Trials

STUDY PROTOCOL

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Time to return of bowel function following perioperative probiotics in colorectal cancer surgery (PICCS-1): study protocol for a randomized controlled trial

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Abstract

Background Postoperative ileus occurs in up to 30% of patients following major oncologic surgery for colorectal cancer, leading to significant morbidity, patient distress, as well as increased utilization of healthcare resources. Various modalities to reduce postoperative ileus rates have been explored. One such modality is the perioperative administration of probiotics which have hitherto achieved inconsistent success. Here, we design a trial to determine whether the perioperative administration with probiotics given together with nutritional supplementation can help to reduce postoperative ileus rates.

Methods We propose a parallel three-arm randomized controlled trial. In Arm 1, no nutritional supplementation is provided to the patient. In Arm 2, Nestle Isocal is provided to the participant. Nestle Isocal provides nutritional supplementation but without any probiotic. In Arm 3, Nestle Boost Optimum is provided to the patient. Nestle Boost Optimum contains a similar nutritional profile to Isocal, but with the addition of *Lactobacillus paracasei*. The primary outcome is the time to first bowel movement in days from the day of surgery. Secondary outcomes are time to first flatus, infective complications, and adverse events related to the administration of nutritional supplementation. Statistical analysis will be conducted in an intention-to-treat approach. ANOVA with the Tukey test will be used to compare continuous variables, while the χ^2 test will be used for categorical variables.

Discussion Nutritional supplementation with probiotics is a convenient, non-pill alternative for patients. Furthermore, the interventions are commonly found in the formulary of many hospitals worldwide. If successful, probiotics in nutritional supplementation could be a cost-effective and simple way to reduce postoperative ileus.

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Thai Clinical Trials Registry TCTR20240706003. This trial was registered on 6 July 2024.

Keywords Colorectal cancer, Colorectal surgery, Nutritional supplementation, Probiotics, Time to bowel movement, Time to flatus, Length of stay, Complications

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Introduction

Background and rationale {6a}

Prolonged ileus following colorectal surgery (CRS) is a common complication that affects 10 to 30% of patients [1–3], resulting in prolonged hospital length of stay [4], and increased hospitalization costs [5]. This complication may also necessitate discomforting interventions to the patient, such as the insertion of a nasogastric tube [6]. More seriously, prolonged ileus could result in aspiration pneumonitis, leading to antibiotic therapy, ventilatory support in the intensive care, potentially resulting in a patient's demise [7]. Due to the seriousness of prolonged ileus, various modalities to reduce its incidence have been considered.

Modalities to reduce the incidence of postoperative ileus after CRS have ranged from simple dietary modifications to the use of pharmacologic agents, each with varying efficacy. One study by Wang et al. demonstrated that early oral feeding within 24 h of surgery was associated with a shorter hospital stay (WMD − 1.76; 95% CI − 2.32 to − 1.21, $p < 0.01$), but this was however associated with both increased nasogastric tube reinsertion (OR 1.69; 95% CI 1.08 to 2.64, $p = 0.02$) and overall complications (OR 0.49; 95% CI 0.37 to 0.65, $p < 0.01$) [8]. The consumption of coffee in the postoperative period has also resulted in mixed results in reducing ileus. Several systematic reviews and meta-analyses have revealed a reduction in the overall time to defecation [9–12], but without a concomitant reduction in the overall length of hospital stay [10, 11]. Furthermore, some patients in the general population might not be coffee drinkers. The impact of sham feeding by means of providing chewing gum to the patient has yielded much more favorable results with a number of systematic reviews confirming its efficacy [13, 14]. Overall, sham feeding appears to reduce the incidence of postoperative ileus by 11% to 59%, resulting in a statistically significant reduction in time to first flatus from − 20.78 and − 8.81 h, and time to defecation by − 33.25 and − 15.4 h [15]. Regarding the administration of pharmacologic agents, the selective opioid antagonist alvimopan provided at both 6 mg and 12 mg doses has been shown to reduce time to recovery of bowel movement, passage of flatus, and toleration of solid foods (GI-3) with HR 1.28; $p = 0.001$ and HR 1.38; $p < 0.001$ respectively, and time to discharge with HR 1.36; $p < 0.001$ and HR 1.43; $p < 0.001$ respectively [16]. More recently, the PyRICo Trial established that the administration of pyridostigmine resulted in a reduction in time to first stool passage and tolerance of oral diet by one day (median 2 vs 3 days; $p = 0.015$) although this did not result in a decrease in hospital stay (median 5 vs 5; $p = 0.921$) [17].

