1600question@swog.org .

c. Phone Interview – Before Surgery

Patients will be called two separate times by nutrition staff from the EDGE Research Laboratory at least 6 days before surgery prior to start of preoperative nutrition therapy for completion of a 15-minute phone interview regarding diet. Nutrition staff will collect diet data for a weekday on one call and a weekend day on the other call (see Section 15.4 and Section 18.6).

For questions about the phone interviews, please contact S1600question@swog.org

7.2 Treatment: Preoperatively

Agent	Dose	Route	Schedule
Blinded Nutrition Drink	3 daily (178 mL per bottle)	oral	5 days before Radical Cystectomy surgery; between meals

a. Patients drink 3 blinded bottles daily (178 mL per bottle) of blinded nutrition drink between meals for 5 days before surgery. Patient should consume 178 ml 3 times a day for 5 days up until the night before surgery as a supplement to their regular diet. The drink should be served chilled. Study oral supplements are offered in addition to regular meal intake and are not intended as meal replacements.

b. Patients complete the **S1600** Intake Calendar to record adherence to the preoperative nutrition therapy and return the calendar to the study staff on the day of surgery (see Section 7.5).

7.3 Radical Cystectomy Surgery

Because blood samples are required to be collected and shipped on Day 2 following surgery (see Section 15.1), surgery should take place on a Monday, Tuesday, or Wednesday.

a. Antibiotics

The recommended antibiotic protocol is 24 hours of cefoxitin. If the patient has penicillin allergy, gentamicin/clindamycin is an allowable substitution. If another regimen is followed, broad spectrum and enteric coverage should be considered and documented.

b. Considerations

Radical Cystectomy must occur within 1 day after the last ingestion of the drink. Study sites must adhere to the following guidelines adapted from the Enhanced Recovery After Surgery (ERAS) principles to preserve gut function so the patients can continue to take nutrition supplements after surgery.

1. No bowel preparation

2. No nasogastric tubes

3. Prescribe opioid-free pain control or minimize narcotics.

4. Feed study nutrition drinks to patients within 24 hours after surgery.

5. In addition, it is recommended that patients receive alvimopan to avoid opioid-induced constipation.

c. Postoperative hydration

It is recommended that patients receive an intravenous solution of 5% glucose and electrolytes to prevent dehydration until recovery of oral food intake.

7.4 Treatment: Postoperatively

Agent	Dose	Route	Schedule
Blinded Nutrition Drink	3 bottles daily (178 mL per bottle)	oral	For 5 days after Radical Cystectomy surgery; between meals

a. After surgery, patients consume 3 blinded bottles daily (178 mL per bottle) of nutrition drink between meals as a supplement to their regular diet for 5 days after surgery, to be administered by the nurse or dietitian. The study staff will deliver the patient's 15 bottles of blinded nutrition drink to the surgical unit (for accessibility to the patient prior to their 24 hours post-surgery time point), along with study staff contact information, a copy of the **S1600** protocol (for the surgical unit's reference), and a copy of the **S1600** Patient Intake Calendar – After Surgery. Study staff should label each bottle with the patient's hospital ID (in addition to the study labeling already included per Section 3.0) to ensure the bottles are administered to the correct patient. Study staff will instruct the patient's nurse or dietitian to keep the bottles refrigerated until dispensed so that the drinks are served cold. The patient should return their **S1600** Patient Intake Calendar – Before Surgery on the day of surgery, so study staff should coordinate with the surgical unit to collect this form.

b. Patients should resume intake within 24 hours after surgery. If resumption of diet is delayed, patients will resume the study drink once they can tolerate it (within 24-72 hours after surgery per protocol recommendation). Every effort should be made to have the patient begin post-operative consumption of the study nutrition drinks within at most 72 hours after surgery, though the patient should still consume the drinks even if resumption of diet is delayed more than 72 hours after surgery. Patient will consume the drinks for five days, regardless of what day diet is

resumed. Nurse or dietitian in the unit will initiate post-operative feeding once the physician order with approval to start the study drink is charted in the participant's medical record.

c. Postoperative Oral Nutrition Therapy Considerations:

1. Start with lower volumes and increase as tolerated to give 178 ml 3 times a day.

2. Educate patient to take the drink very slowly in increments over the course of 2-4 hours or longer. Study drink must be kept chilled.

3. Encourage patient to walk around the unit before taking a second small dose.

4. If patient feels too bloated, nauseous, or exhibits excessive burping, or hiccupping, then it is permissible to stop and wait for several hours before trying another feeding.

5. Patient can receive other food (e.g., regular diet) if allowed by the surgeon, but minimize sugary drinks or foods (sodas, juices, gelatin).

d. The study staff are responsible for getting the remainder of patient-specific study product (15 drink bottles) to the post-op unit for the nurse or dietitian there to dispense to the patient starting the day following surgery as described in Section 7.3a. If the patient is discharged from the hospital before consuming all 5-day supply of study product, the remaining should be sent home with instructions to continue until all are consumed.

e. If patient consented to participating in specimen banking, provide the patient with the kit for stool sample collection for first bowel movement after hospital discharge per Section 15.2.

7.5 Patient Compliance Document

Study staff will provide the patients with the **S1600** Patient Intake Calendar (Section 18.4) for his/her completion. (NOTE: There are two calendars: one for Before Surgery and one for After Surgery.) The patient will complete this intake calendar, recording daily consumption in servings (complete, half or no intake) during pre-op and post-op and return the Before Surgery calendar on the day of surgery and the After-Surgery calendar at the 30-day follow-up visit. Study staff will review and ascertain patient adherence at the end of preoperative treatment and postoperative treatment. The study staff will report drink adherence on the **S1600** Treatment Form (Preoperative and Postoperative). The **S1600** Patient Intake Calendar will be used as a source of evaluation of patient compliance and is expected to serve as a self-reminder and motivational tool for patients to comply with the recommended intake of nutritional support for this study. (NOTE: Compliance will be based on day counts of the study products consumed and confirmed at the end of the study with retrospective plasma fatty acid analysis. See Section 18.2) The completed patient intake calendar should be kept in the patient's clinic chart. Note that the calendar is provided only as a tool for tracking patient compliance. Do not submit patient calendars to the SWOG Data Operations Office.

7.6 Follow-up Visit (Day 2 after Surgery)

a. Patients will have a blood draw for laboratory tests and sample submission for translational studies (see Section 15.1). This will take place on Day 2 after surgery, regardless of what day diet is resumed.
   - Laboratory tests: complete blood count (CBC) with differential, and (if clinically indicated) albumin and prealbumin
   - Blood draw for submission (see Section 15.1). NOTE: The blood for submission and for laboratory tests must be from the same blood draw.

   The patient will be administered the **S1600** Wong-Baker FACES® Pain Rating Scale (FACES). See Section 15.3 for instructions for administration of patient questionnaires.

7.7 Follow-up Visit (Day 30 after Surgery, ± 7 days)

a. Call the patient prior to 30-day follow-up to remind them to bring their stool samples to the visit. If patient does not bring the samples, the site will send a mailer home with instructions to the patient to ship their stool samples to the SWOG Biospecimen Bank (ambient). Sites will be instructed to add a comment in the SWOG Specimen Tracking System.

b. The patient will be assessed by the surgeon for surgical complications per Clavien-Dindo grading (see Section 10.1a) on the **S1600** 30-Day Post-Op Assessment Form and the form must be signed by the surgeon.

c. Patients will have a DXA Scan and a blood draw for laboratory tests and sample submission for translational studies (see Section 15.1 and Section 18.3).
   - Laboratory tests: complete blood count (CBC) with differential, and (if clinically indicated) albumin and prealbumin.
   - Blood draw for submission (see Section 15.1). NOTE: The blood for submission and for laboratory tests must be from the same blood draw.

d. Patients will complete the following questionnaires:
   - **S1600** Functional Assessment of Anorexia Cachexia (FAACT) Questionnaire
   - Scored Patient-Generated Subjective Global Assessment (PG- SGA). NOTE: Clinician will also complete a portion of this form. Refer to Section 7.1a for patient and clinician instructions.
   - **S1600** Wong-Baker FACES® Pain Rating Scale (FACES).

e. The study staff must complete the **S1600** Cover Sheet for Patient-Completed Questionnaires as well as complete and submit required forms per Section 14.4.

f. Patients will be called by staff at the EDGE Research Laboratory for completion of two 15-minute 24-hour dietary recall phone interviews (for one weekday and one weekend day) (see Section 15.4).

g. The study staff should collect the completed **S1600** Patient Intake Calendar – After Surgery from the patient.

7.8 Follow-up Visit (90 Days after Surgery, ± 7 days)

The patient will be assessed by the surgeon for late-phase surgical complications per Clavien-Dindo grading (see Section 10.1a) on the 90-Day Post-Op Assessment Form and the form must be signed by the surgeon.

7.9 Criteria for Removal from Protocol Treatment

a. Patient has completed protocol treatment and the **S1600** 90-day Post-Op Assessment Form has been submitted.

b. Patient does not consume ≥ 80% (12 of 15 bottles) of pre-surgical supplementation.

c. Patient does not undergo planned radical cystectomy surgery.

d. Patient requires tube feeding any time prior to completion of 10 days of study drink.

e. Patients may withdraw from the protocol treatment at any time for any reason.

7.10 Discontinuation of Treatment

All reasons for discontinuation of treatment must be documented on the **S1600** Off Protocol Notice.

NOTE: Patient follow-up must be completed and forms must be submitted for all patients regardless if the Off Protocol Notice is submitted prior to completion of Section 7.9a.

7.11 Follow-Up Period

All patients will be followed for 3 years after radical cystectomy surgery or until death, whichever occurs first. See Section 9.0 and Section 14.4j for follow-up and forms submission guidelines. See COVID-19 Guidance in Section 7.13.

7.12 Unblinding

Patients may be unblinded to their treatment assignment on request at the end of the study, after study results have been published. Institutions will be notified when patient unblinding information is available for the study. For emergency unblinding criteria and procedures, see Section 18.8.

7.13 COVID-19 Guidance

Patient-Reported Outcome Questionnaires via Telemedicine (Phone or Virtual Visit), please see Section 15.3.

Follow-up Visits via Telemedicine (Phone or Virtual Visit):

- Follow-up visits at timepoints indicated in Section 9.0, Footnote (H) of the Study Calendar may be conducted via telemedicine (Phone or Virtual Visit) to provide continuity of care and patient follow-up provided that the Responsible Investigator determines that the phone/virtual visit is adequate to achieve the central purpose of the visit and assure the safety of the patient.
- Study visits may also be delayed or missed if in the judgment of the Responsible Investigator the benefit of delay/omission of a visit outweighs the risks of exposure

of the patient to the virus by coming in for an in-person visit and an alternative method (phone or virtual visit) is not possible.

- The above alterations would need to be thoroughly documented in the medical record by the Responsible Investigator with the reason for the deviation and brief justification for why the deviation was considered to be minor (e.g., routine follow-up on patient no longer on active therapy).

8.0 TOXICITIES TO BE MONITORED AND DOSE MODIFICATIONS

8.1 NCI Common Terminology Criteria for Adverse Events

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 5.0 for toxicity and Serious Adverse Event reporting. A copy of the CTCAE Version 5.0 can be downloaded from the CTEP home page (http://ctep.cancer.gov). All appropriate treatment areas should have access to a copy of the CTCAE Version 5.0.

8.2 Dose Modifications

a. Before surgery, no dose modifications will be allowed.

b. Mild gastrointestinal upset, loose stools and nausea after supplementation may occur. After surgery, if the patient feels bloated, nauseated, or is burping excessively, then he or she will be allowed to wait to resume a few hours before trying the drinks again. If resumption of diet is delayed (within 72 hours of surgery), patients will resume the supplement once they can tolerate it and resumption is cleared by the treating physician.

8.3 Dose Modification Contacts

a. For treatment or dose modification questions, please contact the Study Chairs by phone or email: Jill Hamilton-Reeves, Ph.D., R.D., C.S.O, phone: 913/588-7650 or email jhamilton-reeves@kumc.edu; or Jeffrey M. Holzbeierlein, M.D., phone 913/588-7654 or email jholzbeierlein@kumc.edu.

8.4 Adverse Event Reporting

Toxicities (including suspected reactions) that meet the expedited reporting criteria as outlined in Section 16.1 of the protocol must be reported to the Operations Office, Study Chair and NCI via CTEP-AERS, and to the IRB per local IRB requirements.

9.0 STUDY CALENDAR

REQUIRED STUDIES	Pre-Study	Baseline [A]	D -5	D -4	D -3	D -2	D -1	Day 0 SURGERY [K]	D 1	D 2	D 3	D 4	D 5	D 30 [J]	D 90 [J]	F/U [H]
PHYSICAL																
Medical History & Comorbidities	X	X												X	X	
Zubrod Performance Status		X								X				X		
Body Weight & Height	X	X												X		
Assess Surgical Complications [B]														X	X	
Recurrence Assessment														X	X	X
Review Intake Calendar [C]									X					X		
SPECIMENS																
Blood per Section 15.1		X								X				X		
Stool per Section 15.2 (Optional)		X			X					X						
LABORATORY																
Prealbumin, if clinically indicated		X								X				X		
Albumin, if clinically indicated		X								X				X		
CBC with Differential, Platelets		X								X				X		
SCANS																
DXA Body Composition		X												X		
SURGERY																
Radical Cystectomy								X								
PATIENT COMPLETED QUESTIONNAIRES																
S1600 FAACT [E]		X												X		
S1600 PG-SGA [G]	X													X		
S1600 Pain Scale FACES [E]		X								X				X		
S1600 Patient Intake Calendar			X	X	X	X	X		X	X	X	X	X			
Phone Interview [F]		X												X		
Blinded Nutritional Drink			X	X	X	X	X		X	X	X	X	X			

Click here for Footnotes

NOTE: Forms are found on the protocol abstract page of the CTSU website (www.ctsu.org). Form submission guidelines are found in Section 14.0.

NOTE: Unless indicated otherwise in the protocol, scheduled procedures and assessments (treatment administration, toxicity assessment for continuous treatment, disease assessment, specimen collection and follow-up activities) must follow the established SWOG guidelines as outlined in https://www.swog.org/clinical-trials/protocol-workbench.

Footnotes:

[A] Baseline is after registration and before beginning preoperative nutrition drinks.
[B] Includes Clavien-Dindo (I-V) grading (see Table 1 in Section 10.1a)
[C] Site personnel to review patient reported compliance for preoperative period at the time of surgery, and post-operative period on Day 30 ± 7 days (see Section 7.5).
[E] See Section 15.3 for further details.
[F] The site must complete the **S1600** Telephone Contact Form and FAX it to the EDGE Laboratory at 913/574-0515 within 24 hours after registration. Please phone the EDGE lab at 913/945-7519 to ensure the FAX was received. Nutrition staff from the EDGE Research Laboratory will contact patients directly by phone to conduct diet recall interviews (see Section 15.4).
[G] The Scored Patient-Generated Subjective Global Assessment (PG-SGA) will be completed by the patient and the clinician (see Section 7.1a).
[H] Includes recurrence and vital status at Months 3, 6, 9, 12, 18, 24 and 36 months after radical cystectomy surgery or until death. See Section 14.4j. See COVID-19 Guidance in Section 7.13.
[J] Day 30 visit to take place within 7 days before or after Day 30 (after surgery date). Day 90 visit to take place within 7 days before or after Day 90 (after surgery date).
[K] **Because blood samples are required to be collected and shipped on Day 2 following surgery (see Section 15.1), surgery should take place on a Monday, Tuesday, or Wednesday.**

10.0 CRITERIA FOR EVALUATION AND ENDPOINT ANALYSIS

10.1 Measurement of Complications

a. Primary Endpoint: Post-operative Complications A post-operative complication is defined as a binary indicator variable indicating whether the patient experienced any complication (any/none; Clavien-Dindo grades I-V; Table 1). *(118)*

Table 1. Clavien-Dindo Scheme

Clavien-Dindo Grades	Definition
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic or radiological interventions. Allowed therapeutic regimens are drugs as antiemetic, antipyretics, analgesics diuretics, electrolytes, and physiotherapy.
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
Grade III	Requiring surgical, endoscopic or radiological intervention
Grade IIIa	Intervention not under general anesthesia
Grade IIIb	Intervention under general anesthesia
Grade IV	Life-threatening complications (including central nervous system complications) requiring intermediate care or intensive care unit management
Grade IVa	Single-organ dysfunction (including dialysis)
Grade IVb	Multi-organ dysfunction
Grade V	Death of a patient
Suffix “d”	If the patient suffers from a complication at the time of discharge, the suffix “d” (for “disability”) is added to the respective grade of complication. This label indicated the need for a follow up to fully evaluate the complication.

10.2 Secondary Endpoints

a. In addition to grading, complications will be defined using surgery-specific categories (ileus, deep vein thrombosis, pneumonia, wound infection, urinary tract infection, return to operation room, pulmonary embolus, myocardial infarction, cerebral vascular accident, dehiscence, sepsis, respiratory failure, bowel leak, urine leak, small bowel obstruction, death, or other). Post-operative ileus will be defined as a delay in feeding of greater than or equal to five days post-operatively.

b. Postoperative Infections. Infectious complications are defined by the use of non-prophylactic antibiotics to treat infection. In addition, infections will be categorized by intra-abdominal infection or surgical site infection.

c. Anthropometrics & Body composition. Changes in fat mass and non-bone lean tissue (muscle mass) will be assessed by dual-energy X-ray Absorptiometry (GE Lunar DXA, Software version 13.5 or newer version, Madison, WI, or Hologic, Software version APEX 5.5.3.1 or newer version) at baseline and 30 days. The fat-free mass index (FFMI) and the appendicular skeletal muscle will be examined over time. Body weight (in a hospital gown without shoes) will be measured using a digital scale accurate to ± 0.1 kg. Height will be determined using a wall-mounted stadiometer (± 0.1 cm). See Appendix 18.3 for further information.

d. Quality of Life. Functional Assessment of Anorexia/Cachexia Therapy (FAACT) will be completed by the patient at baseline and 30 days post-operation. *(119)* The FAACT trial outcome index and anorexia subscales were used in our pilot and the SIM showed better scores than the ONS group but the differences were not statistically significant (P=0.15 for both), but the pilot was underpowered for this outcome. Also, the anorexia and cachexia subscale asks about issues common after RC such as: taste alterations, appetite, early satiety, and pain while eating. These data are crucial for optimizing nutrition interventions to help patients.

e. Readmission Rates. Readmission will be defined as admission to any hospital after discharge home until 90 days after surgery. The reason for readmission will be recorded.

10.3 Disease-Free Survival

From date of surgery to date of first documentation of relapse/recurrence or death due to any cause. Patients last known to be alive without report of relapse/recurrence are censored at date of last contact.

10.4 Overall Survival

From date of randomization to date of death due to any cause. Patients last known to be alive are censored at their last contact date.

10.5 Performance Status

Patients will be graded according to the Zubrod Performance Status Scale.

POINT	DESCRIPTION
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of self-care but unable to carry out any work activities; up and about more than 50% of waking hours.
3	Capable of limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair.

