Original Article

PeRioperative Optimization with Nutritional Supplements in Patients Undergoing GastRoIntEStinal Surgery for Cancer (PROGRESS): A Randomized Placebo-Controlled Feasibility Study Protocol

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Abstract

Background: Postoperative morbidity, following major surgery of the gastrointestinal tract, ranges between 40-60%. Surgery-related impairment of the immune system and its function has been associated with postoperative infections. Supplemental perioperative nutrition may influence cell-mediated immunity to reduce the rate of infectious complications after surgery.

Objective: The primary objective of our trial is to determine the proportion of eligible patients randomized in an 18-month period. The primary feasibility outcome will be one of the following: (1) Stop, main study non-feasible: estimated proportion of randomized patients <40%, (2) Continue with protocol modifications: estimated proportion of randomized patients between 40-59%, and (3) Continue without modification: estimated proportion of randomized patients ≥60%. The secondary objectives are to evaluate compliance with the nutritional supplements, to estimate differences in postoperative complications, global health-related quality of life (QoL) and median length of hospital stay between the groups.

Methods: This is a double-blind placebo control feasibility randomized trial. The intervention consists of three nutritional supplements: a protein isolate powder (ISOlution®), immunomodulation (INergy-FLD®), and carbohydrate loading (PreCovery®). Patients will consume one serving of the protein supplement per day from the randomization time up to six days before surgery (30 days in total). The immunomodulation, a solution that contains arginine, protein isolate, omega-6 fatty acids, and RNA, aims to attenuate excessive inflammatory responses and to replenish nutrients. This solution will be consumed three doses per day for five days before and after surgery. Carbohydrate loading helps to reduce the stress from surgery by decreasing insulin resistance; patients will have two servings the evening before surgery and one serving 2-3 hours before surgery. To be eligible, patients must have a resectable gastrointestinal cancer for which an elective operation is planned. Patients will be stratified according to nutritional status. The operation should occur within four weeks from enrolment.

Results: We expect to screen 165 eligible patients, and 60% (100 patients) of them will be randomized to either intervention or placebo. Assuming a two-sided alpha of 0.05, this will give us a 95% confidence interval (CI) around the estimate of 53% to 68%. A sample size of 50 per group will enable us to estimate the treatment effect and corresponding variance of the complication rate and QoL measures with adequate precision. The success is defined as the proportion of eligible patients randomized as equal to or greater than ≥60%. Patients’ compliance is defined as intake of at least 70% of intervention volume.

Conclusion: The results will help to determine the feasibility of a larger randomized controlled trial to implement a perioperative nutritional supplement program for patients undergoing gastrointestinal surgery for cancer.

Trial Registration: ClinicalTrials.gov ID: NCT03445260, https://clinicaltrials.gov/ct2/show/NCT03445260
Keywords: Perioperative nutritional supplements; gastrointestinal cancer surgery; postoperative outcomes.
INTRODUCTION

Despite recent advances in surgical techniques and perioperative management, postoperative morbidity, including infectious complications, following major surgery of the gastrointestinal tract remains high, ranging between 40-60% [1, 2]. Surgery-related impairment of the immune system and its function has been associated with postoperative infections [3, 4]. Additionally, preoperative fasting induces the body to utilize stored nutrients, thereby accelerating the release of stress hormones, exacerbating insulin resistance, delaying wound healing, increasing morbidity and mortality, and extending the length of hospital stay [5].

Patients undergoing surgery often experience disorders of the immune response, which are facilitated by low caloric intake and by intestinal bacterial translocation [2]. With surgical trauma, the balance between T helper 1 (Th1) cells and T helper 2 (Th2) cells are shifted towards more Th2 cells. Th1 cells secrete interferon-δ (IFN-δ) and interleukin 2 (IL-2), and they induce cell-mediated immune responses, whereas Th2 cells produce IL-4, IL-10, and IL-13, providing help for humoral immune responses [1, 6]. Th1 cells activate macrophages and are highly effective in clearing intracellular pathogens, whereas Th2 cells suppress cell-mediated immunity [1]. It is thought that this reported suppression of Th1 response and intensification of Th2 response, often reported in surgical patients, may be one of the factors increasing the susceptibility to infections and septic complications. The presence of any complication within the first 30 days postoperatively is the most important independent determinant of 30-day mortality and overall long-term survival [7]. It has been shown that supplemental perioperative nutrition can influence cell-mediated immunity, the Th1/Th2 differentiation ratio, and can help reduce the rate of infectious complications after surgery, thereby improving the rate of long-term survival [1].