In tandem with our increased understanding of how the intestinal microbiota may contribute to disease, there has been renewed interest in probiotics to alter the intestinal microbiota with the aim of modulating disease patterns and outcomes. In colorectal cancer (CRC), many probiotic strains have been postulated to reduce the proliferation of cancer, including *Levilactobacillus brevis* [18], *Lactobacillus reuteri* [19], and *Lactococcus lactis* [20], just to name a few. Within clinical practice, probiotics have been well proven to reduce infective complications. One meta-analysis of 10 randomized controlled trials (RCTs) demonstrated a decrease in the incidence of surgical site infection (OR 0.44; 95% CI 0.22 to 0.89; $p = 0.023$) in the probiotic group [21]. Another meta-analysis that investigated the effect of probiotic administration on a range of elective abdominal surgeries similarly concluded a protective effect amongst a composite of all infective complications (RR 0.65; 95% CI 0.53 to 0.80; $p < 0.0001$) [22]. This result was similar to yet another meta-analysis which demonstrated a reduction in time to first flatus (MD, − 0.53 days), first defecation (MD, − 0.78 days), first solid diet (MD, − 0.25 days), first fluid diet (MD, − 0.29 days), postoperative hospital stay (MD, − 1.43 days), as well as a reduction in the incidence of abdominal distension (RR, 0.62), and postoperative ileus (RR, 0.47) with symbiotic or probiotic use [23].

While there is little equipoise regarding the effect of probiotic administration to reduce infective complications, there is significantly greater uncertainty regarding its impact in modulating postoperative ileus after CRC surgery. An RCT conducted by Tan et al. in patients undergoing elective CRC surgery with *Lactobacillus acidophilus*, *Lactobacillus casei*, *Lactobacillus lactis*, *Bifidobacterium bifidum*, *Bifidobacterium longum*, and *Bifidobacterium infantis* demonstrated a reduction in time to return of gut function (108.5 vs 156.5 h; $p = 0.021$) and duration of hospital stay (6.5 vs 13 days; $p = 0.012$) in treatment versus placebo groups [24]. In another RCT in patients undergoing elective CRS by Kotzampass et al. which administered a four-probiotic regimen comprising of *Lactobacillus acidophilus* LA-5 (1.75×10^9 cfu), *Lactobacillus plantarum* (0.5×10^9 cfu), *Bifidobacterium lactis* BB-12 (1.75×10^9 cfu) and *Saccharomyces boulardii* (1.5×10^9 cfu), the authors noted a statistically significant reduction in time to first bowel movement ($p < 0.0001$), time to first defecation ($p < 0.0001$) and time to hospital discharge ($p < 0.0001$), although this study was powered for infective complications and not ileus [25]. Other RCTs have conversely revealed no statistically significant difference between experimental and placebo groups for ileus. In one RCT conducted by Park et al. [26], participants were randomized to a placebo powder or a probiotic powder consisting of three probiotic