11.0 STATISTICAL CONSIDERATIONS

11.1 Primary Analysis

The primary objective is to compare, by arm, the proportion of patients who experience any complication (Clavien-Dindo grades I–V) by day 30 after surgery. Prior evidence suggests that approximately 65% of patients will experience complications by Day 30. *(120,121,122,123)* The design stipulates that a 35% relative reduction in the complication rate due to the intervention would be clinically meaningful, representing a reduction in the complication rate from 65% down to 42% (a 23% absolute reduction). The design also anticipates a 5% non-adherence rate (which reduces the nominal effect size). Based on a two-arm binomial design with continuity correction, a one-sided alpha = 0.05 test and 80% power, a total of 146 eligible, randomized patients will be needed. In addition, in this population, it is anticipated that 20% of patients will drop out after surgery by Day 30, and a small portion of patients (3%) will drop out prior to surgery. Incorporation of this dropout rate inflates the required sample size by a factor of 146/0.77 = 190 eligible patients. Finally, assuming a 5% ineligibility rate, a total of 200 registered patients will be required. The high-grade complication rate (Clavien Dindo scheme III-V) will also be examined. If the control arm high grade complication rate is 20%, 200 patients will give ≥ 80% power to detect an absolute reduction of 15% (down to 5%).

The primary analysis will be based on a multivariable logistic regression under intent-to-treat among all randomized patients, irrespective of their eligibility status, adjusting for the specified stratification factors: a. Diversion type (neobladder vs. ileal conduit); b. Prior neoadjuvant chemotherapy (any vs. none); and c. Nutrition status (well-nourished vs. moderate malnutrition). A Fisher's exact test will also be conducted to establish whether the results are sensitive to model assumptions. A single interim analysis for efficacy will be conducted when 50% of patients achieve their endpoint at the alpha=0.005 level. Accordingly, the final analysis will be conducted at the alpha=0.045 level. A separate analysis among all eligible randomized patients will also be conducted.

To minimize missed assessments, SWOG utilizes an electronic system to remind institutions in real-time that patients are due for follow-up assessment. Nonetheless missing data will occur. To bracket the final result, Lachin's worst rank analysis will be used by imputing the missing data in the following manner: 1) all missing observations will be assigned the worst rank; 2) all missing observations will be assigned the best rank; 3) all missing observations in the experimental arm will be assigned the worst rank, and all missing observations in the control arm will be assigned the best rank; and 4) all missing observations in the experimental arm will be assigned the best rank, and all missing observation in the control arm will be assigned the worst rank. Finally, using delta adjustment, we will examine how biased the imputation will need to be to substantively influence statistical significance (i.e. turn from statistically significant to not statistically significant) at any given alpha level. *(124)* In particular, the "truth" will be bracketed by analysis 3 and 4, above. Interpretation will be influenced by the amount of missing data and the magnitude of potential differences between the observed and best/worst-case findings, suggesting uncertainty in the primary result due to missing data.

11.2 Secondary Analysis

A set of secondary objectives will also be examined. Additional factors that are potentially prognostic for complication rates will be examined as covariates in separate logistic regression analyses, to assess the sensitivity of the primary logistic regression model

results to additional covariate adjustment; factors include BMI (< 30 vs. ≥ 30), age (< 65 vs. ≥ 65 years), gender (male vs. female), diabetes mellitus, pathologic staging, pro-inflammatory cytokines known to affect appetite**,** background diet, current use of supplements, and any autoimmune disease. Also, in addition to the primary endpoint assessment of any complication at Day 30, we will assess the complication rate at day 90, as well as a composite endpoint with three levels (complications by Day 30, complication after Day 30 but by Day 90, and no complications by Day 90). In addition, we will examine the impact of SIM use on the Day 30 and Day 90 rates of infection (as determined by antibiotic use outside of prophylaxis), skeletal muscle mass, high-grade post-operative complications (Clavien Dindo Grades III–V), and readmission rates. To consider whether dropout may be non-random (i.e., informative), which could influence the results, a sensitivity analysis will be conducted that counts dropouts as events. Although death rates are anticipated to be low, 2-year overall survival by arm will be explored using Kaplan Meier curves, as will disease-free survival. The relationship between compliance and outcomes will be explored. A set of tertiary objectives will also be examined as indicated in Appendix 18.2.

11.3 Data and Safety Monitoring Committee

A Data and Safety Monitoring Committee will oversee the conduct of the study. The Committee consists of four members from outside of the SWOG, 3 SWOG members, 3 non-voting representatives from the National Cancer Institute (NCI), and the Group Statistician (non-voting). The members of this Committee will receive confidential reports every 6 months from the SWOG Statistical Center, and will meet at the Group's bi-annual meetings as necessary. The Committee will be responsible for decisions regarding possible termination and/or early reporting of the study.

12.0 DISCIPLINE REVIEW

Discipline Review is not required for this study.

13.0 REGISTRATION GUIDELINES

13.1 Registration Timing

Study sites must meet requirements and have approval for study participation before registering patients to the study(See Section 13.2b.3 and Section 18.7).

Patients must be registered prior to initiation of treatment (at least 10 days and no more than 28 days prior to planned surgery).

13.2 Investigator/Site Registration

Prior to the recruitment of a patient for this study, investigators must be registered members of a Cooperative Group. Each investigator must have an NCI investigator number and must maintain an “active” investigator registration status through the annual submission of a complete investigator registration packet to CTEP.

a. CTEP Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register

and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at https://ctepcore.nci.nih.gov/iam. In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN, Rave, or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr.

RCR utilizes five-person registration types.

- IVR — MD, DO, or international equivalent;
- NPIVR — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- AP — clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications (e.g., Roster Update Management System (RUMS), OPEN, Rave,);
- Associate (A) — other clinical site staff involved in the conduct of NCI-sponsored trials; and
- Associate Basic (AB) — individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✔	✔			
Financial Disclosure Form	✔	✔	✔		
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔		
GCP training	✔	✔	✔		
Agent Shipment Form (if applicable)	✔				
CV (optional)	✔	✔	✔		

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Addition to a site roster;
- Assign the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN;
- Act as the site-protocol Principal Investigator (PI) on the IRB approval; and
- Assign the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

In addition, all investigators act as the Site-Protocol PI, consenting/treating/drug shipment, or as the CI on the DTL must be rostered at the enrolling site with a participating organization (i.e., Alliance).

Additional information is located on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the **RCR Help Desk** by email at RCRHelpDesk@nih.gov.

b. CTSU Registration Procedures

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

1. **IRB Approval:**

For CTEP and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases after March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB). In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating with the NCI CIRB must submit the Study Specific Worksheet for Local Context (SSW) to the CIRB using IRBManager to indicate their intent to open the study locally. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by emailing the email address above or calling 1-888-651-CTSU (2878).

In addition, the Site-Protocol Principal Investigator (PI) (i.e. the investigator on the IRB/REB approval) must meet the following criteria to complete processing of the IRB/REB approval record:

- Holds an Active CTEP status;
- Rostered at the site on the IRB/REB approval (*applies to US and Canadian sites only*) and on at least one participating roster;
- If using NCI CIRB, rostered on the NCI CIRB Signatory record;
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile; and
- Holds the appropriate CTEP registration type for the protocol.

Additional Requirements

Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to the following:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO); and
- Compliance with all protocol-specific requirements (PSRs).

2. **Downloading Site Registration Documents:**

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment. To participate, the institution and its associated investigators and staff must be associated with the LPO or a PO on the protocol.

- Log on to the CTSU members' website (https://www.ctsu.org) using your CTEP-IAM username and password;
- Click on *Protocols* in the upper left of your screen
- Enter the protocol number in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand, then select SWOG, and protocol number **S1600**
- Click on *Documents*, select *Site Registration*, and download and complete the forms provided. (Note: For sites under the CIRB initiative, IRB data will load automatically to the CTSU as described above.)

3. **Requirements For S1600 Site Registration:**

- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)
- Site must meet all five criteria listed on the **S1600** Site Requirements Form (see Appendix 18.7). This form must be completed and submitted to the CTSU Regulatory Office via the Regulatory Submission Portal on the CTSU website as a protocol specific requirement prior to registering any patients.

4. **Submitting Regulatory Documents:**

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal on the CTSU website.

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab → Regulatory Submission

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

5. **Checking Your Site's Registration Status:**

You can verify your site's registration status on the members' side of the CTSU website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab at the top of your screen

- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

Note: The status shown only reflects institutional compliance with site registration requirements as outlined above. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

13.3 OPEN Registration Requirements

The individual registering the patient must have completed the appropriate SWOG Registration Worksheet. The completed form must be referred to during the registration but should not be submitted as part of the patient data.

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the Lead Protocol Organization (LPOs) registration/randomization systems or Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.
Requirements for OPEN access:

- A valid CTEP-IAM account;
- To perform enrollments or request slot reservations: Be on a LPO roster, ETCTN Corresponding roster, or PO roster with the role of Registrar. Registrars must hold a minimum of an AP registration type;
- If a Delegation of Tasks Log (DTL) is required for the study, the registrar(s) must hold the OPEN Registrar task on the DTL for the site; and
- Have an approved site registration for a protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR. If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.
Prior to accessing OPEN, site staff should verify the following:

- Patient has met all eligibility criteria within the protocol stated timeframes and the affirmation of eligibility on the Registration Worksheet has been signed by the registering investigator or another investigator designate. Site staff should refer to Section 5.0 to verify eligibility.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

OPEN will also ask additional questions that are not present on the SWOG Registration Worksheet. The individual registering the patient must be prepared to provide answers to the following questions:

a. Institution CTEP ID

b. Protocol Number

c. Registration Step

d. Treating Investigator

e. Credit Investigator

f. Patient Initials

g. Patient's Date of Birth

h. Patient SSN (SSN is desired, but optional. Do not enter invalid numbers.)

i. Country of Residence

j. ZIP Code

k. Gender (select one):
- Female Gender
- Male Gender

l. Ethnicity (select one):
- Hispanic or Latino
- Not Hispanic or Latino
- Unknown

m. Method of Payment (select one):
- Private Insurance
- Medicare
- Medicare and Private Insurance
- Medicaid
- Medicaid and Medicare
- Military or Veterans Sponsored NOS
- Military Sponsored (Including Champus & Tricare)
- Veterans Sponsored
- Self-Pay (No Insurance)
- No Means of Payment (No Insurance)
- Other
- Unknown

n. Race (select all that apply):
- American Indian or Alaska Native
- Asian
- Black or African American
- Native Hawaiian or other Pacific Islander
- White
- Unknown

13.4 Registration Procedures

a. All site staff will use OPEN to enroll patients to this study. Access OPEN at https://open.ctsuorg, from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at https://www.ctsuorg, https://open.ctsu.org, or from the OPEN Patient Registration link on the SWOG CRA Workbench. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

b. The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

c. Further instructional information is provided on the OPEN tab on the CTSU members' side of the website at https://www.ctsuorg or at https://open.ctsuorg. For any additional questions contact the CTSU Help Desk at 888/823-5923 or ctsucontact@westat.com.

13.5 Exceptions to SWOG registration policies will not be permitted.

a. Patients must meet all eligibility requirements.

b. Institutions must be identified as approved for registration.

c. Registrations may not be cancelled.

d. Late registrations (after initiation of treatment) will not be accepted.

14.0 DATA SUBMISSION SCHEDULE

14.1 Data Submission Requirement

Data must be submitted according to the protocol requirements for **ALL** patients registered, whether or not assigned treatment is administered, including patients deemed to be ineligible. Patients for whom documentation is inadequate to determine eligibility will generally be deemed ineligible

14.2 Master Forms

Master forms can be found on the protocol specific page on the CTSU website (www.ctsu.org) and (with the exception of the sample consent form and the Registration Worksheet) must be submitted on-line via the Web; see below for details.

14.3 Data Submission Procedures

a. Data collection for this study will be done exclusively through the Medidata Rave® clinical data management system. Medidata Rave is a clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments. To access Rave via iMedidata:

- Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account; and
- Assigned one of the following Rave roles on the relevant Lead Protocol Organization (LPO) or Participating Organization roster at the enrolling site: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator. Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.
    - To hold Rave CRA or Rave CRA (Lab Admin) role, site staff must hold a minimum of an AP registration type;
    - To hold Rave Investigator role, the individual must be registered as an NPIVR or IVR; and

- To hold Rave Read Only role, site staff must hold an Associates (A) registration type.

If the study has a Delegation of Tasks Log (DTL), individuals requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL.

Upon initial site registration approval for the study in Regulatory Support System (RSS), all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site staff must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the *accept* link in the upper right-corner of the iMedidata page. Site staff will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen. If an eLearning is required and has not yet been taken, the link to the eLearning will appear under the study name in iMedidata instead of the *Rave EDC* link; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will display under the study name.

Site staff that have not previously activated their iMedidata/Rave account at the time of initial registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management > Rave section at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

b. You may also access Rave® via the SWOG CRA Workbench via the SWOG website (www.swog.org).

For difficulties with the CRA Workbench, please email technicalquestion@crab.org.

c. Institutions participating through the Cancer Trials Support Unit (CTSU), please refer to the CTSU Participation Table.

d. Data Quality Portal

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics. The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, and timeliness reports. Review the DQP modules on a regular basis to manage specified queries and delinquent forms. The DQP is accessible by site staff that are rostered to a site and have access to the CTSU website. Staff that have Rave study access can access the Rave study data using a direct link on the DQP. To learn more about DQP use and access, click on the Help icon displayed on the Rave Home, DQP Queries, and DQP Delinquent Forms modules. Note: Some Rave protocols may not have delinquent form details or reports specified on the

DQP. A protocol must have the Calendar functionality implemented in Rave by the Lead Protocol Organization (LPO) for delinquent form details and reports to be available on the DQP. Site staff should contact the LPO Data Manager for their protocol regarding questions about Rave Calendar functionality.

14.4 Data Submission Overview and Timepoints

Please reference the ORP Manual on the CRA Workbench (www.swog.org) for detailed General Forms and Guidelines, as well as some disease-specific and study-specific forms. There are also many other chapters available in the manual to be used for regular reference of SWOG processes and procedures.

a. WITHIN 24 HOURS AFTER REGISTRATION:

FAX the **S1600** Telephone Contact Form directly to the EDGE Research Laboratory at 913/574-0515 per form instructions. Phone the EDGE lab at 913/945-7519 to ensure the FAX was received.

b. WITHIN 7 DAYS AFTER REGISTRATION:

Submit the following:

S1600 Onstudy Form

S1600 Nutrition Status Form

S1600 Wong-Baker Pain Scale

Scored Patient-Generated Subjective Global Assessment (PG-SGA)*

Pathology report from TURBT*

*NOTE: Include all TURBT reports within the last two years including the report with the primary diagnosis. Upload reports via the Source Documentation: Baseline form in Rave®.

c. PRIOR TO BEGINNING PREOPERATIVE TREATMENT, AT DAY 2 AFTER CYSTECTOMY, AND AT DAY 30 ± 7 DAYS AFTER CYSTECTOMY:

Collect, process, and submit specimens as outlined in Section 15.

d. WITHIN 14 DAYS AFTER PREOPERATIVE TREATMENT:

Submit the following:

S1600 Treatment Form

S1600 Adverse Event Form

S1600 Laboratory Values Form

S1600 FAACT form

S1600 Cover Sheet for Patient-Completed Questionnaires

S1600 Body Composition Form

Scan Report from DXA*

Laboratory report including CBC with differential*

*NOTE: Upload the DXA scan report via the Source Documentation: Baseline form in Rave®. Upload lab results via the Source Documentation: Lab folder in Rave.

e. WITHIN 14 DAYS AFTER CYSTECTOMY:

Submit the following:

S1600 Cystectomy Form

Operative report from cystectomy*

Pathology report from cystectomy*

*NOTE: Upload reports via the Source Documentation: Follow Up form in Rave®.

f. IF PATIENT DOES NOT UNDERGO CYSTECTOMY, WITHIN 14 DAYS AFTER PLANNED CYSTECTOMY DATE:

Submit the **S1600** Off Protocol Notice.

g. WITHIN 14 DAYS AFTER POSTOPERATIVE TREATMENT:

Submit the following:

S1600 Adverse Event Form

S1600 Wong-Baker Pain Scale

S1600 Laboratory Values Form

Laboratory report including CBC with differential*

*NOTE: Upload lab reports via the Source Documentation: Lab form in Rave®.

h. WITHIN 14 DAYS AFTER 30-DAY POSTOPERATIVE ASSESSMENT:

Submit the following:

S1600 30-Day Post-Op Assessment Form**

S1600 Treatment Form

S1600 Adverse Event Form

S1600 Laboratory Values Form

S1600 Nutrition Status Form

Scored Patient-Generated Subjective Global Assessment (PG-SGA)*

S1600 FAACT form

S1600 Cover Sheet for Patient-Completed Questionnaires

S1600 Body Composition Form

S1600 Wong-Baker Pain Scale

Scan Report from DXA*

Laboratory report including CBC with differential*

*NOTE: Upload the PG-SGA and DXA scan reports via the Source Documentation: Follow Up form in Rave®. Upload lab reports via the Source Documentation: Lab form in Rave®.

**NOTE: This form must be both submitted electronically, and the completed version signed (paper or electronically) by the surgeon uploaded via the Source Documentation: Follow Up form in Rave®.

i. WITHIN 14 DAYS AFTER 90-DAY POSTOPERATIVE ASSESSMENT:

Submit the following:

S1600 90-Day Post-Op Assessment Form**

S1600 Off Protocol Notice

**NOTE: This form must be both submitted electronically and the completed version signed (paper or electronically) by the surgeon uploaded via the Source Documentation: Follow Up form in Rave®.

j. AT 3 MONTHS, 6 MONTHS, 9 MONTHS, 12 MONTHS, 18 MONTHS, 24 MONTHS, AND 36 MONTHS AFTER CYSTECTOMY OR UNTIL DEATH:

Submit the SWOG Follow Up Form.

k. WITHIN 4 WEEKS OF KNOWLEDGE OF DEATH:

Submit the Notice of Death.

15.0 SPECIAL INSTRUCTIONS

15.1 Blood for Translational Medicine and Banking ***(REQUIRED)***

Blood specimens for translational medicine are required to be submitted as described below.

Please call the EDGE lab at 913/945-7519 when a patient blood draw has been scheduled so they may anticipate sample receipt.

If the patient consents to future testing, any leftover blood will remain at the EDGE Repository for future analysis.

a. Collection

Collect blood in purple top EDTA tubes, but process separately, as two different sets:

- Set A: collect 12 mL of blood in purple EDTA tubes.
- Set B: collect 12 mL of blood in purple EDTA tubes for a total of 24 mL.

NOTE: Different sized tubes may be used to collect the required amount of blood. Avoid using < 3mL collection tubes.

The blood will be collected at the following three time points:

1. After registration prior to starting preoperative nutrition therapy (Baseline Study Visit) – **MUST BE COLLECTED ON MONDAY, TUESDAY, WEDNESDAY, OR THURSDAY ONLY**

2. Day 2 after surgery – May be collected any non-holiday weekday, Monday through Friday

3. Day 30 (±7 days) after surgery – **MUST BE COLLECTED ON MONDAY, TUESDAY, WEDNESDAY, OR THURSDAY ONLY**

NOTE: EDGE Lab cannot receive samples on holidays.