Oral supplements or “immunonutrition” that are considered to boost the immune system in this protocol, is defined as a solution that contains nutrients such as arginine and omega fatty acids. Arginine deficiency after surgical stress was first reported over 30 years ago, and recent studies have demonstrated that the perioperative use of an arginine-supplemented diet has the ability to decrease the rate of postoperative infections [8]. Arginine is an amino acid involved in tissue repair and wound healing. It is an essential metabolic substrate for immune cells and required for normal lymphocyte function [9]. In addition, omega fatty acids, such as n-6 and n-3, are derived from fish oil and they have been shown to attenuate the production of inflammatory compounds and ultimately reduce the cytotoxicity of inflammatory cells [10]. In a single arm phase II trial, DHA supplementation was shown to increase time to disease progression and overall survival in patients receiving adjuvant chemotherapy for metastatic breast cancer. Median time to disease progression was 3.5 months in the low DHA group and 8.7 months in the high DHA group (p=0.02). Median overall survival was 18 months in the low DHA group and 34 months in the high DHA group (P=0.007) [11]. Each element works towards improving the immune response against cancer through modulation of excessive inflammatory responses and replenishing depleted nutrients when the body is in a state of stress, such as surgery [11-13].

Along with impaired immune function, surgery increases the release of stress hormones, pushing the body into a catabolic state. These hormones induce the hepatic production of glucose by gluconeogenesis and glycogenolysis, and reduce glucose uptake in peripheral tissues, thus leading to postoperative hyperglycaemia and a state of and insulin resistance [5]. This period of resistance can be sustained for 3-4 weeks after surgery and is associated with delayed wound
healing, increased morbidity, mortality, and prolonged hospital stay. The degree of postoperative insulin resistance is significantly affected by the metabolic status of the patient at the time of surgical stress. The common practice of fasting patients from the evening before surgery is used to avoid pulmonary aspiration after elective surgery; however, there is no evidence to support this [14]. In fact, preoperative fasting increases metabolic stress, hyperglycaemia, and insulin resistance [15]. The preoperative protocol has since been updated to allow patients to consume clear fluids up until 2 hours before surgery. Preoperative carbohydrate-rich drinks have the ability to achieve a rise in insulin to levels known to change metabolism from a fasted to fed state and reduce postoperative insulin resistance by up to 50%, as well as reduce protein loss and improve muscle function [16]. In order to sustain this anabolic state and reduce the degree of postoperative resistance, it is recommended to consume 100g of complex carbohydrates the evening before surgery, and 50g up to 2 hours before surgery; this practice has been endorsed by several anesthesiology societies [17].

For patients with gastrointestinal cancer, insufficient protein intake, insulin resistance, and postoperative immobility increases the risk of impaired immune function [18]. Insufficient protein intake also results in slower recovery, prolonging hospital stay and immobility [18]. Nutritional depletion is a major determinant of the development of postoperative complications. It is associated with changes in body composition, tissue wasting and impaired organ function, which lead to impaired immune and muscle function. Thus, nutritionally depleted patients are at higher risk of infectious complications, and a direct relationship with increased operative mortality, independent of the type of surgery [19]. Patients with gastrointestinal cancers typically experience malnutrition, significant weight loss and reduced food intake. Thus, optimizing nutritional status both before and after surgery by meeting protein requirements creates an opportunity to reduce patients’ postoperative complications [20]. Whey protein substrates have great potential to be used effectively to support post-surgery anabolism. Whey proteins of high quality, have proved to be effective in modulating muscle protein synthesis, and are a convenient way to supplement protein needs in malnourished patients [21]. Whey proteins also have immunomodulating properties, including biosynthesis of antioxidant glutathione, which could attenuate the catabolic effects of surgery and spare protein [22]. Albumin, muscle function tests, immunological status and weight loss have been used to show the correlation between nutrition depletion and postoperative morbidity and mortality.