strains, *Bifidobacterium animalis* subsp. lactis HY8002 (1×108 cfu), *Lactobacillus casei* HY2782 (5×107 cfu), and *Lactobacillus plantarum* HY7712 (5×107 cfu). The authors observed no difference in ileus rates between experimental and placebo groups (0 vs 1; RR 0.34; 95% CI 0.01 to 8.13; $p>0.05$). In another RCT by Yang et al. [27] in which elective CRC patients were subjected to *Bifidobacterium longum* ($\geq 1.0\times10^7$ cfu/g), *Lactobacillus acidophilus* ($\geq 1.0\times10^7$ cfu/g), and *Enterococcus faecalis* ($\geq 1.0\times10^7$ cfu/g), there was likewise no difference in time to first solid diet (4.87 vs 5.00; $p=0.544$) or duration of hospital stay (15.86 vs 15.00; $p=0.487$) between experimental and placebo groups. Several RCTs investigating the use of probiotics in CRS did not report ileus as an outcome measure [28–31].

Results from the above trials demonstrate a lack of conclusive evidence regarding the role of probiotics in reducing postoperative ileus, perhaps owing to differences in the probiotic regime. These differences not only stem from the different probiotic strains being administered to patients, but also differences in the duration of probiotic administration and dosage. In fact, the probiotic administration route is a key consideration in the design of this trial, leading to our selection of *Lactobacillus paracasei* ,as this strain is present in currently commercially available nutritional supplementation. We considered that probiotics found within nutritional supplementation could lead to increased compliance and uptake. Many of these RCTs were also conducted with low patient numbers. Given the proven safety of probiotic administration in CRC surgery from studies investigating infective complications as the primary outcome, and the relative ease and low cost of administration should probiotics be shown to be effective in reducing postoperative ileus rates, we propose our RCT, the PICCS-1 Trial, to evaluate the efficacy of perioperative administration of probiotics in reducing postoperative ileus rates in patients undergoing elective laparoscopic CRS. We hypothesize that the administration of probiotics in the perioperative period can lead to a reduction in the duration of postoperative ileus.

Objectives {7}

The primary objective of this trial is to determine whether the administration of probiotics taken as an oral nutritional supplement one week before surgery, and for one week after surgery, can result in a reduction in the time to first bowel movement, measured in days, following CRC surgery. Secondary outcomes include the time to first flatus, length of hospital stay from the time of surgery, as well as rates of surgical site infection and anastomotic dehiscence.

Trial design {8}

This trial is an investigator-initiated, single-centre, triple-blinded, parallel-designed, superiority RCT in which there are three arms in total, each allocated in a 1:1:1 ratio. Results will be analyzed in an intention-to-treat approach. Figure 1 shows the overall participant's involvement in this trial as per CONSORT guidelines.

Methods: participants, interventions, and outcomes

Study setting {9}

This trial will be conducted at the National University Hospital, Singapore, an academic medical center affiliated with the National University of Singapore.

Eligibility criteria {10}

Patients will be eligible to be recruited into the study if they meet all the following inclusion criteria:

a. Undergoing elective CRC surgery in which an oncologic resection is planned
b. Age between 21 and 99 years at the time of consent
c. Willing to consider oral nutritional supplementation
d. On our institution's enhanced recovery after surgery (ERAS) pathway [32]
e. Able to provide informed consent

Exclusion criteria for this study include the following:

a. Patients with known contraindications to probiotic use
b. Patients undergoing emergency surgery
c. Taking any other form of probiotics within one month
d. Taking oral antibiotics within 7 days of commencement of study
e. Vulnerable patients including pregnant patients, inmates, and those who are cognitively impaired and therefore are not able to provide informed consent.

Prior to surgery, participants will be responsible for administering the nutritional supplement to themselves, with clear instructions having been provided to them. Post-operatively, this will be administered in the ward by the nurses involved in the clinical care of the patient.