NOTE: The blood for submission must come from the same draw as blood for laboratory tests (see Sections 7.1b, 7.6, and 7.7b).

b. Labeling and Processing

All submitted specimens must be labeled with the:

- SWOG patient number
- Patient initials
- Collection date and time (date the specimen was collected from the patient)
- Date and time plasma was frozen

c. Processing of Set A purple top tubes. Remove 1 mL whole blood and aliquot into 1 Eppendorf tube, 1.5 mL tube size and freeze at -80◦C until shipping. After removing 1 mL whole blood from one of the tubes, centrifuge that tube along with the rest of the Set A purple tops tubes at 180 rcf (relative centrifugal force) for 10 minutes at room temperature.

Remove supernatant from Set A purple top tubes (plasma, top layer), aliquot 250 mcl plasma into each of 11 Eppendorf tubes, 1.5 mL tube size, and 500 mcl plasma into 1 screw cap tube, 2 mL tube size, and freeze at -80°C until shipping. Tubes must be labeled with patient ID using a label that will remain in place at -80°C.

d. Shipment of Set B purple top tubes (12mL)

Set B purple top tubes must be shipped overnight the same day it is collected. Ship at ambient temperature.

Please pack tubes carefully. Cardboard express mail envelopes alone are NOT adequate – please additionally pack the tubes in Styrofoam or with extra padding. If freezing or very warm conditions are anticipated, insulated containers and packing materials are recommended. Samples must be shipped and received at room temperature.

Please call the EDGE lab at 913/945-7519 a few days before shipping the Set B purple tubes so they can watch for its arrival.

If shipping Monday, Tuesday, Wednesday, or Thursday, ship to the following address:

Lab #229: EDGE Research Laboratory
University of Kansas Medical Center
University Receiving Dock
ATTN: Misty Bechtel
2106 Olathe Blvd.
Kansas City, KS 66160

Note that Friday shipments are only permitted for Day 2 Set B purple top tubes. If shipping on a Friday, ship to the following address:

Lab #234: FedEx Office Print and Ship
ATTN: KU Med, Misty Bechtel or EDGE Lab Team
5437 Johnson Drive
Mission, KS 66205

e. Shipment of plasma aliquots and whole blood aliquot (Set A)

Plasma and whole blood aliquots may be batch shipped as long as they are submitted within 3 months after collection. Ship on dry ice overnight Monday through Thursday (NO FRIDAY SHIPMENTS) to the following address:

Lab #229: EDGE Research Laboratory
University of Kansas Medical Center
ATTN: Misty Bechtel
2106 Olathe Blvd.
Kansas City, KS 66160

f. Additional instructions

1. SWOG Specimen Tracking System (STS)

All specimen submissions for this study must be entered and tracked using the SWOG online Specimen Tracking system. SWOG members may log on the online system via the CRA Workbench. To access the CRA Workbench, go to the SWOG Web site (http://swog.org) and logon to the Members Area. After you have logged on using your SWOG roster ID number and password, click on the *CRA Workbench* link to access the home page for CRA Workbench website. Non- SWOG users may log into SpecTrack using their CTSU UserID and password on the SpecTrack login page located at https://spectrack.crab.org (select the option "SWOG – SWOG – CTSU"). SpecTrack start-up instructions (both written and demo) are available after signing in to SpecTrack.

A copy of the Shipment Packing List produced by the online Specimen Tracking system should be printed and placed in the pocket of the specimen bag if it has one, or in a separate resealable bag.

ALL SPECIMENS MUST BE LOGGED VIA THIS SYSTEM; THERE ARE NO EXCEPTIONS.

To report technical problems with Specimen Tracking, such as database errors or connectivity issues, please send an email to technicalquestion@crab.org. For procedural help with logging and shipping specimens, there is an introduction to the system on the Specimen Tracking main page (https://spectrack.crab.org/Instructions); or contact the Data Operations Center at 206/652-2267 to be routed to the Data Coordinator for further assistance.

2. Specimen collection kits are not being provided for this submission; sites will use institutional supplies.

3. Complete specimen collection and submission instructions can be accessed on the SWOG Specimen Submission webpage (https://www.swog.org/member-resources/biospecimen-resources/solid-tissue-specimen-submission).

4. Federal guidelines for the shipment of blood products:

   a. The tube must be wrapped in an absorbent material.

   b. The tube must then be placed in an AIRTIGHT container (like a resealable bag).

   c. Pack the resealable bag and tube in a Styrofoam shipping container.

   d. Pack the Styrofoam shipping container in a cardboard box.

   e. Mark the box "Biohazard".

15.2 Specimens for the TM Stool Microbiome ***(REQUIRED IF PATIENT CONSENTS)***

The fecal microbiome of patients in a randomized controlled trial of perioperative immunonutrition for reduction of complications following radical cystectomy and urinary diversion.

Stool specimens for translational medicine and banking (submitted to the SWOG Biospecimen Bank – Solid Tissue, Myeloma and Lymphoma Division, Lab #201) are considered optional for the participant.

a. With patient's consent specimens must be submitted at the time points listed below.

   1. After registration, but before beginning nutritional drink

   2. After nutrition/before surgery (at least 4 days (+/- one drink) of drinks completed)

3. First bowel movement on return to home (+/- 2 days).

b. Omnigene-GUT Kit Stool Ordering

Immediately after identifying a patient for the trial, sites must contact SWOG Biospecimen Bank to order Omnigene-GUT kits via the following URL: https://kits.bpc-apps.nchri.org. Orders placed by noon Eastern should be received within 3-4 business days.

c. Omnigene-GUT Kit Stool Labeling

Sites will be instructed to label tubes with:

- SWOG patient number
- Patient initials
- Specimen type
- Collection date

NOTE: The collection date will be filled by the patient on the tube and the Intake Calendar. Sites must verify the date has been added on the tube prior to shipping.

d. Specimen Collection and Submission Instructions

Collection kits will be sent home with the patients at 2 different times to reduce patient error.

(1) 2 kits will be provided after registration for the collection of:

- After registration, but before beginning nutritional drink
- After nutrition/before surgery (at least 4 days of drinks completed)

(2) 1 kit will be provided after surgery when site staff provides nutritional drinks

Due to the sensitive nature of the collections, patients will collect the specimens at home. Patients must be instructed to bring their specimen back to the site on a subsequent visit.

Site phone calls

- Call the patient at home six days before the surgery date to remind patients to collect their stool sample.
- Call patient prior to 30-day follow-up to bring their samples to appointment.

Note for the 30-Day Follow-up visit: If the patient did not bring their stool specimen, the site must supply the patient with a mailer, shipping label, and instructions to ship specimen ambient to the SWOG Biospecimen Bank. Shipping labels created using the Kit Management website are valid for 1 week from date created. The site must make a note in STS that the patient will be mailing in their specimen.

The specimens must be shipped to the SWOG Biospecimen Bank within 1-3 days of receiving them from the patient. Specimens remain stable in all weather conditions and are shipped ambient. Collection and shipment instructions are provided with the Omnigene-GUT kit.

Lab #201: SWOG Biospecimen Bank
Solid Tissue, Myeloma & Lymphoma Division
Phone: 614/722-2865
E-mail: bpcbank@nationwidechildrens.org

e. SWOG Specimen Tracking System (STS)

All specimen submissions for this study must be entered and tracked using the SWOG online Specimen Tracking system. SWOG members may log on the online system via the CRA Workbench. To access the CRA Workbench, go to the SWOG Web site (http://swog.org) and logon to the Members Area. After you have logged on using your SWOG roster ID number and password, click on the *CRA Workbench* link to access the home page for CRA Workbench website. Non-SWOG users may log into SpecTrack using their CTSU UserID and password on the SpecTrack login page located at https://spectrack.crab.org (select the option "SWOG – SWOG – CTSU"). SpecTrack start-up instructions (both written and demo) are available after signing in to SpecTrack.

A copy of the Shipment Packing List produced by the online Specimen Tracking system must be printed and placed in the pocket of the specimen bag if it has one, or in a separate resealable bag.

ALL SPECIMENS MUST BE LOGGED VIA THIS SYSTEM; THERE ARE NO EXCEPTIONS.

To report technical problems with Specimen Tracking, such as database errors or connectivity issues, please send an email to technicalquestion@crab.org. For procedural help with logging and shipping specimens, there is an introduction to the system on the Specimen Tracking main page (https://spectrack.crab.org/Instructions); or contact the Data Operations Center at 206/652-2267 to be routed to the Data Coordinator for further assistance.

15.3 Questionnaires: Instructions for administration

Patient-Reported Outcome Questionnaires via Telemedicine (Phone or Virtual Visit):

In response to the COVID-19 pandemic, PROs may be conducted via telehealth when the following conditions are met:

- For all patient reported outcome questionnaire timepoints, participating sites may follow-up with patients via telemedicine (phone or virtual visit) to conduct the questionnaires and patient follow-up provided that the Responsible Investigator determines that the phone/virtual visit is adequate to achieve the central purpose of the visit and assure the safety of the patient.
- Patient must be provided with a copy of the questionnaire via mail or email.
- The staff at EDGE are available to assist with the patient's telemedicine site to perform the Patient-Generated Subjective Global Assessment (PG-SGA) prior to registration. If sites would like assistance, please contact EDGE edgelab@kumc.edu with any questions.

a. Administration of questionnaires

1. The first time the patient completes the questionnaires: Please read to the patient the instructions attached to each patient questionnaire. Explain the specific administration times for this protocol. Patients should be directed to report all symptoms and limitations whether or not they are related to the cancer or its treatment.

2. It is permissible to assist patients with completing the questionnaires being careful not to influence the patient's response. Note on the **S1600** Cover Sheet for Patient-Completed Questionnaires what assistance was required and indicate reason (e.g., elderly, too sick, etc.). Discourage family members from: 1) being present while the patient completes the questionnaire and/or 2) influencing patient responses to the questions.

3. It is very important to review the questionnaires after the patient has completed them to be sure all of the questions have been answered and that only one answer is marked. If the patient has marked more than one answer per question, ask the patient which answer reflects how she is feeling. If the patient has skipped a question, tell the patient that a question was not answered and ask if she would like to answer the question. Always give the patient the option to refuse. Indicate on the form by the question that the patient did not want to answer this question.

4. If a patient refuses or cannot complete the questionnaire for some reason, this must be documented on the **S1600** Cover Sheet for Patient Completed Questionnaires and submitted.

5. If the patient completed on-treatment questionnaires and the patient immediately has disease recurrence:
   - If the patient did not receive any treatment between completing the questionnaires and learning of the recurrence, then the questionnaires can be used as recurrence questionnaires.
   - If the patient received any treatment, then separate recurrence questionnaires must be completed (even if only one day later)

b. Additional quality control procedures:

When a patient is registered on **S1600**, a calendar should be made with dates of upcoming patient-completed questionnaires noted. A copy of this calendar can be given to the patient with the notation that the questionnaires should be completed. You may wish to photocopy the Study Calendar, Section 9.0, and include the patient's name and specific dates. A copy of this should be kept in the patient file.

If a patient refuses or cannot complete the patient questionnaires at one time **point, he or she should be asked to do so at the next scheduled assessment time**. Submit the **S1600** Cover Sheet for Patient-Completed Questionnaires documenting the reason why the questionnaires were not done.

15.4 Phone Interview: 24 Hour Diet Recalls

Within 24 hours after patient registration, study staff must FAX the **S1600** Telephone Contact Form to the Exercise, Diet, Genitourinary, & Endocrinology (EDGE) Research Laboratory at 913/574-0515. Phone the EDGE lab at 913/945-7519 to ensure the FAX was

received. After registration prior to beginning the study nutrition therapy and again around 30 days after surgery, nutrition staff from the EDGE Research Laboratory will interview the patient over the phone to obtain two 24-hour dietary recalls (one weekday and closest weekend day) at each time point. The interview is conducted over the phone so that nutrition staff may be able to clarify ambiguities with the patient and ensure data collection completeness. Each phone interview will take approximately 15 minutes. 24-hour food recalls will be analyzed with Nutrition Data System for Research (NDSR). Energy, macronutrients, fish oil, and amino acid intake will be summarized and reported to control for the background diet.

Note: If the patient is having their visit locally at EDGE, the phone interview can be conducted during the patient's visit.

16.0 ETHICAL AND REGULATORY CONSIDERATIONS

The following must be observed to comply with Food and Drug Administration regulations for the conduct and monitoring of clinical investigations; they also represent sound research practice:

Informed Consent

The principles of informed consent are described by Federal Regulatory Guidelines (Federal Register Vol. 82, No. 12, January 19, 2017) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46). They must be followed to comply with FDA regulations for the conduct and monitoring of clinical investigations.

Institutional Review

This study must be approved by an appropriate institutional review committee as defined by Federal Regulatory Guidelines (Ref. Federal Register Vol. 82, No. 12, January 19, 2017) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46).

Monitoring

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31.

Confidentiality

Please note that the information contained in this protocol is considered confidential and should not be used or shared beyond the purposes of completing protocol requirements until or unless additional permission is obtained.

16.1 Adverse Event Reporting Requirements

a. Purpose

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. (Directions for routine reporting are provided in Section 14.0.) Additionally, certain adverse events must be reported in an expedited manner to allow for more timely monitoring of

patient safety and care. The following guidelines prescribe expedited adverse event reporting for this protocol.

b. Reporting method

This study requires that expedited adverse events be reported to SWOG Operations Office using the Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS). CTEP's guidelines for CTEP-AERS can be found at http://ctep.cancer.gov

c. When to report an event in an expedited manner

When the adverse event requires expedited reporting, submit the report within 10 calendar days of learning of the event as specified in Table 16.1.

In the rare event when Internet connectivity is disrupted notification is made to SWOG by telephone at 210-614-8808 or by email adr@swog.org . An electronic report MUST be submitted immediately upon re-establishment of internet connection.

d. Other recipients of adverse event reports

The SWOG Operations Office will forward reports and documentation to the appropriate regulatory agencies and drug companies as required.

Adverse events determined to be reportable to the Institutional Review Board responsible for oversight of the patient must be reported according to local policy and procedures.

e. Expedited reporting for commercial agents

Commercial reporting requirements are provided in Table 16.1. The commercial agent(s) used are Impact Advanced Recovery and Oral Nutrition Control Drink. If there is any question about the reportability of an adverse event or if Internet connectivity is disrupted please telephone or email the SAE Program Manager at the Operations Office, 210/614-8808 or adr@swog.org before preparing the report.

NOTE: For this study, all adverse events requiring expedited reporting must initially be reported on the Adverse Event Form in the appropriated Treatment Cycle folder in Medidata Rave. Once the adverse event is entered into RAVE, the Rules Engine will confirm whether or not the adverse event requires expedited reporting. The CTEP-AERS report must then be initiated directly from the Adverse Event Form in Medidata Rave. Do not initiate the CTEP-AERS report via the CTEP-AERS website. Sites are encouraged to confirm the Expedited Reporting Evaluation Recommendation with the reporting criteria outlined in Table 16.1.

Table 16.1. Expedited reporting requirements for adverse events experienced by patients on Blinded Nutritional Drink within 30 days of the last administration of the commercial agent(s), Impact Advanced Recovery and Oral Nutrition Control Drink.

ATTRIBUTION	Grade 4		Grade 5[a]	
	Unexpected	Expected	Unexpected	Expected
Unrelated or Unlikely			**CTEP-AERS**	**CTEP-AERS**
Possible, Probable, Definite	**CTEP-AERS**		**CTEP-AERS**	**CTEP-AERS**

CTEP-AERS: Indicates an expedited report is to be submitted via CTEP-AERS within 10 calendar days of learning of the event[b].

[a] **This includes all deaths within 30 days of the last dose of treatment with a commercial agent(s), regardless of attribution. Any death that occurs more than 30 days after the last dose of treatment with a commercial agent(s) and is attributed (possibly, probably, or definitely) to the agent(s) and is not due to cancer recurrence must be reported according to the instructions above.**

[b] Submission of the on-line CTEP-AERS report plus any necessary amendments generally completes the reporting requirements. You may, however, be asked to submit supporting clinical data to the Operations Office in order to complete the evaluation of the event. If requested, the specified data should be sent within 5 calendar days by fax to 210-614-0006.

f. **Reporting Pregnancy, Pregnancy Loss, and Death Neonatal**

1. **Pregnancy:** Study participants who become pregnant while on study; that pregnancy should be reported in an expedited manner via CTEP-AERS as **Grade 3 "Pregnancy, puerperium and perinatal conditions – Other (pregnancy)"** under the **Pregnancy, puerperium and perinatal conditions** SOC.

   Additionally, the pregnancy outcome for patients on study should be reported via CTEP-AERS at the time the outcome becomes known, accompanied by the same Pregnancy Report Form used for the initial report.

2. **Pregnancy Loss:** Pregnancy loss is defined in CTCAE as "Death in utero." Pregnancy loss should be reported expeditiously as **Grade 4 "Pregnancy loss" under the Pregnancy, puerperium and perinatal conditions SOC.**

   A Pregnancy loss should **NOT** be reported as a Grade 5 event under the Pregnancy, puerperium and perinatal conditions SOC, as currently CTEP-AERS recognizes this event as a patient death.

3. **Death Neonatal:** "Death neonatal is defined in CTCAE as "Newborn death occurring during the first 28 days after birth." A neonatal death should be reported expeditiously as **Grade 4 "Death neonatal" under the General disorders and administration SOC.**

   Neonatal death should **NOT** be reported as a Grade 5 event under the General disorders and administration SOC as currently CTEP-AERS recognizes this event as a patient death.

NOTE: When submitting CTEP-AERS reports for "Pregnancy, "Pregnancy loss", or "Neonatal loss", the Pregnancy Information Form should also be completed and faxed with any additional medical information to 210-614-0006. The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section of the CTEP-AERS report.

The Pregnancy Information Form is available at:
http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm

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18.0 Appendix

18.1 Product Compositions

18.2 Tertiary Objectives

18.3 Body Composition Assessment by Dual-Energy X-ray Absorptiometry

18.4 **S1600** Patient Intake Calendar

18.5 PG-SGA

18.6 24-hour Dietary Recall

18.7 **S1600** Site Requirements Form

18.8 Guidelines for Emergency Unblinding of Coded Intervention

18.9 Translational Medicine Study Stool Microbiome

18.10 SWOG Biospecimen Processing Instructions

18.1 Product Compositions

		Impact Advanced Recovery ††	Oral Nutrition Control
Serving Size		6.0 fl oz	6.0 fl oz
Calories	kcal	200	185
Total Fat*	g	8	8
Sodium	mg	200	200
Potassium	mg	450	450
Total Carbohydrate	g	15	15
Total Sugars	g	~13	~13
Protein	g	18	14
Vitamin A**	IU	1126	1126
Vitamin C	mg	20	20
Calcium	mg	270	270
Iron	mg	4	4
Vitamin D	IU	152	152
Vitamin E	IU	14	14
Vitamin K	mcg	22	22
Thiamin	mg	0.4	0.4
Riboflavin	mg	0.6	0.6
Niacin	mg	5.3	5.3
Vitamin B6	mg	0.5	0.5
Folic Acid	mcg	65	65
Vitamin B12	mcg	0.8	0.8
Biotin	mcg	10	10
Pantothenic Acid	mg	2.7	2.7
Phosphorus	mg	240	240
Iodine	mcg	50	50
Magnesium	mg	75	75
Zinc	mg	5	5
Selenium	mcg	16	16
Copper	mg	0.3	0.3
Manganese	mg	0.7	0.7
Chromium	mcg	12	12
Molybdenum	mcg	15	15
Chloride	mg	400	400
Choline	mg	90	90

* Contains 1.3g MCT per 178 mL
**Includes 50% Vitamin A activity from Beta-Carotene
†† Includes 4.2 g of the amino acid L-arginine per 237 mL

18.2 Tertiary Objectives

- Frequencies of Myeloid-derived suppressor cells (MDSCs). Our team discovered that SIM restrains MDSC expansion. (*1*) Expansion of myeloid derived suppressor cells (MDSC) suppresses T-cells, and lowers the resistance to infection. Peripheral blood mononucleocytes (PBMCs) will be collected at baseline, post-operative Day 2 and post-operative Day 30 based on the findings of our pilot study. *(2)* Samples will be analyzed by flow cytometry as they are received at the University of Kansas. MDSC subpopulations are defined according to published methods of grouping granulocytic ((Lin- CD11b+ CD33+ CD14- CD15+), monocytic (Lin- CD11b+ CD33+ CD14+ CD15-), and immature (Lin- CD11b+ CD33+ CD14- CD15-). *(3)* Dr. Augusto Ochoa will run final analyses on all immune data.