It has been proposed that perioperative immunomodulation, carbohydrate loading, and increased protein intake may have the potential to, decrease overall complications, improve patient’s quality of life, improve disease free and overall survival, and reduce overall health care cost by decreasing length of hospital stay and readmissions [23, 24]. There is some evidence that each intervention works separately through different mechanisms of action.

Therefore, we believe that a combination of the three interventions could have an additive effect. We propose to carry out a study to establish the feasibility of a randomized controlled trial comparing perioperative nutritional supplements with placebo, targeted at reducing the postoperative complication rate in patients undergoing gastrointestinal surgery for cancer. The secondary objectives are to evaluate compliance with the intervention (nutritional supplements) and to estimate differences in postoperative complications and the comprehensive complication index (CCI), which is a scoring system to measure postoperative complications for each patient [25]. The results of this study will provide us with the necessary information to plan a larger multicenter randomized controlled trial. Set criteria for success will be clearly outlined in this
proposal to determine whether it is feasible to move forward with a larger trial. The phase III randomized trial would compare the proportion of postoperative complications, patient’s quality of life, time to initiation of adjuvant chemotherapy, and its effect on disease free and overall survival, as well as costs to the health care system between groups.

This study will focus on supplementing patient’s perioperative care with three different products administered around the time of surgery. These products are: ISOlution®, INergy-FLD®, and PreCcovery®. ISOlution® is a neutral-tasting protein isolate supplement that contains no fillers, sweeteners or artificial flavours. It contains a mixture of whey protein isolate and lecithin and is added to foods and drinks without altering its texture or taste due to its neutral consistency. ISOlution® has a 93% protein purity, a Digestible Indispensable Amino Acid Score (DIAAS) of 1.09, and 14.3 grams of leucine per 100 grams of protein, which is an amino acid that has been shown to have an important role in enhancing the anabolic effects of protein. ISOlution® can also be administered as a tube feed. INergy-FLD® is an immune-modulating solution that contains whey protein isolate, refined fish oil with omega 6 fatty acids, antioxidants such as vitamins A, C, D and E, and has an elevated amino acid concentration with 4.2 grams of L-Arginine per serving. It has a natural citrus flavour, low sugar and a trace of lactose, therefore can be tolerated by patients who are lactose intolerant. PreCcovery® contains 50 grams of complex carbohydrates per serving with a 12.5% carbohydrate concentration and easily mixes with water. It has no added sugar, a natural citrus flavour, and maintains a low osmolality of 114 mOsmol/kgH2O, which promotes digestion, gastric emptying, and water absorption. These products are to be used as supplements and not a sole source of nutrition.

The general objective of this study is to improve the postoperative outcomes in patients undergoing any type of gastrointestinal cancer surgery. The primary study objective is to determine the proportion of eligible patients randomized in an 18-month period. The secondary objectives are (1) to determine the proportion of enrolled patients who complete the perioperative nutritional support program (See Secondary Outcomes), (2) to estimate the difference in the proportion of patients experiencing postoperative complications between the intervention and placebo groups at 90 days following index surgery, (3) to estimate the difference in the CCI (a scoring system to measure postoperative complications) between the two groups at 90 days following index surgery, (4) to estimate the difference in the global health related quality of life (QoL) between groups at 90 days following index surgery, and (5) to estimate the median length of hospital stay for each group.

**METHODS**

**Recruitment**

This is a single-center placebo controlled randomized feasibility study comparing the intervention of perioperative nutritional supplements (immunomodulation, carbohydrate loading, and protein isolate) with an identical placebo for each solution in patients with gastrointestinal cancer undergoing surgery. Study participants will be recruited at the Juravinski Hospital and Cancer Centre (JHCC). Eligible participants will be 18 years of age or older with a resectable type of gastrointestinal cancer (e.g. cancers of the gallbladder, liver, pancreas, stomach, small intestine, colon and rectum), for which an elective operation is planned (resection vs. palliative procedure). Patients with distant metastasis and patients who are lactose intolerant are also eligible because the amount of lactose in ISOlution and PreCcovery is minimal.
Patients will be excluded from the study if they have type one diabetes, malabsorption syndrome (e.g. chronic pancreatitis), organ failure (liver, kidney), galactosemia, end stage liver disease with a Child Pugh Score ≥ B [26] or end stage renal disease defined as stages three and four with a glomerular filtration rate between 30-59 for stage three and 15-29 for stage four [27], inflammatory diseases such as rheumatoid arthritis, systemic lupus erythematosus, Crohn’s disease and ulcerative colitis, galactosemia, ongoing infection, or poorly controlled type 2 diabetes mellitus (i.e. patients who have high blood sugars of 12-14 or higher) on a regular basis. Patients who cannot tolerate oral intake (e.g. gastric outlet obstruction or delayed gastric emptying), patients currently on steroids, female patients who are pregnant and/or lactating will not be included in this study.