Who will take informed consent? {26a}

Patients identified by their surgeons will inform the study team about the potential recruitment of a participant into the trial. A pool of predetermined research assistants who have been trained by the Principal

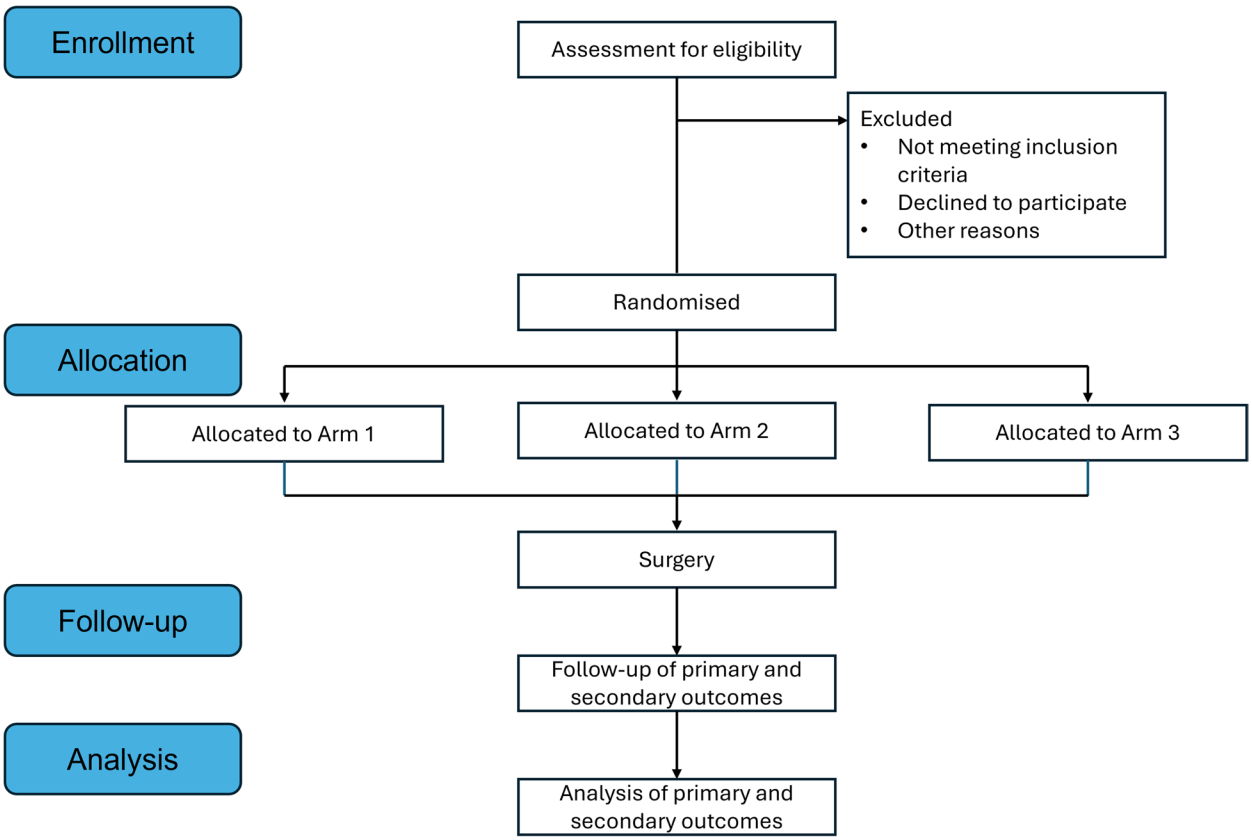

Fig. 1 Flowchart showing the participant's involvement in this trial as per CONSORT guidelines

Investigator on the intricacies of this trial will take informed consent from the patient.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

Consent will also be obtained to collect data relating to the participant's demographics, clinical characteristics, operative details, as well as postoperative recovery. No biological specimens will be collected, and hence, no consent will be obtained for the collection of biological specimens.

Interventions

Explanation for the choice of comparators {6b}

This trial comprises of three arms. Arm A is the first control arm, in which no additional nutritional supplementation is administered to the participant. This arm constitutes current standard care. Arm B is the second control arm, in which participants receive Nestle Isocal, and Arm C is the experimental arm, in which participants receive Nestle Boost Optimum. Boost Optimum contains the probiotic *Lactobacillus paracasei*.