- Neutrophil-to-lymphocyte ratio (NLR). NLR has been suggested as a biomarker for predicting clinical course in surgical populations. *(4)* In our pilot study, NLR was significantly lower in the SIM group compared to the ONS group 3 hours after incision (P = 0.04). *(5)* The complete blood count (CBC) with differential is taken as part of routine care. The ratio of the absolute neutrophil to lymphocyte count is obtained from this test. The lymphocyte count is also used to calculate the absolute number of MDSCs.

- Inflammation biomarkers related to complications and muscle wasting. Elevated IL-6 is associated with post-operative complications and muscle loss. Also, a depressed Th1 and dominant Th2 response after surgery is associated with infectious complications. In our pilot study, the change in plasma IL-6 levels from surgery to POD2 was significantly lower in the SIM group compared to the ONS group (P = 0.022), and the average IL-6 concentration in the plasma was significantly lower in SIM group compared to the ONS group on POD 2 (P=0.020), suggesting earlier resolution of inflammation in the SIM group. *(6)* SIM intake has reduced plasma IL-6 compared to control groups in other clinical trials. *(7,8,9,10,11)* Our pilot study also showed that Th1-Th2 balance was shifted towards Th1 three hours after incision, which may mean that participants were better able to ward off an infection. We measure Th1-Th2 balance by evaluating the ratios of IFNγ:IL-4 and TNFα:IL-13. SIM intake has improved Th1-Th2 balance after colorectal surgery, which further supports our prediction. *(12)* Cytokines will be analyzed in our lab by MILLIPLEX MAP Human Th17 Panel, Magnetic, 8-plex with IL-6, IL-4, IFN gamma, IL-13, TNF alpha, IL-1b, IL-31, IL-5, and IL-17A run on all three blood draws (baseline, post-operative day 2, post-operative day 30) for each patient.

- Arginine deficiency & Plasma Amino Acid Metabolism. The systemic inflammatory response affects carbohydrate (glucose), lipid, and amino acid metabolism which all contribute to the adverse nutritional impact of cancer, surgical response, and infection. However, it is amino acid metabolism that is the final pathway responsible for lean tissue maintenance, loss, and repletion. Analyses of amino acid profiles are a critical piece to foster a better understanding of whether amino acid deficiencies persist even after SIM supplementation. These data are key to optimizing new nutrition interventions to help patients. Amino acid profiles provide insight regarding the dysregulated amino acid metabolism thought to play a role in how SIM supports the immune system, improves wound healing, prevents muscle degradation, and increases blood flow and tissue oxygenation. The theory surrounding the efficacy of SIM involves preventing arginine deficiency after surgery. *(13)* Our preliminary data revealed that prior to surgery, RC patients were arginine deficient. Sufficient levels of plasma arginine are based on the reference range, 80-100 µmol/L. *(14)* However, SIM supplementation prevented further depletion of arginine at post-operative day 2, whereas arginine plummeted in the ONS group after surgery. Furthermore, our data

showed that the SIM group had significantly higher plasma ornithine concentrations compared to the ONS group at the time of surgery (P = 0.001) and ornithine concentrations were significantly different between the two groups over time (P = 0.04). Ornithine is the product of arginine metabolism by arginase, and these data suggest that the increase in ornithine reflects a greater availability of proline and polyamines, which contribute to better wound healing through collagen formation. Several ratios are available to help interpret the amino acid flux around trauma. A full panel of amino acids will be measured in the plasma using the Ultraperformance liquid chromatography (UPLC) with ultraviolet detection at the Institute for Metabolomic Disease, Baylor Research Institute. *(15)*

- Nutrition Status. We will screen and assess for malnutrition using the Patient-generated subjective global assessment (PG-SGA), version 2014, a validated tool for the oncology population which captures nutrition impact symptoms. *(16)* The PG-SGA will be completed by the patient and study team staff. A training video is available on the **S1600** study abstract page on the SWOG web site. The PG-SGA will be obtained at baseline to identify and categorize patients at risk for nutrition deficiency and will be repeated at the 30 day visit to monitor subjective short-term changes in nutritional status. The Scored PG-SGA includes patient-generated historical components (Weight History, Food Intake, & Nutrition Impact Symptoms) and a professional assessment (Diagnosis, Age, Metabolic stress, and Physical Exam). The malnutrition assessment will be used to categorize whether patients are: 1) well nourished, 2) moderately malnourished, or 3) severely malnourished. Change in grades of malnutrition at baseline and 30 days will also be evaluated. Nutrition status will be considered as a potential covariate as we analyze the data.

- Background Dietary Intake. On baseline and day 30, two 24-h dietary recalls (one weekday and closest weekend day) will be analyzed with Nutrition Data System for Research (NDSR). If the patient consents, his or her contact information will be obtained at registration. A study dietitian, staffed by Dr. Hamilton-Reeves, will interview the patient by phone at scheduled times. Dietary intake data gathered by interview is governed by a multiple-pass interview approach. *(17)* Five distinct passes provide multiple opportunities for the participant to recall food intake. The first pass involves obtaining from the participant a listing of all foods and beverages consumed in the previous 24 h. This listing is reviewed with the participant for completeness and correctness (second pass). The interviewer then collects detailed information about each reported food and beverage, including the amount consumed and method of preparation (third pass). In the fourth pass, the interviewer then probes for commonly forgotten foods. Finally, the detailed information is reviewed for completeness and correctness (fifth pass). Energy, macronutrients, fish oil, arginine, EPA, DHA, vitamin A, and dietary supplement intake will be summarized and reported to control for the background diet. Background diet will be summarized and reported to control for the background diet.

- Measures of Treatment Compliance Biomarkers. Plasma fatty acid profiles are biomarkers of intake compliance enhancing the rigor of our study. The high concentrations of EPA and DHA in the formula will be reflected in the plasma phospholipid fatty acid composition as demonstrated by Senkal et al. Plasma fatty acid profiles reflect fat intake over the previous days to weeks and triacylglycerides reflect fat intake over the previous hours to days making these ideal compliance markers for our intervention. Plasma fatty acid profiles will be analyzed by gas chromatography and reported as weight percent of total fatty acids. The fatty acid profiles from the day 2 post-surgery blood will be measured by collaborator Dr. Susan Carlson.

- Neutrophil Extracellular Traps (NETs). NETs are meshes of DNA with associated neutrophil enzymes, including proteases such as Neutrophil Elastase and myeloperoxidase. NETs are detected in plasma from humans and mice with lung inflammation using a sandwich enzyme-linked immunosorbent assay (ELISA). The amount of NETs is determined by a sandwich ELISA using antibodies against the DNA scaffold and the NET-associated protease neutrophil elastase. ABTS is used as a substrate for the HRP (HorseRadish Peroxidase) conjugated Anti-DNA antibody and given an absorbance reading value (at 405 nm) used to compare the samples. 50 microliters of plasma are needed to perform this assay (150 microliter would be the best to be on the safe side and to perform duplicates). In this assay, developed by the Egeblad lab, healthy donors have no detectable NETs while transfusion related acute lung injury (TRALI) patients have values of ≈200-times that of healthy donors. The NETs will be measured at baseline, post-operative Day 2 and post-operative Day 30 by collaborator Dr. Mikala Egeblad.

Tertiary objectives include comparing the impact of consuming SIM compared to ONS for restraining MDSCs, decreasing inflammation, and modulating nutrient metabolism. To limit the influence of outliers and aid interpretation across a panel of markers, the marker level results will be log normal–standardized and split at the median level, creating an indicator variable (high vs. low levels of each marker). Assuming complete information, the accrual goal of n = 200 total patients will provide adequate power (≥80%) to detect a ≥20% change in the proportion of patients with high or low marker levels due to SIM, based on a two-arm normal design, one-sided alpha = 0.05 testing, and assuming the average rate of high or low marker levels across arms of 50%.

In addition, we will examine whether these biomarkers influence the association between intervention and the clinical outcomes. As a more exploratory analysis, we will use a two-sided nominal *P*-value = 0.10 to identify potentially significant interactions. *(18)* Under a binomial interaction design, equal sample sizes in each cell, a one-sided alpha = 0.10, and a 65% event probability for the ONS arm, n = 200 patients will give adequate power (≥ 80%) to detect a 3.8-fold increased odds of complications on the ONS arm in stratum 1 (i.e., high-expression group) if there is no effect in stratum 2 (i.e., low-expression group). In the case of a significant interaction indicating differential complication rates by arm between marker categories, further specific analyses will be performed to identify the actual differences. It is recognized that these results will not be definitive due to the limited power and multiple testing problem, although hypotheses will be based on biologic rationale. Promising observations will need to be validated in future data sets due to the exploratory nature of this component of the study.

We will also explore whether dietary intake variables, derived from data obtained from the dietary intake telephone interview, influence the association between intervention and outcome. The specific variables of interest include calorie intake, protein intake, nutrition status, and immune-enhancing nutrients.

Analyses will be based on multivariable logistic regression, adjusting for appropriate covariates, including stratification factors. Descriptive statistics will be used to express means and standard deviations of different marker levels by time point. We will examine marker levels at both 2 days post-operation and 30 days post-operation. To examine measures over time (baseline, day 2, and day 30), linear mixed models will be used.

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18.3 Body Composition Assessment by Dual-Energy X-ray Absorptiometry

1. Use the DXA scanner manufacturer's recommendations for QA (phantom) block scanning. At minimum, the QA (phantom) block should be used for calibration every day or 3 times per week if the DXA scanner is idle.
2. Refer to the participant's body positioning and imaging guidelines recommended by your DXA scanner's manufacturer. In general, the participant's body should be positioned with hands at the side (not touching the legs) with feet positioned as if standing.
3. Ensure your DXA machine gets yearly service and calibration by an authorized technician. There should be a record of this on site.
4. The participant pre-scanning procedures are:
   a. no radio contrast dye within 72 hours
   b. have the participant change into a gown
   c. participant should be free of all metal
   d. A height and weight are needed prior to performing the scan.
   e. If a participant is wider than the scan area, the patient can be positioned for a half body (mirror image) scan. Refer to the guidelines recommended by your DXA scanner's manufacturer for half body positioning.

18.4 **S1600** Patient Intake Calendar

a. ENGLISH Version

S1600 Patient Intake Calendar
Before Surgery

(Please bring this form with you at time of surgery and give to the study coordinator)

SWOG Patient ID_____Patient Initials (L, F, M) _____

Study Physician Name_____

If applicable, Stool Collection Dates

1. Stool Collection Date:_____

2. Stool Collection Date:_____

If you have questions, contact:_____Telephone _____

Keeping record of how much of the Nutrition Drink you consume is an important part of the study. Please use this calendar to help you. As a guideline, remember the following:

- Check the box next to the drink when you consume it
- Answer all **BOLDED** questions
  - Check "Yes" or "No" to answer if you finished all of the drink or not
  - Choose the answer for how much you estimate is left

Other important reminders:

- Drinks can be stored in the refrigerator or at room temperature, but the taste is better when consumed cold. Remember to gently shake the drink before consuming.
- Discontinue any supplements containing fish oil until after the completion of the study.

BEFORE SURGERY:

DAY 1: **Date:** _____ (MM/DD/YYYY)	□ 1st DRINK **Time consumed:** _____ ☐ a.m. ☐ p.m. **Did you finish it?** ☐ Yes ☐ No **How much is left?** ☐ None ☐ Less than half ☐ About half ☐ More than half	□ 2nd DRINK **Time consumed:** _____ ☐ a.m. ☐ p.m. **Did you finish it?** ☐ Yes ☐ No **How much is left?** ☐ None ☐ Less than half ☐ About half ☐ More than half	□ 3rd DRINK **Time consumed:** _____ ☐ a.m. ☐ p.m. **Did you finish it?** ☐ Yes ☐ No **How much is left?** ☐ None ☐ Less than half ☐ About half ☐ More than half	**Comments for the day** (include side effects from the nutrition drinks)**:**
DAY 2: **Date:** _____ (MM/DD/YYYY)	□ 1st DRINK **Time consumed:** _____ ☐ a.m. ☐ p.m. **Did you finish it?** ☐ Yes ☐ No **How much is left?** ☐ None ☐ Less than half ☐ About half ☐ More than half	□ 2nd DRINK **Time consumed:** _____ ☐ a.m. ☐ p.m. **Did you finish it?** ☐ Yes ☐ No **How much is left?** ☐ None ☐ Less than half ☐ About half ☐ More than half	□ 3rd DRINK **Time consumed:** _____ ☐ a.m. ☐ p.m. **Did you finish it?** ☐ Yes ☐ No **How much is left?** ☐ None ☐ Less than half ☐ About half ☐ More than half	**Comments for the day** (include side effects from the nutrition drinks)**:**
DAY 3: **Date:** _____ (MM/DD/YYYY)	□ 1st DRINK **Time consumed:** _____ ☐ a.m. ☐ p.m. **Did you finish it?** ☐ Yes ☐ No **How much is left?** ☐ None ☐ Less than half ☐ About half ☐ More than half	□ 2nd DRINK **Time consumed:** _____ ☐ a.m. ☐ p.m. **Did you finish it?** ☐ Yes ☐ No **How much is left?** ☐ None ☐ Less than half ☐ About half ☐ More than half	□ 3rd DRINK **Time consumed:** _____ ☐ a.m. ☐ p.m. **Did you finish it?** ☐ Yes ☐ No **How much is left?** ☐ None ☐ Less than half ☐ About half ☐ More than half	**Comments for the day** (include side effects from the nutrition drinks)**:**

DAY 4: **Date:** _____ (MM/DD/YYYY)	□ 1st DRINK **Time consumed:** _____ ☐ a.m. ☐ p.m. **Did you finish it?** ☐ Yes ☐ No **How much is left?** ☐ None ☐ Less than half ☐ About half ☐ More than half	□ 2nd DRINK **Time consumed:** _____ ☐ a.m. ☐ p.m. **Did you finish it?** ☐ Yes ☐ No **How much is left?** ☐ None ☐ Less than half ☐ About half ☐ More than half	□ 3rd DRINK **Time consumed:** _____ ☐ a.m. ☐ p.m. **Did you finish it?** ☐ Yes ☐ No **How much is left?** ☐ None ☐ Less than half ☐ About half ☐ More than half	**Comments for the day** (include side effects from the nutrition drinks)**:**
DAY 5: **Date:** _____ (MM/DD/YYYY)	□ 1st DRINK **Time consumed:** _____ ☐ a.m. ☐ p.m. **Did you finish it?** ☐ Yes ☐ No **How much is left?** ☐ None ☐ Less than half ☐ About half ☐ More than half	□ 2nd DRINK **Time consumed:** _____ ☐ a.m. ☐ p.m. **Did you finish it?** ☐ Yes ☐ No **How much is left?** ☐ None ☐ Less than half ☐ About half ☐ More than half	□ 3rd DRINK **Time consumed:** _____ ☐ a.m. ☐ p.m. **Did you finish it?** ☐ Yes ☐ No **How much is left?** ☐ None ☐ Less than half ☐ About half ☐ More than half	**Comments for the day** (include side effects from the nutrition drinks)**:**

Date of surgery: _____

Bring this completed form with you to your surgery and give to the study coordinator.
We will be thinking of you, especially during your surgery!

S1600 Patient Intake Calendar

After Surgery

(Please bring this form with you to your 30-day visit and give to the study coordinator)

SWOG Patient ID_____Patient Initials (L, F, M) _____

Study Physician Name_____

If you have questions, contact:_____Telephone _____

Keeping record of how much of the Nutrition Drink you consume is an important part of the study. Please use this calendar to help you. As a guideline, remember the following:

- Check the box next to the drink when you consume it
- Answer all **BOLDED** questions
    - Check "Yes" or "No" to answer if you finished all of the drink or not
    - Choose the answer for how much you estimate is left
    - If applicable, please provide stool collection date:

1. Stool Collection Date:_____

Other important reminders:

- After surgery, start drinking the Nutrition Drink the same day your doctor clears you to drink liquids. Please make a note of the date in the DAY 1 box below.
- Drinks can be stored in the refrigerator or at room temperature, but the taste is better when consumed cold. Remember to gently shake the drink before consuming.
- Discontinue any supplements containing fish oil until after the completion of the study.