**Randomization**
Randomization will be conducted centrally by the Ontario Clinical Oncology Group (OCOG). Study participants will be identified by screening all patients scheduled for surgery at the JHCC. Eligibility must be confirmed by the treating physician or designate prior to enrolment. After confirmation and documentation of written informed consent, patients will be randomized by accessing OCOG’s web-based Interactive Registration and Randomization System (IRIS). Randomization will be performed according to a prescribed computer-generated schedule.

**Stratification**
Stratification will be employed prior to enrolment to ensure balance between treatment arms for factors that may influence the primary outcome, including the nutritional status of the patient. Prior to randomization patient’s overall risk of malnutrition will be determined using the Malnutrition Universal Screening Tool (MUST) [28]. Patients will be stratified by risk status, low risk of malnutrition (MUST score of 0) vs. medium and high risk of malnutrition (MUST score of 1 or 2).

**Blinding**
This is a double-blinded study design. All research personnel and study participants will be blinded throughout the trial. To ensure all investigators and research personnel remain blinded, the company producing the nutritional supplements and placebo will be responsible for providing the Pharmacy Research Support Services (PReSS) and IT technician with the allocation information specific to each lot number. All pre-packaged kits for pre-operative intake and post-operative intake will be sent directly to PReSS. The kits received by PReSS will include a lot number that will correspond to either the intervention or placebo, however as mentioned above, the only personnel aware of the lot numbers and associated randomization allocation will be the independent pharmacy lead and pharmacy technicians at PReSS and independent IT technician responsible for the randomization sequence. To ensure all research personnel remain blinded to the patient’s allocation, PReSS will remove the lot number from each kit. PReSS will also be responsible for the accountability of the supplements throughout the study.

After entering the patient information into the IRIS randomization system, PReSS will be responsible for dispensing the appropriate kit number and ensuring the lot number has been blinded from the patient and the research personnel. The individual packets within the kits will be labelled from “30 days before surgery” and up to “5 days after surgery.”
Study Agents

Patients undergoing gastrointestinal cancer surgery will either receive perioperative nutritional supplements or placebo. (Table 1) The operation should occur within 4 weeks from study enrolment. Upon assessment, patients will have a consultation with their physician where standard recommendations on nutrition prior to their surgery will be provided. This consultation will happen in the B3 wing or the Surgical Oncology Clinics of the JHCC. Immediately following randomization (same day), patients will receive the intervention or placebo. The intervention consists of the following three different solutions:

1. A protein isolate powder (ISOlution®). This will be consumed by the patient to increase muscle protein synthesis and achieve the recommended per meal protein intake prior to surgery, as well as after surgery. Each serving delivers 20g of protein, stirred into a minimum of 250mL of liquid or soft foods. Patients will be asked to consume 1 serving per day (20g of protein powder in total per day) from the time of randomization up to 6 days before surgery (up to 30 days in total).

2. Immunomodulation – formulated liquid diet (FLD) (INergy-FLD®). In preparation for surgery patients will consume an immune modulating formula containing various ingredients including arginine, protein isolate, omega-6 fatty acids, and RNA, aimed to attenuate excessive inflammatory responses without being immunosuppressive, and to replenish nutrients that are depleted in a state of stress (i.e. surgery) thereby enhancing the recovery process [1]. The volume of this solution is 250mL per dose (51g of powder reconstituted in 250mL of cold water). Patients will be asked to consume 3 doses per day for 5 days prior to surgery and 5 days following surgery.