Nutritional supplements in the form of Isocal and Boost Optimum were chosen because these represent nutritional supplements which are readily available in the hospital formularies of most hospitals in Singapore and worldwide. They are therefore approved for administration to patients and have an established safety profile as a nutritional supplement, compared to probiotic pills or tablets, which might need to undergo additional regulatory body approval. Our trial seeks to investigate the use of probiotics in reducing the duration of postoperative ileus. We therefore needed to have control groups consisting of.

a. Not having any nutritional supplementation at all (Arm A)
b. Nutritional supplementation but lacking the probiotic agent (Arm B—Nestle Isocal).

Furthermore, Isocal and Boost Optimum have almost equivalent nutritional ingredients, therefore allowing Isocal to be an effective control for Boost Optimum (Table 1). Both are also available in a powder form, and the manufacturer Nestle has agreed to help with randomization by providing the powder in unmarked tins.

Table 1 Comparison of nutritional contents between Isocal and Boost Optimum

	Isocal (per 56 g powder)	Boost optimum (per 55 g powder)
Energy (kcal)	263.2	245
Total fat (g)	11.0	9.6
Cholesterol (mg)	-	13.8
Omega 6 (mg)	-	1.5
Omega 3 (mg)	-	0.3
Protein (g)	8.6	10.2
Carbohydrate (g)	33.0	29.4
Fibre (g)	0.0	2.8
Total sugar (g)	-	6.0
Sodium (mg)	131.6	115.0
Vitamin A (μg)	197	245
Vitamin B1 (mg)	0.5	0.5
Vitamin B2 (mg)	0.6	0.5
Vitamin B3 (mg)	6.6	1.9
Vitamin B5 (mg)	3.3	1.8
Vitamin B6 (mg)	0.7	0.7
Vitamin B9 (μg)	52.6	72.0
Vitamin B12 (μg)	2.0	0.7
Vitamin C (mg)	39.4	21.2
Vitamin D (μg)	1.3	3.5
Vitamin E (mg)	6.6	5.2
Vitamin K (μg)	32.9	22.0
Biotin (μg)	39.2	9.0
Choline (mg)	65.7	115.5
Calcium (mg)	157.9	275.0
Phosphorus (mg)	131.6	146.0
Potassium (mg)	328.7	377.0
Manganese (μg)	657.4	0.5
Copper (μg)	263.2	0.3
Chromium (μg)	-	15.4
Iron (mg)	2.4	3.5
Iodine (μg)	19.6	40.0
Zinc (mg)	2.6	2.6
Selenium (μg)	-	12.4
Magnesium (mg)	52.6	55.0
Molybdenum (μg)	-	19.3
Chloride (mg)	263.2	151.0
Probiotics (CFU)	None	*Lactobacillus paracasei*, 550 million

Intervention description {11a}

Interventions for participants who have been randomized to either Arms B or C will undergo the same regime. The participant will be provided with a tin of unmarked powder which will constitute either Isocal or Boost Optimum. Participants will consume one serving, or 55 g, of powder dissolved in 210 ml of water twice per day. This will commence one week before the date of surgery. On the day of surgery, no nutritional supplementation will be consumed by the participant. The day after surgery, the nursing staff looking after the participant will be responsible for administering the nutritional supplementation. Again, this will involve one serving, or 55 g, to be served once per day during the lunch meal service, for another seven days.

Criteria for discontinuing or modifying allocated interventions {11b}

Given that the nutritional supplements are not pharmacologic agents, the likelihood of harm arising directly from the nutritional supplement is unlikely. However, one common complaint following the consumption of probiotics may be abdominal bloatedness. If the study team is informed, we would advise the participant to stop consuming the nutritional supplement. As we have planned this trial to be analyzed in an intention-to-treat format, we will continue to observe our primary and secondary outcomes. We will also note the occurrence of bloatedness as a potential side effect of the intervention.