AFTER SURGERY:

DAY 1: **Date:** _____ (MM/DD/YYYY)	□ 1st DRINK **Time consumed:** _____ ☐ a.m. ☐ p.m. **Did you finish it?** ☐ Yes ☐ No **How much is left?** ☐ None ☐ Less than half ☐ About half ☐ More than half	□ 2nd DRINK **Time consumed:** _____ ☐ a.m. ☐ p.m. **Did you finish it?** ☐ Yes ☐ No **How much is left?** ☐ None ☐ Less than half ☐ About half ☐ More than half	□ 3rd DRINK **Time consumed:** _____ ☐ a.m. ☐ p.m. **Did you finish it?** ☐ Yes ☐ No **How much is left?** ☐ None ☐ Less than half ☐ About half ☐ More than half	**Comments for the day** (include side effects from the nutrition drinks)**:**
Day 2: **Date:** _____ (MM/DD/YYYY)	□ 1st Drink **Time consumed:** _____ ☐ a.m. ☐ p.m. **Did you finish it?** ☐ Yes ☐ No **How much is left?** ☐ None ☐ Less than half ☐ About half ☐ More than half	□ 2nd Drink **Time consumed:** _____ ☐ a.m. ☐ p.m. **Did you finish it?** ☐ Yes ☐ No **How much is left?** ☐ None ☐ Less than half ☐ About half ☐ More than half	□ 3rd Drink **Time consumed:** _____ ☐ a.m. ☐ p.m. **Did you finish it?** ☐ Yes ☐ No **How much is left?** ☐ None ☐ Less than half ☐ About half ☐ More than half	**Comments for the day** (include side effects from the nutrition drinks)**:**
DAY 3: **Date:** _____ (MM/DD/YYYY)	□ 1st DRINK **Time consumed:** _____ ☐ a.m. ☐ p.m. ☐ **Did you finish it?** ☐ Yes ☐ No **How much is left?** ☐ None ☐ Less than half ☐ About half ☐ More than half	□ 2nd DRINK **Time consumed:** _____ ☐ a.m. ☐ p.m. **Did you finish it?** ☐ Yes ☐ No **How much is left?** ☐ None ☐ Less than half ☐ About half ☐ More than half	□ 3rd DRINK **Time consumed:** _____ ☐ a.m. ☐ p.m. **Did you finish it?** ☐ Yes ☐ No **How much is left?** ☐ None ☐ Less than half ☐ About half ☐ More than half	**Comments for the day** (include side effects from the nutrition drinks)**:**

DAY 4: **Date:** _____ (MM/DD/YYYY)	□ 1st DRINK **Time consumed:** _____ ☐ a.m. ☐ p.m. **Did you finish it?** ☐ Yes ☐ No **How much is left?** ☐ None ☐ Less than half ☐ About half ☐ More than half	□ 2nd DRINK **Time consumed:** _____ ☐ a.m. ☐ p.m. **Did you finish it?** ☐ Yes ☐ No **How much is left?** ☐ None ☐ Less than half ☐ About half ☐ More than half	□ 3rd DRINK **Time consumed:** _____ ☐ a.m. ☐ p.m. **Did you finish it?** ☐ Yes ☐ No **How much is left?** ☐ None ☐ Less than half ☐ About half ☐ More than half	**Comments for the day** (include side effects from the nutrition drinks)**:**
DAY 5: **Date:** _____ (MM/DD/YYYY)	□ 1st DRINK **Time consumed:** _____ ☐ a.m. ☐ p.m. **Did you finish it?** ☐ Yes ☐ No **How much is left?** ☐ None ☐ Less than half ☐ About half ☐ More than half	□ 2nd DRINK **Time consumed:** _____ ☐ a.m. ☐ p.m. **Did you finish it?** ☐ Yes ☐ No **How much is left?** ☐ None ☐ Less than half ☐ About half ☐ More than half	□ 3rd DRINK **Time consumed:** _____ ☐ a.m. ☐ p.m. **Did you finish it?** ☐ Yes ☐ No **How much is left?** ☐ None ☐ Less than half ☐ About half ☐ More than half	**Comments for the day** (include side effects from the nutrition drinks)**:**

Your blood will be drawn for the S1600 study two days after your surgery.

Your next study visit will be about 30 days after your surgery. At the 30-day visit, you will meet with the surgeon, have a blood draw, DXA body scan, and complete two questionnaires.

Your 30-day visit is on:

Date: _____

Time: _____

Please bring this form with you to your 30-day visit and give to the study coordinator.

We appreciate your participation in this study!

b. SPANISH Version

S1600 Calendario de Consumo del Paciente

Antes de la Cirúgia

(Por favor traiga este formulario con usted en el día de la cirugía y entréguelo al coordinador del estudio)

ID del Paciente SWOG_____ Iniciales del Paciente (L, F,M)_____

Nombre del Médico del Estudio _____

Si corresponde, fechas de recolección de heces

1. Fecha de recolección de heces:_____

2. Fecha de recolección de heces:_____

Si tiene alguna pregunta o inquietud póngase en contacto con: _____

Teléfono:_____

Mantener un registro de la cantidad de bebida nutricional que consume es una parte importante del estudio. Utilice esta hoja de seguimiento para ayudarlo(a). Como pauta, recuerdo lo siguiente:

- Marque la casilla junto a la bebida cuando la consuma
- Responda todas las preguntas en **NEGRITA**
    - Marque “Sí” o “No” cuando responda si bebió toda la bebida o no
    - Verifique la respuesta para saber cuánto de bebida quedo en la botella si usted no bebió todo

<u>Otros recordatorios importantes:</u>

- Las bebidas se pueden almacenar en el refrigerador o a temperature ambiente, pero el sabor es mejor cuando se consume frío. Recuerdate de agitar suavemente la bebida antes de beberla.
- Suspenda cualquier suplemento nutricional que contenga aceite de pescado hasta después de la finalización del estudio.

Antes de la Cirúgia:

Día 1: **Fecha**: _____ (MM/DD/AAAA)	☐ *1er BEBIDA* **Hora consumo:** _____ ☐ a.m. ☐ p.m. **¿La terminaste?** ☐ Sí ☐ No **¿Cuanto quedo en la botella?** ☐ Nada ☐ Menos de la mitad ☐ Mitad ☐ Más de la mitad	☐ *2ª BEBIDA* **Hora consumo** _____ ☐ a.m. ☐ p.m. **¿La terminaste?** ☐ Sí ☐ No **¿Cuanto quedo en la botella?** ☐ Nada ☐ Menos de la mitad ☐ Mitad ☐ Más de la mitad	☐ *3ª BEBIDA* **Hora consumo** _____ ☐ a.m. ☐ p.m. **¿La terminaste?** ☐ Sí ☐ No **¿Cuanto quedo en la botella?** ☐ Nada ☐ Menos de la mitad ☐ Mitad ☐ Más de la mitad	**Comentarios para el día** (incluidos los efectos secundarios de las bebidas nutricionales):
Día 2: **Fecha**: _____ (MM/DD/AAAA)	☐ *1er BEBIDA* **Hora consumo** _____ ☐ a.m. ☐ p.m. **¿La terminaste?** ☐ Sí ☐ No **¿Cuanto quedo en la botella?** ☐ Nada ☐ Menos de la mitad ☐ Mitad ☐ Más de la mitad	☐ *2ª BEBIDA* **Hora consumo** _____ ☐ a.m. ☐ p.m. **¿La terminaste?** ☐ Sí ☐ No **¿Cuanto quedo en la botella?** ☐ Nada ☐ Menos de la mitad ☐ Mitad ☐ Más de la mitad	☐ *3ª BEBIDA* **Hora consumo** _____ ☐ a.m. ☐ p.m. **¿La terminaste?** ☐ Sí ☐ No **¿Cuanto quedo en la botella?** ☐ Nada ☐ Menos de la mitad ☐ Mitad ☐ Más de la mitad	**Comentarios para el día** (incluidos los efectos secundarios de las bebidas nutricionales):
Día 3: **Fecha**: _____ (MM/DD/AAAA)	☐ *1er BEBIDA* **Hora consumo** _____ ☐ a.m. ☐ p.m. **¿La terminaste?** ☐ Sí ☐ No **¿Cuanto quedo en la botella?** ☐ Nada ☐ Menos de la mitad ☐ Mitad ☐ Más de la mitad	☐ *2ª BEBIDA* **Hora consumo** _____ ☐ a.m. ☐ p.m. **¿La terminaste?** ☐ Sí ☐ No **¿Cuanto quedo en la botella?** ☐ Nada ☐ Menos de la mitad ☐ Mitad ☐ Más de la mitad	☐ *3ª BEBIDA* **Hora consumo** _____ ☐ a.m. ☐ p.m. **¿La terminaste?** ☐ Sí ☐ No **¿Cuanto quedo en la botella?** ☐ Nada ☐ Menos de la mitad ☐ Mitad ☐ Más de la mitad	**Comentarios para el día** (incluidos los efectos secundarios de las bebidas nutricionales):

Día 4: **Fecha**: _____ (MM/DD/AAAA)	☐ *1er BEBIDA* **Hora consumo** _____ ☐ a.m. ☐ p.m. **¿La terminaste?** ☐ Sí ☐ No **¿Cuanto quedo en la botella?** ☐ Nada ☐ Menos de la mitad ☐ Mitad ☐ Más de la mitad	☐ *2a BEBIDA* **Hora consumo** _____ ☐ a.m. ☐ p.m. **¿La terminaste?** ☐ Sí ☐ No **¿Cuanto quedo en la botella?** ☐ Nada ☐ Menos de la mitad ☐ Mitad ☐ Más de la mitad	☐ *3a BEBIDA* **Hora consumo** _____ ☐ a.m. ☐ p.m. **¿La terminaste?** ☐ Sí ☐ No **¿Cuanto quedo en la botella?** ☐ Nada ☐ Menos de la mitad ☐ Mitad ☐ Más de la mitad	**Comentarios para el día** (incluidos los efectos secundarios de las bebidas nutricionales) :
Día 5: **Fecha**: _____ (MM/DD/AAAA)	☐ *1er BEBIDA* **Hora consumo** _____ ☐ a.m. ☐ p.m. **¿La terminaste?** ☐ Sí ☐ No **¿Cuanto quedo en la botella?** ☐ Nada ☐ Menos de la mitad ☐ Mitad ☐ Más de la mitad	☐ *2a BEBIDA* **Hora consumo** _____ ☐ a.m. ☐ p.m. **¿La terminaste?** ☐ Sí ☐ No **¿Cuanto quedo en la botella?** ☐ Nada ☐ Menos de la mitad ☐ Mitad ☐ Más de la mitad	☐ *3a BEBIDA* **Hora consumo** _____ ☐ a.m. ☐ p.m. **¿La terminaste?** ☐ Sí ☐ No **¿Cuanto quedo en la botella?** ☐ Nada ☐ Menos de la mitad ☐ Mitad ☐ Más de la mitad	**Comentarios para el día** (incluidos los efectos secundarios de las bebidas nutricionales) :

Fecha de la cirugía: _____

Lleve este formulario completo a su consulta y entréguelo al coordinador del estudio.
¡Estamos pendientes de usted, especialmente durante su cirugía!

S1600 Calendario de Consumo del Paciente

Después de la Cirúgia

(Por favor traiga este formulario con usted a su visita de 30 días y entrégueselo al coordinador del estudio)

ID del Paciente SWOG_____ Iniciales del Paciente (L, F,M)_____

Nombre del Médico del Estudio _____

Si tiene alguna pregunta o inquietud póngase en contacto con: _____
Teléfono:_____

Mantener un registro de la cantidad de bebida nutricional que consume es una parte importante del estudio. Utilice esta hoja de seguimiento para ayudarlo(a). Como pauta, recuerdo lo siguiente:

- Marque la casilla junto a la bebida cuando la consuma
- Responda todas las preguntas en **NEGRITA**
    - Marque “Sí” o “No” cuando responda si bebió toda la bebida o no
    - Verifique la respuesta para saber cuánto de bebida quedo en la botella si usted no bebió todo
    - Si corresponde, por favor proporcionar fecha de recolección de heces:
    - 1. Fecha de recolección de heces:_____

Otros recordatorios importantes:

- Después de la cirugía, comience a tomar la bebida nutricional en el mismo día que su medico le autorizar a tomar líquidos. Por favor tome nota de la fecha.
- Las bebidas se pueden almacenar en el refrigerador o a temperature ambiente, pero el sabor es major cuando se consume frío. Recuerdate de agitar suavemente la bebida antes de beberla.
- Suspenda cualquier suplemento que contenga aceite de pescado hasta después de la finalización del estudio.

Después de la Cirúgia:

Día 1: **Fecha**: _____ (MM/DD/AAAA)	☐ *1er BEBIDA* **Hora consumo:** _____ ☐ a.m. ☐ p.m. **¿La terminaste?** ☐ Sí ☐ No **¿Cuanto quedo en la botella?** ☐ Nada ☐ Menos de la mitad ☐ Mitad ☐ Más de la mitad	☐ *2a BEBIDA* **Hora consumo** _____ ☐ a.m. ☐ p.m. **¿La terminaste?** ☐ Sí ☐ No **¿Cuanto quedo en la botella?** ☐ Nada ☐ Menos de la mitad ☐ Mitad ☐ Más de la mitad	☐ *3a BEBIDA* **Hora consumo** _____ ☐ a.m. ☐ p.m. **¿La terminaste?** ☐ Sí ☐ No **¿Cuanto quedo en la botella?** ☐ Nada ☐ Menos de la mitad ☐ Mitad ☐ Más de la mitad	**Comentarios para el día** (incluidos los efectos secundarios de las bebidas nutricionales):
Día 2: **Fecha**: _____ (MM/DD/AAAA)	☐ *1er BEBIDA* **Hora consumo** _____ ☐ a.m. ☐ p.m. **¿La terminaste?** ☐ Sí ☐ No **¿Cuanto quedo en la botella?** ☐ Nada ☐ Menos de la mitad ☐ Mitad ☐ Más de la mitad	☐ *2a BEBIDA* **Hora consumo** _____ ☐ a.m. ☐ p.m. **¿La terminaste?** ☐ Sí ☐ No **¿Cuanto quedo en la botella?** ☐ Nada ☐ Menos de la mitad ☐ Mitad ☐ Más de la mitad	☐ *3a BEBIDA* **Hora consumo** _____ ☐ a.m. ☐ p.m. **¿La terminaste?** ☐ Sí ☐ No **¿Cuanto quedo en la botella?** ☐ Nada ☐ Menos de la mitad ☐ Mitad ☐ Más de la mitad	**Comentarios para el día** (incluidos los efectos secundarios de las bebidas nutricionales):
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Día 4: **Fecha**: _____ (MM/DD/AAAA)	☐ *1er BEBIDA* **Hora consumo** _____ ☐ a.m. ☐ p.m. **¿La terminaste?** ☐ Sí ☐ No **¿Cuanto quedo en la botella?** ☐ Nada ☐ Menos de la mitad ☐ Mitad ☐ Más de la mitad	☐ *2ª BEBIDA* **Hora consumo** _____ ☐ a.m. ☐ p.m. **¿La terminaste?** ☐ Sí ☐ No **¿Cuanto quedo en la botella?** ☐ Nada ☐ Menos de la mitad ☐ Mitad ☐ Más de la mitad	☐ *3ª BEBIDA* **Hora consumo** _____ ☐ a.m. ☐ p.m. **¿La terminaste?** ☐ Sí ☐ No **¿Cuanto quedo en la botella?** ☐ Nada ☐ Menos de la mitad ☐ Mitad ☐ Más de la mitad	**Comentarios para el día** (incluidos los efectos secundarios de las bebidas nutricionales) :
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Se le tomará una muestra de sangre para el estudio S1600 dos días después de la cirugía.

Su próxima visita del studio será aproximadamente 30 días después de su cirugía. En la visita de 30 días, se reunirá con el cirujano, le extraerán sangre, le realizarán una exploración corporal con DEXA y completarán dos cuestionarios.

Su visita de 30 días es en:

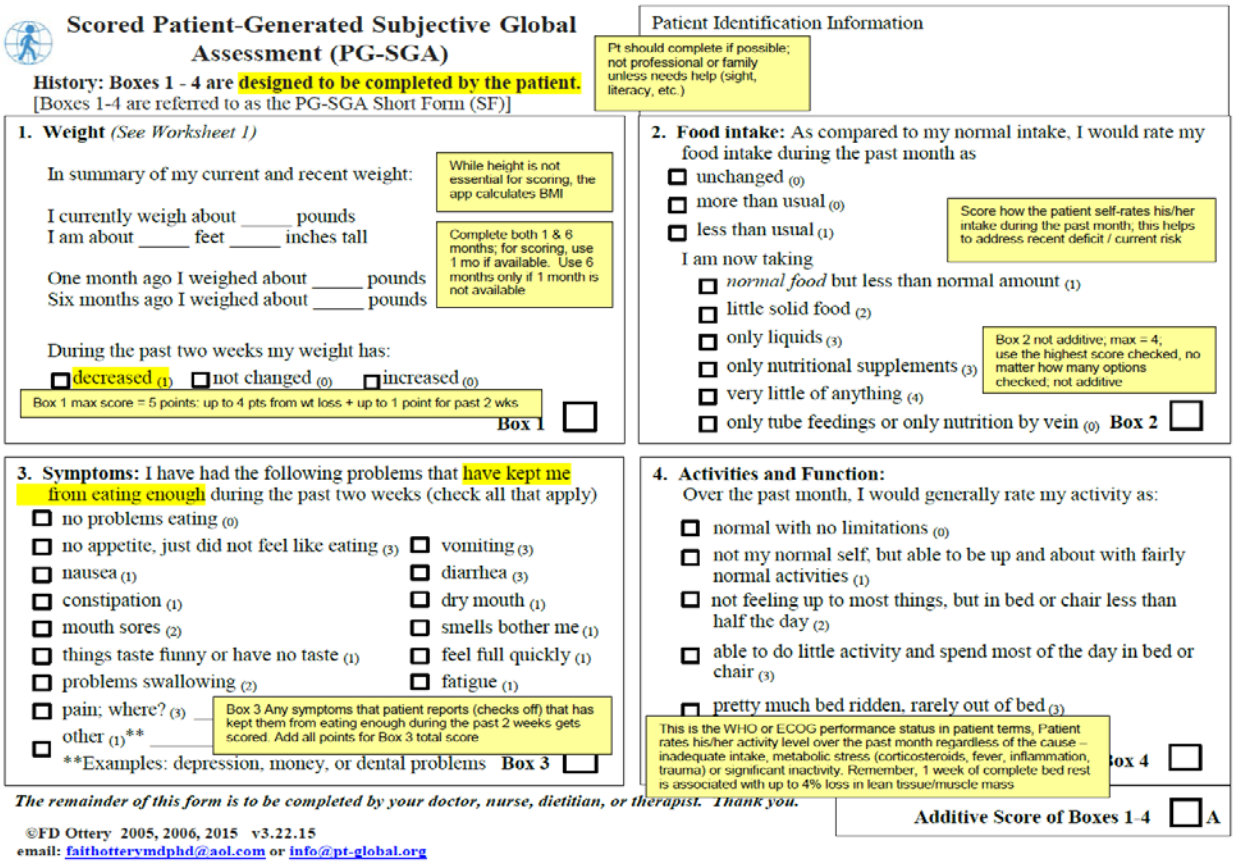
Fecha: _____

Hora: _____

Por favor, lleve este formulation a su visita de 30 días y entréguelo al coordinador del estudio.

¡Agradecemos su participación en este estudio

18.5 PG-SGA



Scored Patient-Generated Subjective Global Assessment (PG-SGA)

History: Boxes 1 - 4 are designed to be completed by the patient.
[Boxes 1-4 are referred to as the PG-SGA Short Form (SF)]

Patient Identification Information

Pt should complete if possible; not professional or family unless needs help (sight, literacy, etc.)

1. Weight *(See Worksheet 1)*

In summary of my current and recent weight:

While height is not essential for scoring, the app calculates BMI

I currently weigh about _____ pounds
I am about _____ feet _____ inches tall

Complete both 1 & 6 months; for scoring, use 1 mo if available. Use 6 months only if 1 month is not available

One month ago I weighed about _____ pounds
Six months ago I weighed about _____ pounds

During the past two weeks my weight has:
☐ decreased (1) ☐ not changed (0) ☐ increased (0)

Box 1 max score = 5 points: up to 4 pts from wt loss + up to 1 point for past 2 wks

Box 1 ☐

2. Food intake: As compared to my normal intake, I would rate my food intake during the past month as
☐ unchanged (0)
☐ more than usual (0)
☐ less than usual (1)

Score how the patient self-rates his/her intake during the past month; this helps to address recent deficit / current risk

I am now taking
☐ *normal food* but less than normal amount (1)
☐ little solid food (2)
☐ only liquids (3)
☐ only nutritional supplements (3)
☐ very little of anything (4)
☐ only tube feedings or only nutrition by vein (0)

Box 2 not additive; max = 4; use the highest score checked, no matter how many options checked; not additive

Box 2 ☐

3. Symptoms: I have had the following problems that have kept me from eating enough during the past two weeks (check all that apply)
☐ no problems eating (0)
☐ no appetite, just did not feel like eating (3)
☐ nausea (1)
☐ constipation (1)
☐ mouth sores (2)
☐ things taste funny or have no taste (1)
☐ problems swallowing (2)
☐ pain; where? (3) ___
☐ other (1)** ___
☐ vomiting (3)
☐ diarrhea (3)
☐ dry mouth (1)
☐ smells bother me (1)
☐ feel full quickly (1)
☐ fatigue (1)

Box 3 Any symptoms that patient reports (checks off) that has kept them from eating enough during the past 2 weeks gets scored. Add all points for Box 3 total score

Examples: depression, money, or dental problems **Box 3 ☐

4. Activities and Function:
Over the past month, I would generally rate my activity as:
☐ normal with no limitations (0)
☐ not my normal self, but able to be up and about with fairly normal activities (1)
☐ not feeling up to most things, but in bed or chair less than half the day (2)
☐ able to do little activity and spend most of the day in bed or chair (3)
☐ pretty much bed ridden, rarely out of bed (3)

This is the WHO or ECOG performance status in patient terms, Patient rates his/her activity level over the past month regardless of the cause – inadequate intake, metabolic stress (corticosteroids, fever, inflammation, trauma) or significant inactivity. Remember, 1 week of complete bed rest is associated with up to 4% loss in lean tissue/muscle mass

Box 4 ☐

The remainder of this form is to be completed by your doctor, nurse, dietitian, or therapist. Thank you.