3. Carbohydrate loading (PreCovery®). On the day of surgery, a carbohydrate-rich solution will be consumed by the patient to reduce stress of surgery, reduce insulin resistance and accelerate recovery. The volume of this solution is 400mL per dose (55g of powder reconstituted in 400mL of cold water), it contains 50g of complex carbohydrates at a 12.5% carbohydrate concentration, including 2g of glucides or sugars. Patients will be administered 2 servings the evening before surgery and 1 serving 2-3 hours before anaesthesia.

The intervention or placebo could be administered orally or via alternate enteral feed such as gastrostomy or jejunostomy feeding tubes. ISOlution™ and INergy™ can be administered enterally via oral intake or a tube feed. This procedure is only administered if oral intake cannot be tolerated. Tube feeding administration is as follows: ISOlution™: Mix one to three servings of ISOlution™ into 60-1120 mL of water. Stir until completely dissolved. Infuse via syringe down feeding tube. Flush tube with 30-60 mL of water before and after administration. INergy™: Mix one serving of INergy™ with 250ml of water. Stir until completely dissolved. Infuse via syringe down feeding tube. Flush tube as necessary (30-60ml water). ISOlution™ and INergy™ contain lactose at 0.03 and 0.06 grams per serving respectively. A single threshold of lactose for lactose intolerant subjects cannot be determined, however the trace amount of lactose found in ISOlution and INergy is not predicted to cause adverse effects.

Placebo

There will be a placebo control for each of the solutions administered to patients in the intervention arm. The placebo will look exactly as the intervention externally (package) and internally (white powder). Each placebo is composed of a collagen-based filler with exactly the
same taste and texture as the intervention. The placebo will be produced and provided by the start-up company, Enhanced Medical Nutrition.

**Administration**

Following randomization, patients will receive the blinded packages of either the intervention or placebo, which will be administered by the Pharmacy Research Support Services (PReSS), located in the A4 wing at the JHCC. The patients themselves will be responsible for administering their own supplements while at home.

Patients will be asked to consume 1 serving of 20g of protein isolate powder mixed in 250mL of liquid or soft foods, every day from the date of randomization and up to 6 days before surgery. Additionally, they will be asked to consume 3 servings of 51g of an immune-modulating formula mixed in 250mL of cold water for 5 days before and after surgery, as well as 2 servings of 55g of carbohydrate-rich powder mixed in 400mL of cold water the evening before surgery and 1 serving 2-3 hours before anesthesia. Administration of the carbohydrate loading substance will be modified for patients following the Enhanced Recovery After Surgery (ERAS) Protocol. All study participants who are also taking part in the ERAS Protocol will be asked not to take the carbohydrate loading supplement as per the ERAS Protocol and will be asked to take the carbohydrate loading substance (or placebo) provided for this study.

At this point, patients will fill out a daily compliance diary from the date of randomization and up to 5 days after surgery. This compliance diary will be transcribed into a case report form (Preoperative Compliance-CRF) that includes the number of packets the patient took every day, the volume that was ingested and the days it was ingested for and the reasons patients were not compliant. While in the hospital, the nurses will be responsible for administration as PReSS will facilitate the administration of the supplements (INergy-FLD®) by adding them to the nursing care pathway of the patients. Compliance during this time will be obtained from the nurses’ log, which includes the amount of solution the patient ingested during each administration and the days the patient ingested the solution. If for some reason, the patients are unable to tolerate an oral diet (postoperative complications such as delayed gastric emptying, ileus, bowel obstruction, etc.) then the nurse will contact the principal investigator of the study and the order to suspend the administration of the solution will be assessed for each patient. This will be noted in the nurses’ chart and transcribed to the Postoperative Compliance CRF. Patients will continue to be part of the study.