In addition to the above, the intervention may be discontinued either at the participant's request or if a change in the participant's postoperative recovery necessitates strict oral fasting. For example, this could occur if the participant develops an anastomotic dehiscence and requires a return to the operating theatre. In such cases, the participant's nutritional supplements would be stopped.

Strategies to improve adherence to interventions {11c}

The study team will emphasize the safety of taking the intervention and also discuss the potential health benefits of taking the intervention, given that the intervention is in fact a nutritional supplement that could improve the nutritional status of the participant prior to surgery. In addition, the study team will drop the participant a text message daily to remind the participant about compliance to the trial intervention.

Relevant concomitant care permitted or prohibited during the trial {11d}

All patients in our institution presenting for colorectal cancer surgery in our institution are enrolled in an

ERAS program, which has been detailed elsewhere previously [32]. All patients are also reviewed by an anesthetist 1 week prior to surgery at the anesthesia outpatient clinic for optimization of patient comorbidities. Diabetic patients are encouraged to comply with a low sugar diet and to maintain tight sugar control prior to surgery. Sodium-glucose cotransporter-2 (SGLT2) inhibitors are withheld 48 h prior to surgery. Hypertensive patients are also encouraged to comply with a low sodium diet and to maintain good blood pressure control prior to surgery. Anti-hypertensives are consumed on the day of surgery, except for calcium channel blockers.

All required clinically appropriate investigations and treatments as deemed by the managing clinical team will be permitted during the trial. This includes and is not limited to, the use of intravenous blood products or fluids, surgical or radiological interventions, as well as other pharmacologic drugs.

The administration of another probiotic during the trial is prohibited. This includes probiotics administered in the form of a tablet, or as a health supplement/drink.

Provisions for post-trial care {30}

No post-trial care has been organized for this trial. The primary and secondary outcomes will be collected at the point of discharge from the hospital, and no further follow-up is required. However, as these participants are CRC patients who have undergone major CRS, they will continue to receive the appropriate post-operative and oncologic care that they require by their managing clinicians. Any patient who suffers from an adverse effect is covered by the National Clinical Trials Insurance initiated by the Singapore Ministry of Health Holdings.

Outcomes {12}

This trial is designed to compare the effectiveness of probiotic administration perioperatively in reducing the incidence of postoperative ileus. Hence, the primary outcome of this study is the time to first bowel movement, measured in days from the day of surgery. This is an objective measurement that is recorded in the clinical charts and hence, subjected to less bias. First bowel movement is defined as the first episode in which solid stool is passed. The secondary outcomes are time to first flatus, and length of hospital stay, both measured in days from the day of surgery. We opted not to include time to first flatus as the primary outcome because the passage of flatus cannot be physically evidenced, as opposed to a bowel movement. We also opted not to use the length of hospital stay as this could be prolonged due to factors unrelated to postoperative ileus, such as social care situations following discharge, or the long waiting times for step-down community resources faced in our healthcare system. We also plan to collect the incidence of infective complications, which can be subdivided into surgical site skin infection, anastomotic dehiscence, and other non-surgical infections including urinary tract infection, and pneumonia. An infection is defined as a condition that necessitates the commencement of either oral or parenteral antibiotic therapy through clinical observation. Finally, adverse events relating to probiotic use will be recorded, and this includes symptoms of diarrhea, nausea, constipation, abdominal distension, and abdominal cramps [22].

Participant timeline {13}

The timeline for enrolment, intervention, and completion of the trial can be found in Fig. 1.

Sample size {14}

Sample size calculation was performed based on the primary outcome, which was the time to defecation measured in days from the day of surgery. Based on a previous study by Yang et al. [27], the difference in the mean time to defecation between treatment and control was given as 0.66 days, with the mean time to defecation of the control having a standard deviation of 1.11 days. With a power of 80% and an α level of 0.05, and assuming a dropout rate of 20%, we estimate that we would require 54 participants in each arm, therefore leading to the recruitment of 162 participants in total. Power calculation was performed using the pwr package on *R* with a two-sample *t*-test power calculation. An interim analysis will be undertaken after 20 participants have been recruited in each arm.