Additive Score of Boxes 1-4 ☐ **A**

email: faithotterymdphd@aol.com or info@pt-global.org

Scored Patient-Generated Subjective Global Assessment (PG-SGA)

Worksheet 1 – Scoring Weight Loss

To determine score, use 1-month weight data if available. Use 6-month data only if there is no 1-month weight data. Use points below to score weight change and add one extra point if patient has lost weight during the past 2 weeks. Enter total point score in Box 1 of PG-SGA.

Weight loss in 1 month	Points	Weight loss in 6 months
10% or greater	4	20% or greater
5-9.9%	3	10- 19.9%
3-4.9%	2	6- 9.9%
2-2.9%	1	2- 5.9%
0-1.9%	0	0- 1.9%

Numerical score from Worksheet 1 ☐

Additive Score of Boxes 1-4 (See Side 1) ☐ **A**

5. Worksheet 2 – Disease and its relation to nutritional requirements:

Score is derived by adding 1 point for each of the following conditions:

- ☐ Cancer
- ☐ AIDS
- ☐ Pulmonary or cardiac cachexia
- ☐ Chronic renal insufficiency
- ☐ Presence of decubitus, open wound or fistula
- ☐ Presence of trauma
- ☐ Age greater than 65

Other relevant diagnoses (specify) _____

Primary disease staging (circle if known or appropriate) I II III IV Other ___

Numerical score from Worksheet 2 ☐ **B**

6. Worksheet 3 – Metabolic Demand

Score for metabolic stress is determined by a number of variables known to increase protein & caloric needs. **Note:** Score fever inte… a patient who has a fever of 38.8 °C (3 points) for < 72 hrs (1 point) and who is on 10 mg of prednisone chronically (2 points) would l…

Fever: Score fever intensity or duration, whichever is greater. (99°F= 37.2°C 101°=38.3° and 102° = 38.9°)

See www.pt-global.org for prednisone equivalents chart and metric and additional language version (as available)

Stress	none (0)	low (1)	moderate (2)	high (3)
Fever	no fever	> 99 and < 101	≥ 101 and < 102	≥ 102 °F
Fever duration	no fever	< 72 hours	72 hours	> 72 hours
Corticosteroids	no corticosteroids	low dose (< 10 mg prednisone equivalents/day)	moderate dose (≥ 10 and < 30 mg prednisone equivalents/day)	high dose (≥ 30 mg prednisone equivalents/day)

Even short term use of corticosteroids can adversely impact protein status and muscle mass

Numerical score from Worksheet 3 ☐ **C**

7. Worksheet 4 – Physical Exam

Exam includes a subjective evaluation of 3 aspects of body co… nce this is subjective, each aspect of the exam is rated for degree. Muscle deficit/loss impacts point score more than fat deficit/loss. Definition of categories: 0 = no abnormality, 1+ = mild, 2+ = …se categories is *not* additive but are used to clinically assess the degree of deficit (or presence of excess fluid).

Muscle Status				
temples (temporalis muscle)	0	1+	2+	3
clavicles (pectoralis & deltoids)	0	1+	2+	3
shoulders (deltoids)	0	1+	2+	3
interosseous muscles	0	1+	2+	3
scapula (latissimus dorsi, trapezius, deltoids)	0	1+	2+	3
thigh (quadriceps)	0	1+	2+	3
calf (gastrocnemius)	0	1+	2+	3
Global muscle status rating	**0**	**1+**	**2+**	**3**

…ores				
…at pads	0	1+	2+	3+
…kin fold	0	1+	2+	3+
…ying lower ribs	0	1+	2+	3+
…al fat deficit rating	**0**	**1+**	**2+**	**3+**
…tatus				
…dema	0	1+	2+	3+
…dema	0	1+	2+	3+
	0	1+	2+	3+
…al fluid status rating	**0**	**1+**	**2+**	**3+**

These are examples of areas that can/should be considered in deter-mining loss/deficit (or excess fluid). RELAX… One does NOT have to assess all of these to have a global sense for loss or deficit of muscle or fat. Remember the maximum point score for physical exam is only 3 points – and you are not likely to be off by more than 1 point…

Point score for the physical exam is determined by the overall subjective rating of the total body deficit.

No deficit	score = 0 points	
Mild deficit	score = 1 point	**Again, muscle deficit/loss takes precedence over fat loss or fluid excess.**
Moderate deficit	score = 2 points	
Severe deficit	score = 3 points	

Numerical Score for Worksheet 4 ☐ **D**

Total PG-SGA Score (Total numerical score of A+B+C+D) ☐

Clinician Signature _____ …er _____ Date _____

Global PG-SGA Category Rating (Stage A, Stage B or Stage C) ☐

Worksheet 5 – PG-SGA Global Assessment Categories

	Stage A Well-nourished	Stage B Moderate/suspected malnutrition	Stage C Severely malnourished
Category			
Weight	No weight loss OR recent non-fluid wt gain	≤ 5% loss in 1 month (≤10% in 6 months) OR Progressive weight loss	> 5% loss in 1 month (>10% in 6 months) OR Progressive weight loss
Nutrient intake	No deficit OR Significant recent improvement	Definite decrease in intake	Severe deficit in intake
Nutrition Impact Symptoms (NIS)	None OR significant recent improvement allowing adequate intake	Presence of NIS (Box 3 of PG-SGA)	Presence of NIS (Box 3 of PG-SGA)
Functioning	No deficit OR Significant recent improvement		
Physical Exam	No deficit OR chronic deficit but with recent clinical improvement	Evidence of mild to moderate loss of muscle mass &/or muscle tone on palpation &/or loss of SQ fat	Obvious signs of malnutrition (e.g., severe loss muscle, fat, possible edema)

Worksheet 5 May be helpful to circle relevant statement for each PG-SGA category to visually help identify the overall global assessment

Nutritional Triage Recommendations: Additive score is used to define specific nutritional interventions including patient & family education, symptom management including pharmacologic intervention, and appropriate nutrient intervention (food, nutritional supplements, enteral, or parenteral triage).

First line nutrition intervention includes optimal symptom management.

Triage based on PG-SGA point score

0-1	No intervention required at this time. Re-assessment on routine and regular basis during treatment.
2-3	Patient & family education by dietitian, nurse, or other clinician with pharmacologic intervention as indicated by symptom survey (Box 3) and lab values as appropriate.
4-8	Requires intervention by dietitian, in conjunction with nurse or physician as indicated by symptoms (Box 3).
≥ 9	Indicates a critical need for improved symptom management and/or nutrient intervention options.

email: faithotterymdphd@aol.com or info@pt-global.org

18.6 24-hour Dietary Recall

Purpose

To obtain detailed information about all foods, beverages and dietary supplements consumed on a given day.

Description

A 24-hour dietary recall is a structured interview intended to capture detailed information about all foods, beverages and dietary supplements consumed by a respondent in the past 24 hours, most commonly, from midnight to midnight the previous day.

At the baseline study visit, each participant will receive a “Food Amounts Booklet”, which includes helpful images and measurements to assist them in estimating their dietary intake. These images and measurements can be readily converted to specific amounts needed for research purposes.

Each interviewer will have received detailed training in how to conduct a 24-hour recall. The interviewer will explain to the participant that she/he will be asking about food types and amounts from the beginning of their day, from the time they wake up in the morning, until the end of their day, to the time they go to sleep at night. The interviewer may suggest that the participant refer to the “Food Amounts Booklet”.

When asking the participant what they ate yesterday, the interviewer will:

- Record their consumption chronologically
- Record what time they consumed the food
- Record the amount of food consumed. Use descriptive props (i.e. a deck of cards for 3 ounces of meat) to report portion size and the interviewer copy of the Food Amounts Booklet
- Record the preparation of each item listed making sure to note how the food was prepared (i.e. baked, fried, etc.), what was used to prepare the food (i.e. olive oil, soy oil, salt, etc.), and any other relevant information that the participant wishes to share.

After the first “pass” of information is obtained, the interviewer will ask the respondent to fill in more detailed information that may have been missed. A total of five passes will occur to ensure detailed and accurate information.

The data obtained from the 24-hour dietary recall will be used to examine food patterns and nutrient intake estimates from foods and dietary supplements.

The information collected during the 24-hour recall interview will be entered directly into the Nutrition Data System for Research (NDSR). This software includes comprehensive food and supplement databases. NDSR has built-in, standard prompts for guiding the interviewer in obtaining from the study participant detailed information about the foods they ate and supplements used. The NDSR requires specialized training and extensive practice in order to effectively utilize it to conduct a research interview. Consequently, all interviewers will be required to complete NDSR training and certification prior to collection of dietary and supplement recalls from participants. The NDSR User Manual will be used by interviewers as a resource. The Manual provides documentation on program features as well as Data Entry Rules (DER) which assist in standardizing decisions for situations

when participants cannot provide information. NDSR was developed and is supported by the University of Minnesota Nutrition Coordinating Center (NCC).

a. Appendix A: English Script for 24-hour dietary recall

Introduce the Recall Process

"Hi (insert participant's name), my name is (insert your name). During this part of your visit, I will be performing a 24hr dietary recall where you tell me everything you had to eat and drink during the past 24 hours. Everything you tell me is confidential and this will take about 15 minutes. Is this OK?"

"First, we'll make a list of all the foods and beverages you had from 12 am yesterday morning until 12 midnight last night. This includes all meals, snacks, drinks (including water and alcoholic beverages), as well as tastes or samples of foods.

"Then, we'll go back through the list and fill in the details."

"At the very end, I'll also ask you about any vitamins, minerals or other supplements you took."

"Do you have any questions before we begin?"

PASS 1: Collect the Quick List

The participant is encouraged to say whatever comes to mind about the previous day's intake with minimal interruption.

Time of meal, place of meal and meal type will be collected.

No additional questions regarding details or amounts will be asked.

Prompts:
"After midnight, what was the first time that you had something to eat or drink?" "What would you consider this meal to be?" "Where did you consume this meal?" "What time did you consume this meal?" "What did you have at that time?" "When was the next time you had something to eat or drink?"

PASS 2: Review the Quick List

This enables the interviewer to identify gaps in time when no food or beverages are reported, forgotten eating occasions and missed meals or beverages.

Prompts:
"Now let's review what we have so far."
"Did you have anything between midnight and (insert time of first meal)?"
Repeat the next two questions for each meal/snack:
"At (insert meal time), you had (read all foods). Can you think of anything else you had at that time?"
"Did you have anything to eat or drink between (insert meal time) and (meal time)?"
When appropriate ask: "Did you have a beverage with that meal?"
"Finally, did you have anything to eat or drink between (insert time of last meal) and midnight?"

PASS 3: Collect detailed information

This allows the interviewer to probe for additions and obtain detail for foods and beverages, and amounts consumed.

- Collect time, name and location of eating occasion if not provided during the Quick List.
- Details for each food and beverage:
  - Brand and/or type of item
  - Preparation details
  - Cooking details
  - Any additions (condiments) added
  - How much of item was consumed (this can be asked at the end of each meal)

Prompts:

These will vary depending on the type of food or beverage consumed.

PASS 4: Ask about commonly forgotten foods

This focuses on the participant's attention on specific foods and beverages that tend to be most forgotten during a recall. Ask each question and wait for a response.

Prompts:

"That is everything from your list. There are some foods that people might forget when doing a recall so to make sure this is as complete as possible, listen to the following and let me know if we need to add anything."

1. "Besides what you already reported, did you drink any water?"
2. "Any additional coffee, tea, soft drinks, milk or juice?"
3. "Did you have any cookies, candy, ice cream or other sweets?'
4. "Did you have any fruit, vegetables or cheese?"
5. "What about any bread, rolls or tortillas?"
6. "Did you have any chips, crackers, popcorn, pretzels, nuts or other snack foods?"
7. "did you have any beer, wine, cocktails or other drinks?"

PASS 5: Review detailed information

The interviewer will confirm what has been stated and document meals that are skipped or include nontraditional eating (i.e. meals without beverages, bread or bun removed from sandwich, no milk on cereal, etc.)

Prompts:
"At (time) you had (amount) of (food). Is this correct?"
"At the end of each meal: Did you have anything else at that time?"

The interviewer will continue to probe about between-meal snacks or missed meals, looking for large gaps in time when no food or beverages are reported and making sure that no information was inadvertently omitted.

NEXT STEP: Complete the trailer questions (Is it a typical day and is it reliable data)

- Ask the participant
  - "In terms of the amount of food you ate, would you say this was: Close to the amount you usually eat? A lot more than you usually eat? A lot less than you usually eat?" If more or less, have them explain why.

Interviewer discretion:

Was information: Reliable? Unable to recall one or more meals? Unreliable for other reasons? Explain why recall is incomplete/unusable.

FINAL STEP: Complete the dietary supplements assessment questions

The interviewer can obtain supplement information for the past 24 hours.

Ask the participant:
"Now I have questions about dietary supplements you took yesterday".

1. "Did you take any vitamins or minerals?" (i.e. One a Day, Centrum, Vitamin C)
2. "Did you take any amino acids?" (i.e. glutamine, arginine, lysine)
3. "Did you take any supplements containing oils or omega-3 fatty acids?" (i.e. fish oil, flaxseed oil, krill oil, DHA)
4. "Yesterday, did you take any herbal or botanical products?" (i.e. Echinacea, ginseng, ginkgo or St John's Wort)
5. "Did you take any fiber supplements?" (i.e. Metamucil, Benefiber or Fibercon)
6. "Did you take any other dietary supplements that you haven't told me about?" (i.e. garlic extract, brewer's yeast, coenzyme Q10, glucosamine chondroitin, or weight loss supplements)
7. "Did you take any over-the-counter antacids? (i.e. Tums, Rolaids, Mylanta)

"Now, I'll ask for details about each of the products that you reported. It will be helpful to have the containers for as many of these products as possible."

For each supplement taken, the interviewer will ask the following questions:

1. "Do you have the container for this product?" Yes No
2. "Please provide the complete name of the product." (include dosage and serving size)
3. "How many times did you take this product yesterday?"
4. "How many tablets did you take when you used the product yesterday?"

The interviewer will then end the 24-hour dietary recall by thanking the participant for the time and participation.

b. Appendix B: Spanish Guion para recordar la dieta de 24 horas

Introducir el proceso de recordatorio

"Hola (diga el nombre del participante), mi nombre es (diga su nombre). Durante esta parte de su visita, realizaré un recordatorio dietético de 24 horas en el que me contará todo lo que comió y bebió durante las últimas 24 horas. Todo lo que me diga es confidencial y tardará unos 15 minutos. ¿Está bien?"

“Primero, haremos una lista de todos los alimentos y bebidas que consumió desde las 12 am de ayer por la mañana hasta las 12 de la noche de anoche. Esto incluye todas las comidas, refrigerios, bebidas (incluyendo agua y bebidas alcohólicas), así como pruebas o muestras de alimentos.”

“Luego, repasaremos la lista y completaremos los detalles”.

“Al final también le preguntaré sobre las vitaminas, minerales u otros suplementos que haya tomado”.

“¿Tiene alguna pregunta antes de que comencemos?”

PASO 1: Recopila la Lista Rápida

Se anima al participante a decir lo que se le ocurra sobre la ingesta del día anterior con una interrupción mínima.

Se recopilará la hora de la comida, el lugar de la comida y el tipo de comida.

No se harán preguntas adicionales sobre detalles o cantidades.

Indicaciones:

“Después de la medianoche, ¿cuál fue la primera vez que comió o bebió algo?”
“¿Cómo considerarías esta comida?” “¿Dónde consumió esta comida?”
“¿A qué hora consumió esta comida?” “¿Qué tenía en ese momento?” “¿Cuándo fue la próxima vez que comió o bebió algo?”

PASO 2: Revise la Lista Rápida

Esto permite al entrevistador identificar brechas en el tiempo cuando no se reportan alimentos o bebidas, ocasiones de comidas olvidadas y comidas o bebidas omitidas.

Indicaciones:

“Ahora revisemos lo que tenemos hasta aquí”.
“¿Tuvo algo entre la medianoche y (diga la hora de la primera comida)?”
Repita las siguientes dos preguntas para cada comida / refrigerio:
“En (diga la hora de la comida), tenia (leer todos los alimentos). ¿Puede pensar en algo más que tuvieras en ese momento?”
“¿Comió o bebió algo entre (diga la hora de la comida) y (la hora de la comida)?”
Cuando sea apropiado, pregunte: “¿Tomó una bebida con esa comida?”
“Finalmente, ¿comió o bebió algo entre (diga la hora de la última comida) y la medianoche?”

PASO 3: Recopilar Información Detallada

Esto le permite al entrevistador buscar información adicional y obtener detalles de alimentos y bebidas, y cantidades consumidas.

- Recopile la hora, el nombre y la ubicación de la ocasión para comer si no se proporciona durante la lista rápida.
- Detalles de cada comida y bebida:
    - Marca y / o tipo de artículo
    - Detalles de preparación
    - Detalles de cocción
    - Cualquier adición (condimentos) añadida
    - Cuánto del artículo se consumió (esto se puede preguntar al final de cada comida)

Indicaciones:

Estos variarán según el tipo de comida o bebida consumida.

PASO 4: Pregunte acerca de los alimentos comúnmente olvidados

Esto se centra en la atención del participante en alimentos y bebidas específicas que tienden a ser más olvidados durante un recordatorio. Haga cada pregunta y espere una respuesta.

Indicaciones:

"Eso es todo en tu lista. Hay algunos alimentos que la gente puede olvidar al hacer un recordatorio, así que para asegurarse de que sea lo más completo posible, escuche lo siguiente y avíseme si necesitamos agregar algo".

1. "Además de lo que ya informó, ¿bebió algo de agua?"
2. "¿Algún café, té, refrescos, leche o jugo adicional?"
3. "¿Comió galletas, dulces, helados u otros postres?"
4. "¿Comió alguna fruta, verdura o queso?"
5. "¿Qué tal pan, panecillos o tortillas?"
6. "¿Comió papas fritas, galletas saladas, palomitas de maíz, pretzels, nueces u otros bocadillos?"
7. "¿Tomó cerveza, vino, cócteles u otras bebidas?"