**Patient Follow-up**

At the baseline visit, patients will have a complete history and physical examination recorded including height, current weight and weight 6 months prior. Patients will complete a baseline QoL assessment during their clinic visit. (Table 1 and Figure 1) Patients will be asked to complete a Health Resource Utilization Form at 15 and 6 days before surgery. (Table 1). Immediately after surgery, patients will be followed on a daily basis during their hospital stay to collect postoperative complications and compliance data, and length of hospital stay. (Table 1) Following discharge from the hospital, patients will then be assessed at their first post-operative clinic visit, 4 weeks (± 1 week) following the index operation. The second postoperative follow up will happen at 12 weeks (± 2 weeks) following surgery. At each assessment, physical examination will be completed. QoL questionnaire will be given to patients to complete while they wait in the surgical clinics. They will also be asked to complete a Health Resource Utilization Form at each assessment. Mortality will be recorded 90 days after surgery.
**Data Management**
In addition to physical examination and QoL data, a research assistant will gather postoperative complication data from patients’ charts or electronic medical records and transcribe it onto case report forms, which will be updated daily while the patient is in the hospital. Before surgery, a compliance diary will be provided to patients to evaluate their adherence. Compliance data will also be collected while the patient is in the hospital from the nurses’ charts, with a specific case report form designed to collect the volume of the supplement the patient has taken after surgery. A feasibility CRF will include reasons two different processes: 1) reasons for not consenting and 2) reasons for not randomizing if patient was consented. Data will be stored in a secured electronic database at OCOG.

**Sample Size and Feasibility**
Currently, there are 200 gastrointestinal resections performed annually for gastrointestinal cancer at the JHCC (300 over an 18-month period). We expect at least 165 (55%) patients to be eligible for the study. Additionally, we expect 100 (60%) eligible patients will be randomized to either intervention or placebo. Assuming a two-sided alpha of 0.05, this will give us a 95% confidence interval (CI) around the estimate of 53% to 68%. A sample size of 100 (50 per group) will enable us to estimate the treatment effect and corresponding variance of the complication rate, CCI and QoL measures with adequate precision. Given the number of patients that undergo surgery at JHCC and the number of patients’ eligible for the study, we believe we can complete accrual to the study in 18-21 months. Given that the follow up is 3 months, we expect the study will be finalized within 21-24 months of commencement.

**Statistical Analysis**
Patient baseline characteristics and demographics by treatment group will be presented using descriptive statistics. The proportion of eligible patients randomized and its corresponding 95% confidence interval (CI) will be calculated using the Wilson method. The criteria for success of this study is defined as the proportion of eligible patients randomized as ≥60%. If the estimated proportion is <40%, the trial will be considered not feasible. If the proportion is between 40%-59%, the trial will be considered feasible with modifications to improve enrolment.

The difference in the proportions of any postoperative complication between groups and its corresponding 95% CI will be calculated using the Wilson method. The proportion of patients who are compliant with study therapy and 95% CI will also be calculated. Difference in compliance between treatment groups will be described. Good compliance will be defined as consumption of at least 70% of the study intervention before and after surgery. If the compliance is ≥70%, there will be no exploratory analysis to evaluate the reasons for no compliance. Compliance of <70% will be considered poor and reasons for non-compliance will be further explored (e.g. problems with the distribution or administration of the supplements, bad taste, side effects, inability to tolerate oral intake, etc.) These reasons will be clearly stated in the compliance case report forms.

The mean and standard deviation of the CCI at 90 days from the index operation will be estimated for each group, and the mean difference between groups will be estimated with its corresponding 95% CI. QoL scores will be summarized using means and corresponding standard deviations. Mean difference in the QoL scores between groups at one and 3 months will be estimated using linear models adjusting for baseline QoL scores.
**Ethical Consideration**
The study will be performed in accordance with the recommendations guiding physicians in biomedical research involving human patients by the 18\textsuperscript{th} World Medical Assembly, Helsinki, Finland, 1964. There are no perceived risks with respect to the carbohydrate loading, protein solution and immunomodulation solution as they are unlikely to interfere with the cancer. The supplements being used are classified as food products and as a result, there are no requirements in the Health Canada Food and Drug Regulations for this study. REB has approved the study protocol and documents prior to initiation. Written informed consent will be obtained from all patients prior to enrolment in compliance with ICH/GCP guidelines and the Research Ethics Board.

**RESULTS**

**Primary Outcome**
The primary outcome for each eligible patient will be defined as being randomized to intervention or placebo. The primary feasibility outcome will be one of the following: (1) Stop, main study non-feasible: estimated proportion of randomized patients <40%, (2) Continue with protocol modifications: estimated proportion of randomized patients between 40-59%, and (3) Continue without modification: estimated proportion of randomized patients equal or greater than 60%.