Recruitment {15}

The study site is a busy academic medical center that performs more than 300 resections for CRC annually. This recruitment target of 162 patients is well within the annual number of patients and should be achievable. In addition, participants will be followed up by the study team regularly to ensure compliance to the intervention modality. It will also be emphasized to participants at the point of recruitment that the interventions are nutritional supplements which can also aid in ensuring adequate nutrition in preparation for major oncologic surgery. To reduce recruitment bias, all patients who will undergo colorectal resection for cancer in the institution will be approached for informed consent and recruitment to the trial.

Assignment of interventions: allocation

Sequence generation {16a}

A research coordinator (RC) will assist with the randomization. The RC is solely responsible for the randomization process, as well as holding a master copy of

the intervention assigned to each participant should the need for unblinding due to adverse events occur. The RC will have no direct contact with any participants. A computer-generated sequence will be used for randomization.

Concealment mechanism {16b}

The RC will be solely responsible for the randomization process including the concealment of the sequence. After obtaining a computer-generated sequence, the RC will record the randomization sequence into sealed envelopes, to which only the RC has access to. The RC will hold a mobile phone so as to be contactable when a participant has been recruited. The RC will then retrieve the next sealed envelope, open the envelope, and record the randomization on a master list. The RC will be the only person with access to this master list.

Implementation {16c}

All potential participants will be screened for eligibility. Eligible participants will be recruited. A phone call will be made to the RC in charge of randomization. If the participant has been randomized to Arm 1, the RC will inform the medical team managing the patient. This segment of the trial is unblinded. If the participant is instead assigned into either Arms 2 or 3, the RC will pass an unmarked tin containing either Isocal or Boost Optimum to the medical team, who will then instruct the participant on how to consume the nutritional supplement. This segment of the trial is blinded to the patient, the medical team, as well as to the research team who will assist with outcome collection.

Assignment of interventions: blinding

Who will be blinded {17a}

With respect to Arm 1 of the trial, trial participants and the medical team will not be blinded. This is because participants in Arm 1 do not receive any nutritional supplementation. However, there will be blinding to the outcome assessors as well as to data analysts.

Between Arms 2 and 3, there will be blinding to the participant, medical team, outcome assessors as well as data analysts. This is facilitated by obtaining unmarked tins of either Isocal or Boost Optimum directly from Nestle. Nestle has used the same tins to store both types of supplementations and the unmarked tins are indistinguishable from each other. There is also no difference in taste between Isocal and Boost Optimum.

The randomization scheme will be hidden from the trial participants and the medical team to minimize the risk of inadvertent unblinding. Furthermore, the unblinded outcome assessors and data analysts will ask questions as per the data collection form in a matter-of-fact fashion which avoids asking leading questions that could hint at the intervention.

Procedure for unblinding if needed {17b}

At the point of randomization and allocation, the RC will keep a master list of the allocation of each participant. Only the RC will have access to this list. Unblinding will only occur under the following circumstances:

1. The participant requests to withdraw from the study and seeks to know what intervention he or she was assigned to
2. The participant suffers from an adverse event for which the treating medical team believes could be related to the intervention.

All unblinding events will be documented. In concordance with our institution's safety protocols, unblinding due to safety events must be relayed expediently to the DSRB. All such events will also be discussed by the trial's Data Monitoring Committee. Changes to the protocol as a result of such events will require a cessation of trial recruitment and a formal application for a protocol amendment to the DSRB.