PASO 5: Revise la información detallada

El entrevistador confirmará lo que se ha dicho y documentará las comidas que se saltan o que incluyen comidas no tradicionales (es decir, comidas sin bebidas, pan extraído del sándwich, sin leche en el cereal, etc.)

Indicaciones:
"En (momento) tenia (cantidad) de (comida). ¿Es esto correcto?"
"Al final de cada comida:¿comió algo más en ese momento?"

El entrevistador continuará investigando sobre refrigerios entre comidas o comidas omitidas, buscando grandes brechas en el tiempo cuando no se informan alimentos o bebidas y asegurándose de que no se haya omitido ninguna información sin darse cuenta.

SIGUIENTE PASO: Complete las preguntas del avance (¿es un día típico y son los datos confiables?)

- Preguntar al participante
    - “En términos de la cantidad de comida que comió, ¿diría que esta fue: cerca de la cantidad que come habitualmente? ¿Mucho más de lo que suele comer? ¿Mucho menos de lo que suele comer? Si es más o menos, pídale que le explique por qué.

A discreción del entrevistador:

¿Fue la información: confiable? ¿No puede recordar una o más comidas? ¿No es confiable por otras razones? Explique por qué el recordatorio está incompleto / inutilizable.

PASO FINAL: Complete las preguntas de evaluación de suplementos dietéticos

El entrevistador puede obtener información complementaria de las últimas 24 horas.

Pregunte al participante:
“Ahora tengo preguntas sobre los suplementos dietéticos que tomó ayer”.

1. “¿Tomó vitaminas o minerales?” (es decir, One a Day ®, Centrum ®, Vitamina C)
2. “¿Tomó algún aminoácido?” (es decir, glutamina, arginina, lisina)
3. “¿Tomó algún suplemento que contenga aceites o ácidos grasos omega-3?” (es decir, aceite de pescado, aceite de linaza, aceite de krill, DHA)
4. “Ayer, ¿tomó algún producto herbal o botánico?” (es decir, equinácea, ginseng, ginkgo o hierba de San Juan)
5. “¿Tomó algún suplemento de fibra?” (es decir, Metamucil, Benefiber o Fibercon)
6. “¿Tomó algún otro suplemento dietético del que no me haya hablado?” (es decir, extracto de ajo, levadura de cerveza, coenzima Q10, glucosamina condroitina o suplementos para bajar de peso)
7. “¿Tomó antiácidos de venta libre?” (es decir, Tums, Rolaids, Mylanta)

“Ahora, le pediré detalles sobre cada uno de los productos que informó. Será útil tener los contenedores para tantos de estos productos como sea posible”.

Por cada suplemento tomado, el entrevistador hará las siguientes preguntas:

1. “¿Tiene el contenedor para este producto?” Sí No
2. “Por favor proporcione el nombre completo del producto”. (incluya la dosis y el tamaño de la porción)
3. “¿Cuántas veces tomó este productor ayer?”
4. “¿Cuántas tabletas tomó cuando usó el producto ayer?”

El entrevistador luego finalizará el recordatorio dietético de 24 horas agradeciendo al participante por el tiempo y la participación.

18.7 **S1600 Site Requirements Form**

Prior to registering its first patient, each site must complete this form and submit it to the CTSU via the Regulatory Submission Portal. (Log in to www.ctsu.org and select the Regulatory Submission sub-tab under the Regulatory tab.)

For the site to be eligible to participate in the study, the answer to all five questions below must be "yes".

Name of person completing this form: _____

CTEP-IAM Account Number: _____

CTEP site code(s) for **all sites** to which these answers apply (e.g., TX123): _____

_____

_____

1. Does your surgical team follow the ERAS principle of no bowel preparation for radical cystectomy procedures?

   ___Yes ___No

2. Does your surgical team routinely avoid nasogastric tube intubation for radical cystectomy procedures?

   ___Yes ___No

3. Does your surgical team allow early oral intake within 24 hours after radical cystectomy surgery?

   ___Yes ___No

4. Does your surgical team prescribe opioid-free pain control or minimize narcotics?

   ___Yes ___No

5. Does your site have access to a DXA scanner to measure body composition?

   ___Yes ___No

18.8 Guidelines for Emergency Unblinding of Coded Intervention

a. The following events MAY require emergency unblinding of Coded Intervention:

- A compelling medical need as determined by a physician, e.g., occurrence of a severe or life-threatening reaction, inclusive of an adverse drug reaction, which may have been attributable to Coded Intervention, or existence of a condition where the knowledge of the patient's treatment assignment would directly influence or affect his/her immediate care;
- ingestion of the Coded Drug by persons other than the patient or in excessive quantity;
- exposure of a pregnant woman to the Coded Intervention;
- exposure of a child to the Coded Intervention;

Note: Adverse drug reactions should be reported as required per Section 16.0 of this protocol.

b. Procedure for Emergency Unblinding

The procedure for unblinding the treatment assignment for a patient is as follows:

- All unblinding must be done by the registering physician or designee.
- Call the Washington Poison Control (WPC) collect at 206/526-2121 or at 800/732-6985 if calling from within Washington State. The WPC is accessible 24 hours per day, 365 days per year for unblinding calls. Informational calls should be directed to the Data Operations Center in Seattle during standard business hours.
- Provide the WPC with the following information:

  Study number: **S1600**
  SWOG patient number
  Patient name
  Coded Intervention ID number and bottle number
  Name and telephone number of the caller
  Reason unblinding is required

- Unblinding for ingestion of the Coded Intervention by a pregnant woman will not require the authorization of a resource physician. (The resource physicians for this study are listed at the end of this section.)
- Unblinding for ingestion of the Coded Intervention by a child will not require the authorization of a resource physician.
- Unblinding for ingestion of the drug either in excessive amounts or by a person other than the patient will be done ONLY when a compelling medical need exists and/or unblinding has been authorized by a resource physician.
- Unblinding for a "compelling medical need" must be authorized by a physician designated as a resource physician for this protocol.

The treating physician (or designee) would provide the WPC with the information needed to determine if unblinding is required for the patient. The WPC would contact the resource physician, provide the required information, and obtain the authorization to unblind, if necessary. Based on the decision of the resource physician, the WPC would call the treating physician with either the unblinded treatment assignment or a treatment recommendation from the resource physician.

If a resource physician cannot be reached by the WPC, treatment of the patient should proceed as if the drug ingested were an active agent.

- Unblinding of Coded Intervention for any reason must be documented on the **S1600** Treatment Form and the **S1600** Off Treatment Notice.

All unblinded participants are taken off treatment and followed per the requirements of the Southwest Oncology Group protocol.

Any questions regarding unblinding may be directed to one of the following resource physicians:

Norah Lynn Henry, M.D., Ph.D. (Medical Oncology)
Daniel F. Hayes MD Breast Cancer Research Professor
Division of Hematology/Oncology
Disease Lead, Breast Oncology
University of Michigan Rogel Cancer Center
1500 E. Medical Center Dr, Rm 7322
Ann Arbor, MI 48109
Phone: 734/936-9868
FAX: 734/647-9480
E-mail: norahh@med.umich.edu

Jeffrey M. Holzbeierlein, M.D., F.A.C.S. (Medical Urology)
John W Weigel Endowed Professor & Chair
Director of Urologic Oncology
3901 Rainbow Boulevard, MS 3016
Kansas City KS 66160
Phone: 913/588-7654
FAX: 913/588-7625
E-mail: jholzbeierlein@kumc.edu

18.9 Translational Medicine Study Stool Microbiome

The stool microbiome of patients in a randomized control trial of perioperative immunonutrition for reduction of complications following radical cystectomy and urinary diversion.

a. Objectives:

1. To describe the microbiome of the gut in patients undergoing radical cystectomy and urinary diversion prior to initiation of immunonutrition or a nutrition control.

2. To define the microbiome change in patients undergoing radical cystectomy and urinary diversion after they have received blinded immunonutrition or control nutritional supplement.

3. To correlate cancer treatments, postoperative complications, specifically infections, and nutritional status with microbiome composition

b. Background

Radical cystectomy is associated with significant complication rates; most studies find 60% complication rates across the world and 30% readmission rates. The **S1600** clinical trial is examining a novel immunonutritional intervention with the goal of reducing these post-operative complications.

Microbiomes are made up of microbiota that live in and on humans; microbiomes exist in the urinary tract, skin, gut/GI tract and other systems of the body. A great deal of research has been done with the microbiome in patients undergoing colorectal and pancreatic surgery. *(1,2)* The microbiome for both of these surgeries has been found to be associated with perioperative outcomes and complications. *(3,4)* Complications and infections specifically are associated with microbiome in the perioperative period. *(5,6)* A serious complication of surgery can be an intestinal anastomotic leak, which is potentially driven by the microbiome. *(7,8)* There is data in humans that the gut microbiota have a role in recovery from surgery involving the gastrointestinal tract, specifically anastomotic leak and infections. (9) Testing of probiotics has demonstrated that the complex mucosal immune system can be modified with probiotics in colorectal cancer and can improve the hosts' immune responses. *(10)* In addition, modifications of the microbiota have been used to optimize therapeutic interventions in mice receiving immunotherapy. *(11)* In addition, a recent meta-analysis of patients undergoing gastrointestinal surgery benefited from probiotics and synbiotics, and they were associated with lower infectious complications. *(12,13,14,15)* Therefore, microbiome profiling may enable tailored interventions specific to each patient to prevent postoperative complications. The microbiome may also be modified by the nutrition, specifically immunonutrition, synbiotics or probiotics. *(16)*

There is a critical gap in knowledge about which radical cystectomy patients are most likely to experience postoperative complications and how best to prevent them. Importantly, there are no consistent predictors of which patients will develop postoperative complications. Given the high rate of complications and the frequent occurrence of this operation, there is enormous room for improvement in the perioperative care for these patients, and identification of an intervention to reduce complications could have a large impact. In this proposal we will examine

associations between the gut microbiome and postoperative complications, in an attempt to identify a potentially modifiable predictor of complications. In addition, we will investigate the impact of the immunonutrition intervention on the gut microbiome in patients undergoing radical cystectomy.

Preliminary studies

Key publications include details on how the microbiome drives key portions of disease and can be modulated with novel therapies. In particular, using 16sRNA sequencing has been established as an association between the gut microbiome and immune modulated diseases in cancer patients, which has led to the identification of novel microbiome-targeted therapeutics. *(17)*

An additional key publication describes the diversity of the gut microbiome and how the host factors of the microbiome vary between different hosts (different humans with varying diseases) and over time. The presence of more diverse intestinal microbiomes has been correlated with anti-inflammatory properties. *(18)* This provides insight that the microbiome can be modified by increasing diversification of the microbiome with factors such as nutrition. Importantly the microbial community can be targeted with clinical treatments. *(19)* For example, one large study found a difference in C. difficile infection rates among patients with and without immunonutrition, indicating that there may be advantages to modulating the gut with immunonutrition. *([20])*

c. Endpoint(s) to be used in analyses:

1. Post Operative complications (any vs. none)
2. Post Operative infections (yes/no)
3. Nutritional status (malnourished vs. adequate nutrition)
4. Other cancer treatments (preoperative chemotherapy vs no preoperative chemotherapy)

d. Experimental approach, validated assays employed and expertise:

This translational study to examine changes in the gut microbiome with intervention is being incorporated into the currently activated and enrolling SWOG **S1600** trial. Patients' stool samples will be collected with the Omnigene-GUT kit. This kit allows the patient to collect and preserve the samples from the comfort of their own home. Patients will be asked to collect a stool specimen and place a small sample on the kit spatula. This is then placed into the tube provided. With the Omnigene-GUT kit the yield of DNA is not influenced by temperature, thus it should be able to be shipped at any time of the year in any climate.*(* 21*)* Once the samples have been collected they are stable in the test tube for 60 days at room temperature. Collection timepoints and instructions are located in Section 15.2. They will begin their nutritional supplements 5 days before surgery and then undergo surgery per the **S1600** protocol. As the **S1600** protocol dictates strict timing of drink delivery, the first specimen can be collected anytime after **S1600** enrollment, but before initiation of their first nutritional drink (control or immunonutrition). After discharge from the hospital, we will have them collect the first bowel movement that occurs at home (+/- 2 days). Although waiting until after discharge means the timing of collection of the post-surgical sample will vary based on each patient's duration of hospitalization, collection of the sample during hospitalization at each participating institution is anticipated to be logistically

difficult and therefore unreliable. These kits have been used in Dr. Lozupone's lab previously for other studies that require shipping the specimens internationally, and extraction of these shipped samples has yielded the same results as fresh samples collected locally in the lab. *(22)* SWOG Biospecimen Bank will process specimens per the Omnigene-GUT website. The samples will be stored in -80 degree freezer until end of study. Frozen samples will be shipped from SWOG Biospecimen Bank to the University of Colorado for analysis. DNA will be extracted and sequenced using standard 16s rRNA technique, using the DNeasy PowerSoil kit from Qiagen using the manufacturer's instructions, with the addition of a 65 degree incubation step and homogenization with bead-beating rather than vortex. *(23)* The bead-beating will facilitate release of DNA from gram positive bacteria.

Bioinformatic analysis of the 16s rRNA amplicon sequences will be conducted as follows: The reads will be processed using QIIME v1.9.1. After filtering out reads containing Phred scores <30 or chimeric sequences detected by USEARCH v6.1, then clustered forward reads will be used for *de novo* operational taxonomic units at a 97% similarity threshold using UCLUSTref v1.2.22q and greengenes v13_8. After that, the operational taxonomic units are translated to taxa (for example, genus and species) using RDP v2.2. A phylogenetic tree of operational taxonomic units with FastTree v2.1.3 will be used to evaluate bacterial diversity (phylogenetic diversity index, sums total phylogenetic branch length observed in a subject) (unweighted and weighted UniFrac distances quantify unique versus shared phylogenetic tree branch length between two samples). Rarefaction will be used to accommodate differential library sizes. This bioinformatics analysis is standard operating procedure for Dr. Lozupone's lab and is available freely reproduced using Qiita (qiita.ucsd.edu/study/description/10564). *(24)* The bioinformatics processing pipelines for microbiome data continue to evolve with best-practices and the state-of-the-art constantly improving. Accordingly, alternative processing pipelines may be considered at the time of analysis.
Once all the samples have been sequenced, bioinformatics analysis (described above) will be conducted at the University of Colorado by analysts experienced in the bioinformatics analysis of stool microbiome. *(25)* Statistical analyses and correlations with endpoints (described in Section 18.9.e) will be conducted at the SWOG Statistics and Data Management Center.

e. Statistical Plan:

Aim 1: The objective of Aim 1 is to describe the baseline microbiota. Alpha-diversity metrics for each patient's baseline samples will be calculated from rarefied data. Beta-diversity metrics including UniFrac distance, Bray-Curtis dissimilarity, and Aitchison distance will be calculated from rarefied data and ordination plots will be generated. For individual taxon level data, rank abundance plots will be generated and prevalence of particular bacterial taxa will be estimated. Clustering, based on beta-diversity, will be used to examine possible enterotypes.

Aim 2: The objective of Aim 2 is to assess change in the microbiota between baseline, after nutrition drinks and surgery (post-operative). We will first assess the change using all patients (across both arms). To assess the change in alpha-diversity, the difference in Shannon Index between predrink, pre- and post-operative profiles will be calculated for each individual and compared using a paired t-test at the nominal $\alpha=0.05$ level. Similarly, beta diversity distance matrices will be calculated using the pooled (baseline and post operative) samples to generate a 2n X 2n matrix which will be compared using PERMANOVA with patient

as a stratification variable; 9,999 permutations will be used to generate a p-value with significance called at the α=0.05 level.

For individual taxon level analyses (quantified at the genus level), taxa present in less than 15% of samples or with average relative abundance <0.1% will be filtered. Sparsity will be reduced by adding a pseudocount to raw counts or by application of Bayesian-multiplicative replacement. De-sparsified relative abundance data will be center-log-ration transformed to accommodate compositionality concerns and encourage normality. Subsequently, the change between post- and pre-operative (transformed) data will be calculated for each taxon (on each patient) and the change will be compared using a paired t-test. Benjamini-Hochberg false discovery rate (FDR) will be controlled at the 10% level.

We will repeat the analyses within each arm, separately. Comparisons (in change) across arms will be conducted in Aim 3 (below).

Aim 3: The objective of Aim 3 is to assess the association between microbiome profiles and dichotomous clinical outcomes, including preoperative chemotherapy, post operative complications, post-operative infections, and post-operative nutritional status. Each outcome will be analyzed separately.

For the primary outcome of post-operative complications, we will assess whether (1) baseline microbiome profiles (2) post-operative microbiome profiles and (3) change in microbiome profiles are associated with post-operative complications.

For the baseline analyses (1) and post operative analyses (2), we will first restrict attention to patients randomized to the specialized immune-modulating nutrition drink arm. Then we will assess the association between alpha diversity (Shannon index) and complications by regressing alpha diversity on indicator for complications and additional covariates. A 1-df test will be used to evaluate the association with complications at the nominal α=0.05 level. Beta-diversity analysis will proceed by calculating UniFrac, Bray-Curtis, and Aitchison metrics which will be compared between patients with and without complications using a logistic version of the microbiome regression-based kernel association test (MiRKAT), a generalization of PERMANOVA with improved covariate adjustment, calling significance at the α=0.05 level. Finally, transformed taxon abundances (as in Aim 2) will be compared between patients with/without complications by regressing taxon abundance on an indicator for complications, again adjusting for additional covariates. A 1-df test will again be used with FDR controlled at the 10% level.

For baseline and post operative microbiome samples, we will then repeat these analyses restricting analyses to patients in the control arm and also pooling across arms (with adjustment for arm). Finally, within the pooled analyses, we will further assess whether the microbiome modifies the association between treatment and outcomes. For alpha diversity and individual taxon analyses, we will include two-way interactions between Shannon index or individual taxon abundances, respectively, in the corresponding models and again evaluate significance using a 1-df with FDR controlled at 10%. For beta-diversity analysis, we will embed the distance matrices into kernel metrics (as in MiRKAT), but then we will use a logistic kernel-machine interaction test to assess whether associations between outcome and treatment are heterogeneous by microbiome beta-diversity profiles.

To examine whether change in microbiome profiles is related to preoperative chemotherapy, will conduct similar analyses as in the baseline and post-operative samples, except for alpha diversity and individual taxa, we will, respectively, use change in Shannon Index and change in taxon abundance. For beta-diversity analysis, we will calculate paired analogues of the UniFrac, Bray-Curtis, and Aitchison distances developed by SWOG.

Following analysis of the primary endpoint, we will repeat the analysis using post-operative complication and infection status and post-operative nutritional status as endpoints instead.

For all analyses, robust and non-parametric alternatives, as well as other data transformations, will be used if statistical assumptions are violated. If necessary, analyses will be adjusted for additional covariates, possibly including: age, BMI, underlying disease (renal disease/etc), sex, baseline nutritional status, preoperative chemotherapy, muscle mass, etc. If necessary, we will also adjust for technical covariates such as storage time and time from surgery to collection (of the post-operative sample). Possible batch effects will be assessed and removed if present per SWOG TM guidelines: the SWOG statistical center has previously validated the use of ComBat (on CLR transformed data) for mitigating batch effects in 16S data.