**Secondary Outcomes**
The secondary outcomes of the study will be defined as follows: 1) Compliance: Defined as intake of at least 70% of study intervention volume, 2) Overall Complications: Occurrence of any postoperative complication (major or minor) from surgery following each patient’s hospital stay and up to 90 days from the initial operation. Occurrence of any postoperative infections will also be calculated. 3) Comprehensive Complication Index (CCI) at 90 days from the index operation will be determined for each patient. This index can be calculated for each patient using the CCI online calculator [25, 29] following the grading of each postoperative complication according to Clavien-Dindo [30]. 4) QoL: The global health related QoL at baseline, 1 and 3 months following randomization measured using the EORTC-QLQ-C30 [31, 32] instrument and the FACT-G scale [33]. 5) Length of Hospital Stay will be determined for each patient. Compliance with the intervention is a secondary objective and will be taken into consideration for the success of its feasibility, as modifications on the protocol may be needed if compliance is poor. Compliance will be measured as the percentage volume of prescribed study intervention consumed, which will be measured by a patient diary in the preoperative period and nurses’ charts in the postoperative period. Postoperative complication (major or minor) will be determined following each patient’s hospital stay and up to 90 days from the initial operation. This is classified according to Clavien-Dindo [25, 30, 34].

**Adjudication**
An adjudication committee, consisting of two experts in field will review each patient’s complications using de-identified source documents including discharge summaries, operative reports, interventional radiology reports, imaging reports and microbiology reports, physician hospital and clinic progress notes as well as consultation notes from other physicians. The first adjudicator will review each complication, confirming that all reported complications are accurate, not duplicated and appropriately classified. Whenever there is agreement with the site
reported outcome, then the outcome is confirmed. If there is disagreement between the site and the first adjudicator, then the second adjudicator will review that particular file. Any disagreement will be resolved by consensus, either by agreeing with the site or with the first adjudicator. Variables recorded include: length of hospital stay, blood work results, microbiology data, operating room time, estimated blood loss, number of blood transfusions during surgery and during the hospital stay, and reoperations or readmissions. Each complication must be supported by source documents. The outcome assessment will follow strict criteria set by Clavien-Dindo [25, 30, 34] and the Comprehensive Complication Index [25, 30]. The outcome assessors will undergo adjudication training.

Adverse Events
The study will be conducted according to the International Conference of Harmonization (ICH) and Good Clinical Practice (GCP) consolidated guidelines. Currently, there are no foreseeable risks in administering nutritional supplements to patients who meet the eligibility criteria. Nutritional supplements are safe when used by adults as instructed [35, 36]. If an adverse event occurs during the study and is deemed related to the administration of the study treatment, this will be reported using Version 4.0 of the Common Terminology Criteria for Adverse Events (CTCAE) (Multimedia Appendix 1) [37]. This data will be collected from the first administration of treatment until the last study visit.

The investigational food products are ISOlution® (whey protein isolate), INergy-DFL® (immunonutrition), and PreCcovery® (carbohydrate loading). AEs will be considered related to study product if they are deemed to be related specifically to administration of ISOlution®, INergy-DFL®, and PreCcovery®.

Worsening of gastrointestinal cancer is expected and therefore will not be considered an AE for the purpose of this study. Deaths due to gastrointestinal cancer are Outcome Events and will not be reported as AEs.

Scientific Reporting and Publication
The Steering Committee is responsible for the scientific reporting, publishing and/or presentation of the study results. All investigators participating in this study must agree to delegate the primary publication or presentation responsibility to the Steering Committee. Any other publication or presentation related to the study and the results by any investigator or participant must receive prior approval from the Steering Committee. No other publication or presentation is allowed before the primary publication or presentation by the Steering Committee. Authorship will be determined by the Steering Committee. The information developed during the conduct of this study is considered confidential.