Sample Size and Power Considerations:

For Aim 1, with a sample size of 73 patients per arm (146 patients, total), we will be able to estimate the prevalence of particular enterotypes or particular bacterial taxa to within 8.1% (95% confidence interval) using all baseline samples.

For Aim 2, we anticipate 80% power to detect a change in alpha-diversity from baseline to post-surgery of 0.23 and 0.33 standard deviations (sds) using all patients and patients in a particular arm, respectively. For individual taxa, conservatively assuming that 90% of taxa do not have change from baseline to post-surgery, then at the FDR=10% level, we anticipate 80% average power to identify a taxon with change in abundance of 0.29 and 0.41 sds, using all patients and patients in an individual arm, respectively.

For Aim 3, we calculate minimal detectable effect sizes assuming 42%, 65%, and 53% complication rates in the experimental arm, control arms, and overall, respectively. Then for the baseline and post-operative microbiome analyses, we anticipate 80% power to detect a difference in alpha diversity between patients with/without complications of 0.67, 0.69, and 0.46 sds, in the experimental arm, control arm, and pooled across arms, respectively. For individual taxon analyses, again assuming that 90% of taxa are not differentially abundant between, then we anticipate 80% average power to identify a taxon with difference in abundance between patients with/without complications of 0.83, 0.86, and 0.58 sds, in the experimental arm, control arm, and pooled across arms, respectively. Minimal detectable effect sizes for analyses examining change are analogous except based on differences in alpha diversity and taxon abundance.

f. Data analysis performed by:
The CU bioinformatics department (informatics and quantification) and SWOG statistical center (correlative analyses)

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18.10 SWOG Biospecimen Processing Instructions

The SWOG Biospecimen Bank will receive stool in Omnigene-Gut kits. Upon receipt, the Bank will accession, barcode, homogenize and aliquot stool samples. Aliquots of stool in the Omnigene-Gut media will be stored in a -80°C freezer for future studies

Consent Form **S1600**

Study Title for Study Participants: Testing the Effect of Nutrition on Bladder Cancer Surgery

Official Study Title for Internet Search on http://www.ClinicalTrials.gov: A Randomized Phase III Double Blind Clinical Trial Evaluating the Effect of Immune-Enhancing Nutrition on Radical Cystectomy Outcomes (SIMmune)

What is the usual approach to bladder cancer surgery?

You are being asked to take part in this study because you have bladder cancer and will undergo surgery to remove all of the bladder (the organ that holds urine) as well as nearby tissues and organs. In men, this includes removal of the prostate and seminal vesicles. In women, this may include the uterus, cervix, along with the fallopian tubes and ovaries. Nearby lymph nodes, and some or all of the urethra are also removed. The study group will receive the nutritional supplements of interest in the study. The control group for this study will receive a nutritional supplement but not the supplements of interest for the trial.

People who are undergoing this surgery and are not participating in a study are usually not treated with nutritional supplements.

What are my other choices if I do not take part in this study?

If you decide not to take part in this study, you have other choices. For example:

- you may choose to have the usual approach described above, without nutritional supplements
- you may choose to take part in a different study, if one is available
- you may choose not to undergo surgery
- you may take a nutritious supplement which you purchase yourself over the counter

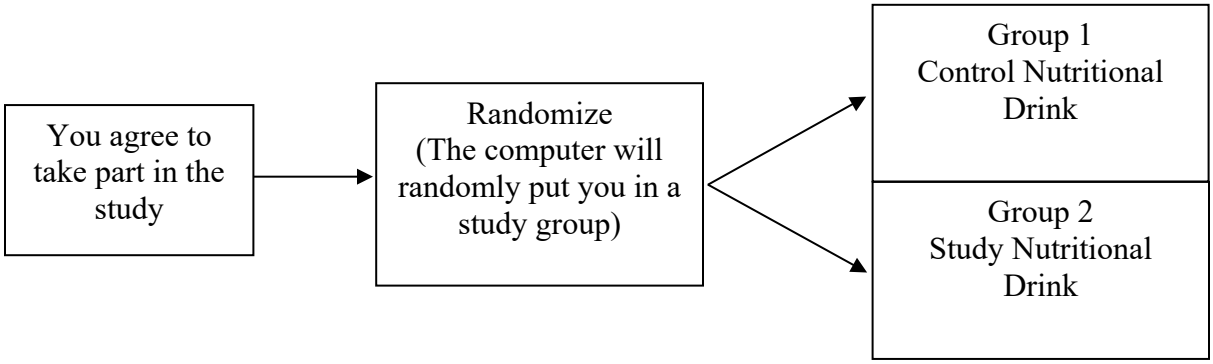
Why is this study being done?

You have bladder cancer and will be having surgery. Many patients don't get enough of certain types of nutrients before going in to surgery, which may cause infections and other problems such as muscle wasting, rapid weight loss, slow wound healing, and inflammation. The purpose of this study is to test whether improving nutrition before and after surgery can reduce the infections and other problems that sometimes occur after surgery. The effects of a special nutrition drink will be compared to a control. A control is a liquid that looks like the study liquid but does not contain the nutrients to be studied. There will be about 200 people taking part in this study.

What are the study groups?

This study has two study groups. One group will receive the study nutrition drink containing special additional nutrients, and the other group will receive the control nutrition drink that does not contain the special nutrients to be studied but is otherwise the same. We do not know if the special nutrients are helpful or harmful for your cancer. Both drinks contain milk, soy and fish ingredients. Both drinks are appropriate for these diets: lactose intolerance, gluten-free, kosher, and halal.

A computer will by chance assign you to one of the two treatment groups in the study. This is called randomization. This is done by chance because no one knows if one study group is better or worse than the other. Once you are put in one group, you cannot switch to the other group. Neither you nor your doctor can choose or will know which group you will be in. You will have an equal chance of being placed in either group.



How long will I be in this study?

You will drink the study drinks for five days before your surgery and five days after. After you finish the study drinks, your doctor will continue to watch you for side effects and follow your condition for 3 years after your surgery.

What extra tests and procedures will I have if I take part in this study?

Most of the exams, tests, and procedures you will have are part of the usual approach for your cancer. However, there are some extra exams, tests, and procedures that you will need to have if you take part in this study.

If the exams, tests, and procedures show that you can take part in the study, and you choose to take part, then you will need the following extra tests and procedures. They are not part of the usual approach for your type of cancer and will be provided at no cost to you.

During the study:

- DXA Body Scan – You will have a DXA Body Scan before surgery and another scan 30 days after surgery. The DXA Body Scan that you get in this study will expose you to low amounts of radiation. Every day, people are exposed to low levels of radiation that come from the sun and the environment around them. This type of radiation is called "background radiation. No one knows for sure whether exposure to these low amounts of radiation is harmful to your body. The DXA Body Scan that you get in this study will expose you to less radiation than you get from everyday background radiation. Most of the time, this amount of extra radiation is not harmful to you. However, scientists believe that being exposed to too much radiation can cause harmful side effects. This could include getting a new cancer. We estimate that this could happen in about 1 out of every 1000 people who get a very large amount of extra radiation. For this test you lie down on an open "table" for approximately 8 minutes while your body is scanned. The DXA test measures body fat, lean tissue and bone mineral content for the arms, legs, and trunk. Neither you nor your health care plan/insurance carrier will be billed for the DXA Body Scan that will be used for this study.

- Blood draws – You will have one blood draw before receiving the nutrition supplements prior to surgery, another blood draw 2 days after surgery, and another 30 days after surgery. At each time point, about 5 teaspoons of blood will be collected. This sample is required in order for you to take part in this study because the research on the sample is an important part of the study. Blood samples for research will be drawn at the same time as the blood draws for labs. Neither you nor your health care plan/insurance carrier will be billed for the collection of the blood sample that will be used for this study. Your privacy is very important and the researchers will make every effort to protect it. Your test results will be identified by a unique code and the list that links the code to your name will be kept separate from your sample and health information. The results will be available to the study doctor.

- Questionnaires – There will be three separate occasions you will need to complete two to three questionnaires to collect information about how you are feeling physically and emotionally, and whether you are at risk for malnutrition during your treatment. It will take about 20 minutes to complete the questionnaires. The questionnaires will be given to you before the surgery, 2 days after surgery, and 30 days after surgery. If any questions make you feel uncomfortable, you may skip those questions and not give an answer. Although the questionnaires are not part of regular cancer care, they are being conducted as part of this research study to learn more about how your diagnosis and treatment(s) are affecting your life. This information along with that collected from other patients will help researchers in better understanding patients' needs and concerns. Additionally, should you choose to stop taking the study drink early, you will still be given the questionnaires to complete.

- Calendar – You will be provided a calendar and will be asked to make note of the time that you drink the nutritional drinks. You will be asked to do this for the 5 days prior to and the 5 days after your surgery. There is also a study calendar below that shows how often the extra tests will be done as well as the schedule for the intake of the nutritional drinks.

- Phone Interview- You will be interviewed by phone to collect information about your eating habits four times. It will take about 15 minutes to complete each interview. You will be required to provide your contact information and the best times to contact you for the phone interviews in order for you to take part in the study. Two interviews will take place at the beginning of the study (before starting the nutritional drinks) and two interviews will take place about 30 days after surgery. The interview is not part of regular cancer care, but is being done as part of this research study to learn more about how your diagnosis and treatment is impacting your life. This information along with that from other patients will help researchers better address patients' needs and concerns. If you stop the study drinks early, you will still be interviewed by phone.

Here is a calendar of the study procedures:

First study visit	Blood draw for research Blood draws to test your blood count and liver function DXA body scan Complete questionnaires
Around the time of the first study visit	Phone interviews Stool sample collection before starting study drinks (optional)
Every day, for five days before surgery	Study drinks Stool sample collection after at least 4 days of taking study drinks prior to surgery (optional)
	Surgery
Every day, for five days after surgery	Study drinks Stool sample collection after return home from hospital (optional)
2 days after surgery	Blood draw for research Blood draws to test your blood count and liver function Complete questionnaire
30 days after surgery	Evaluation by surgeon for complications DXA body scan Blood draws to test your blood count and liver function Blood draw for research Complete questionnaires
About 30 days after surgery	Phone interviews
About 3, 6, 9, 12, 18, 24, and 36 months after surgery	Evaluation for complications

Optional samples: You will be given the option to store your stool samples and/or any leftover blood from the blood draws during this study in a biobank. Storing samples is called "biobanking." The biobank for the stool samples from this study is called SWOG Biobank and is supported by the NCI. The biobank for the leftover blood from this study is called the EDGE Research Lab biobank. This will be discussed in the section under "Optional studies" below.

What possible risks can I expect from taking part in this study?

- You may be asked sensitive or private questions which you normally do not discuss.
- The study approach may not be better, and could possibly be worse, than the usual approach for your cancer.

Let your study doctor know of any questions you have about possible side effects. You can ask the study doctor questions about side effects at any time.

Possible Side Effects of both Study Nutritional Drinks:

COMMON, SOME MAY BE SERIOUS
• **Diarrhea** • **Nausea** • **Vomiting** • **Loose Stools**

What possible benefits can I expect from taking part in this study?

It is not possible to know at this time if the study approach is better than the usual approach so this study may or may not help you. This study will help researchers learn things that will help people in the future.

Can I stop taking part in this study?

Yes. You can decide to stop at any time. If you decide to stop for any reason, it is important to let the study doctor know as soon as possible so you can stop safely. If you stop, you can decide whether or not to let the study doctor continue to provide your medical information to the organization running the study.

The study doctor will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

The study doctor may take you out of the study:

- If your health changes and the study is no longer in your best interest
- If new information becomes available
- If you do not follow the study rules
- If the study is stopped by the sponsor, Institutional Review Board (IRB) or FDA

What are my rights in this study?

Taking part in this study is your choice. No matter what decision you make, and even if your decision changes, there will be no penalty to you. You will not lose medical care or any legal rights.

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

What are the costs of taking part in this study?

The nutritional drinks will be supplied at no charge while you take part in this study. It is possible that the nutritional drinks may not continue to be supplied while you are on the study. Although not likely, if this occurs, your study doctor will talk to you about your options.

The cost of the DXA scans and of the research blood tests will also be covered by the study.

You and/or your health plan/insurance company will need to pay for all of the other costs of treating your cancer while in this study, including the cost of tests, procedures, or medicines to manage any side effects, unless you are told that certain tests are supplied at no charge. Before you decide to be in the study, you should check with your health plan or insurance company to find out exactly what they will pay for.

You will not be paid for taking part in this study.

What happens if I am injured or hurt because I took part in this study?

If you are injured or hurt as a result of taking part in this study and need medical treatment, please tell your study doctor. The study sponsors will not offer to pay for medical treatment for injury. Your insurance company may not be willing to pay for study-related injury. If you have no insurance, you would be responsible for any costs.

If you feel this injury was a result of medical error, you keep all your legal rights to receive payment for this even though you are in a study.

Who will see my medical information?

Your privacy is very important to us and the researchers will make every effort to protect it. Your information may be given out if required by law. For example, certain states require doctors to report to health boards if they find a disease like tuberculosis. However, the researchers will do their best to make sure that any information that is released will not identify

you. Some of your health information, and/or information about your specimen, from this study will be kept in a central database for research. Your name or contact information will not be put in the database.

There are organizations that may inspect your records. These organizations are required to make sure your information is kept private, unless required by law to provide information. Some of these organizations are:

- The company supporting the study, Nestle Healthcare Nutrition, and SWOG (a national cancer trials network)
- The Institutional Review Board, IRB, a group of people who review the research with the goal of protecting the people who take part in the study
- Researchers from the University of Kansas Medical Center and Louisiana State University who are involved in this study
- The Food and Drug Administration and the National Cancer Institute

Where can I get more information?

You may visit the NCI Web site at http://cancer.gov/ for more information about studies or general information about cancer. You may also call the NCI Cancer Information Service to get the same information at: 1-800-4-CANCER (1-800-422-6237).

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Who can answer my questions about this study?

You can talk to the study doctor about any questions or concerns you have about this study or to report side effects or injuries. Contact the study doctor _____ *(insert name of study doctor[s])* at _____ *(insert telephone number).*

ADDITIONAL STUDIES SECTION:

This section is about optional studies you can choose to take part in

This part of the consent form is about optional studies that you can choose to take part in. You will not get health benefits from any of these studies. The researchers leading these optional studies hope the results will help other people with cancer in the future.

The results will not be added to your medical records and you or your study doctor will not know the results.

You will not be billed for these optional studies. You can still take part in the main study even if you say 'no' to any or all of these studies. If you sign up for but cannot complete any of the studies for any reason, you can still take part in the main study.

Circle your choice of "yes" or "no" for each of the following studies.

1. Future contact

Occasionally, researchers working with SWOG may have another research idea that relates to people who were on a SWOG study. In some cases, to carry out the new research, we would need to contact participants in a particular study. You can agree or not agree to future contact.

I agree to allow my study doctor, or someone approved by my study doctor, to contact me regarding future research involving my participation in this study.

Yes **No**

2. Biobanking for possible future studies

Researchers are trying to learn more about cancer, diabetes, and other health problems. Much of this research is done using samples from your blood. Through these studies, researchers hope to find new ways to prevent, detect, treat, or cure health problems.

Some of these studies may be about genes. Genes carry information about features that are found in you and in people who are related to you. Researchers are interested in the way that genes affect how your body responds to treatment.

WHAT IS INVOLVED?

If you agree to take part, here is what will happen next:

1) Any blood samples left over after the testing done for the main part of the study and some related health information may be stored in the EDGE Research Lab biobank, along with samples and information from other people who take part. The samples will be kept until they are used up. Information from your medical record will be updated from time to time.
2) A stool sample will be collected at three timepoints during the study and will be sent to the SWOG Biobank for use in future studies. The samples will be kept until they are used up. Information from your medical record will be updated from time to time.
3) Qualified researchers can submit a request to use the materials stored in the Biobanks. A science committee at the clinical trials organization, and/or the National Cancer Institute, will review each request. There will also be an ethics review to ensure that the request is necessary and proper. Researchers will not be given your name or any other information that could directly identify you.

4) Neither you nor your study doctor will be notified when research will be conducted or given reports or other information about any research that is done using your samples.
5) Some of your genetic and health information may be placed in central databases that may be public, along with information from many other people. Information that could directly identify you will not be included.

WHAT ARE THE POSSIBLE RISKS?

1) The most common risks related to drawing blood from your arm are brief pain and possibly a bruise.
2) There is a risk that someone could get access to the personal information in your medical records or other information researchers have stored about you.
3) There is a risk that someone could trace the information in a central database back to you. Even without your name or other identifiers, your genetic information is unique to you. The researchers believe the chance that someone will identify you is very small, but the risk may change in the future as people come up with new ways of tracing information.
4) In some cases, this information could be used to make it harder for you to get or keep a job or insurance. There are laws against the misuse of genetic information, but they may not give full protection. There can also be a risk in knowing genetic information. New health information about inherited traits that might affect you or your blood relatives could be found during a study. The researchers believe the chance these things will happen is very small, but cannot promise that they will not occur.

HOW WILL INFORMATION ABOUT ME BE KEPT PRIVATE?

Your privacy is very important to the researchers and they will make every effort to protect it. Here are just a few of the steps they will take:

1) When your sample(s) is sent to the researchers, no information identifying you (such as your name) will be sent. Samples will be identified by a unique code only.
2) The list that links the unique code to your name will be kept separate from your sample and health information. Any Biobank and SWOG staff with access to the list must sign an agreement to keep your identity confidential.
3) Researchers to whom SWOG sends your sample and information will not know who you are. They must also sign an agreement that they will not try to find out who you are.
4) Information that identifies you will not be given to anyone, unless required by law.
5) If research results are published, your name and other personal information will not be used.

WHAT ARE THE POSSIBLE BENEFITS?

You will not benefit from taking part. The researchers, using the samples from you and others, might make discoveries that could help people in the future.

ARE THERE ANY COSTS OR PAYMENTS?

There are no costs to you or your insurance. You will not be paid for taking part. If any of the research leads to new tests, drugs, or other commercial products, you will not share in any profits.

WHAT IF I CHANGE MY MIND?

If you decide you no longer want your samples to be used, you can call the study doctor, _____, *(insert name of study doctor for main trial)* at _____ *(insert telephone number of study doctor for main trial)* who will let the researchers know. Then, any sample that remains in the bank will no longer be used and related health information will no longer be collected. Samples or related information that have already been given to or used by researchers will not be returned.

WHAT IF I HAVE MORE QUESTIONS?

If you have questions about the use of your samples for research, contact the study doctor, _____, *(insert name of study doctor for main trial)*, at _____ *(insert telephone number of study doctor for main trial)*.

Please circle your answer to show whether or not you would like to take part.

SAMPLES FOR FUTURE RESEARCH STUDIES:

1. **My leftover blood samples and related information may be kept in a Biobank for use in future health research.**

   YES NO

2. **My stool samples and related information may be collected and kept in a Biobank for use in future health research.**

   YES NO

This is the end of the section about optional studies.

My Signature Agreeing to Take Part in the Main Study

I have read this consent form or had it read to me. I have discussed it with the study doctor and my questions have been answered. I will be given a signed copy of this form. I agree to take part in the main study and any additional studies where I circled 'yes'.

Participant's signature_____

Date of signature_____

Signature of person(s) conducting the informed consent discussion

_____

Date of signature_____