The timeline for the study can be found in Table 2. We obtained Research Ethics approval from our local Research Ethic Board (HiREB) in December 2017. We aim to recruit 50% of the patients by September 2018. The estimated study completion date is February 2020.
Table 2. The Study Timeline

<table>
<thead>
<tr>
<th>Planned Completion Date</th>
<th>Study Goals</th>
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<tbody>
<tr>
<td>December 2017</td>
<td>Attain REB approval and begin recruiting patients</td>
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<tr>
<td>September 2018</td>
<td>Have 50% of participants enrolled in the study (n=50)</td>
</tr>
<tr>
<td>June 2019</td>
<td>Complete study enrolment - Have 100% of participants enrolled in the study (n=100)</td>
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<tr>
<td>June 2019 - September 2019</td>
<td>Complete final follow-up visits</td>
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<tr>
<td>October 2019 – December 2019</td>
<td>Complete final statistical analysis and begin preparing manuscript</td>
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<tr>
<td>February 2020</td>
<td>Have final manuscript completed and ready for publication</td>
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DISCUSSION

Many patients in Ontario undergo surgery for gastrointestinal cancer each year. These surgeries are often associated with postoperative morbidity and infectious complications. Therefore, it is crucial to actively take steps to aid in recovery and improve patient quality of life through perioperative optimization. Despite the debate on the role of perioperative nutritional supplements in improving post-surgical outcomes, we feel there is enough clinical interest in the surgical community to support a well-designed, randomized controlled trial addressing this question. The study will provide the quality preliminary evidence for perioperative nutritional supplements, determine the feasibility of recruitment, randomization and compliance, therefore providing the necessary information to design a phase III trial if the results of the study are favourable.
Acknowledgements
The study is funded by the JHCCF (Juravinski Hospital and Cancer Centre Foundation).

Conflict of Interests
PES, SP, SN, LR, MS, OL, ED, CR have no conflict of interest.

Multimedia Appendix 1
Common Terminology Criteria for Adverse Events (CTCAE) v4.0
References


Advisory Group (MAG), a Standing Committee of BAPEN. 2003;Redditch, Worcs(BAPEN).


**Abbreviations**

CI: Confidence of Interval  
CCI: Comprehensive Complication Index  
CRF: Case Report Form  
CTCAE: Common Terminology Criteria for Adverse Events  
DHA: Docosahexaenoic Acid  
DIAAS: Digestible Indispensable Amino Acid Score  
ERAS: Enhanced Recovery After Surgery  
EORTC-QLQ: European Organization for Research and Treatment of Cancer- Quality of life Questionnaire  
FACT-G: Functional Assessment of Cancer Therapy-General  
GCP: Good Clinical Practice  
ICH: International Conference of Harmonization  
IFN: Interferon  
IL: Interleukin  
IRIS: Interactive Registration and Randomization System  
JHCC: Juravinski Hospital and Cancer Centre  
MUST: Malnutrition Universal Screening Tool  
OCOG: Ontario Clinical Oncology Group  
PReSS: Pharmacy Research and Support Services  
QoL: Quality of Life  
REB: Research Ethic Board  
Th: T helper
Table 1. Schedule of Study Procedures

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<th>STUDY PROCEDURE</th>
<th>Screening</th>
<th>Baseline</th>
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<th>Follow-Up 1</th>
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QOL = Quality of Life Assessment  
POC = Postoperative Complication Assessment  
MUST = Malnutrition Universal Screening Tool  
HRU = Health Resource Utilization Assessment  
OR = Operating Room (Index Surgery)
Figure 1. Study Schema

QOL = Quality of Life Assessment
HRU = Health Resource Utilization Assessment
POC = Postoperative Complication Assessment
OR = Operating Room (Index Surgery)
MUST = Malnutrition Universal Screening Tool

Resectable Gastrointestinal Cancer with Planned Resection

Assessment of Eligibility

Inclusion in the Study

1. Baseline QOL
2. MUST Score
3. Consent

Placebo

Randomization

Intervention

Placebo up to 30 days prior to OR

HRU 15 days prior to OR

HRU and Placebo 6 days prior to OR

Placebo Day Prior and Day of Surgery

Placebo for 5 Days after OR

QOL, POC, Weight
Postop F/U #1 at 4 weeks 1 after OR

QOL, POC
Postop F/U #2 (12 weeks 2 after OR)

ISOlution up to 30 days prior to OR

HRU 15 days prior to OR

HRU and INergy 6 days prior to OR

PRECovery Day Prior and Day of Surgery

INergy for 5 Days after OR

QOL, POC, Weight
Postop F/U #1 at 4 weeks 1 after OR

QOL and POC
Postop F/U #2 (12 weeks 2 after OR)