Data collection and management

Plans for assessment and collection of outcomes {18a}

Given that most patients are admitted to the hospital only on the day of surgery, data collection will commence from post-operative day (POD) one. In order to evaluate compliance to the nutritional supplementation prior to hospital admission, a daily text message reminder will be sent to the participant to remind the participant of the need to consume the nutritional supplement. The study team will utilize a standardized Data Collection Form (DCF), which can be found as a supplementary document to this protocol. The study team will follow up on any pre-operative adverse events relevant to this trial on POD1. Thereafter, the study team will check on recruited participants once daily for any bowel movement, flatus, infective complications, and adverse events. The study team will also record the date of discharge from the hospital. These data will be used to obtain the primary and secondary outcomes of this trial.

Plans to promote participant retention and complete follow-up {18b}

Given that all participants are also patients who are undergoing surgery for CRC, it is not likely for participants to drop out from the study, unless they express a desire to withdraw their consent to participate in this study. Furthermore, there is also no lengthy follow-up procedure and the participant's involvement in the trial concludes at the point

of discharge. For these reasons, we do not anticipate there to be a significant problem with participant retention.

However, if there are dropouts from the trial, to preserve the integrity of the final data analysis, any data collected prior to the point at which a participant chooses to withdraw from the study will still be analyzed. Finally, data will be analyzed based on an intention-to-treat approach, and hence any outcomes affected by deviations will still be included in our final analysis. This reflects the real-world scenario in which patients would need to administer the nutritional supplementation by themselves before surgery. This issue is less likely to occur in the post-operative stage as the supplements will be administered by the nursing team looking after the patient.

Data management {19}

All trial data will first be recorded on the DCF, which can be found as a supplementary material to this protocol. This is to facilitate ease of recording. Thereafter, this data will be entered onto an electronic database. This database will be password protected and will only be accessible to the study team. The transcribing of data from the DCF to the electronic database will first be done by one study team member and checked by a second study team member. The original DCFs will be filed and will not be discarded.

Confidentiality {27}

All participants will be identified by a unique trial number both on the DCF and on the electronic database. Patient identifiers will not be recorded. The hardcopy DCFs will be stored in the Principal Investigator's office once they have been transcribed onto the electronic database. This office is locked and only the PI possesses the key. The electronic database will be password encrypted, and the password will only be shared with the study team members. In line with our institution's data management policies, data must be retained for at least seven years from the completion of the study. After this period, the DCFs will be destroyed, and the electronic database will be erased.

Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

No biological specimens will be collected in this trial.

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

The primary and secondary outcomes are as defined in {12}. The primary outcome of time to the first bowel movement is a continuous outcome. Summary statistics including the number of participants, mean, SD, minimum, and maximum quartiles will be calculated. Analysis of variance (ANOVA) will be used as an initial test for comparison of means across all three arms. Subsequently, Tukey's test will be used to perform pairwise comparisons across two arms.

The secondary outcomes comprise both continuous and categorical outcomes. Continuous outcomes will be compared between intervention groups as above. For categorical outcomes, summary statistics including the number of participants, and the proportion of outcome will be calculated. Differences in proportions of secondary outcomes will be compared using χ^2 test, with a 95% CI.

Interim analyses {21b}

An interim analysis will be conducted after 20 participants in each arm of the trial have been recruited. This interim analysis will be conducted by the study team and led by the PI. The trial will be terminated if there is a statistically significant increase in intervention-related adverse events between the treatment and the control groups.

Methods for additional analyses (e.g., subgroup analyses) {20b}

There are no plans to conduct subgroup analyses presently. However, if demographic and baseline factors differ between intervention arms, an analysis of covariance (ANCOVA) may be undertaken.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

Data collected will be analyzed in an intention-to-treat manner to reflect the real-world scenario where patients are required to consume nutritional supplementation before and after surgery. Hence, protocol non-adherence will be analyzed based on the assigned treatment arm at the point of randomization.

Every attempt should be made to minimize missing data. Imputation will not be performed for missing data.

Plans to give access to the full protocol, participant-level data and statistical code {31c}

The complete study protocol will be released upon reasonable request to the PI.

Oversight and monitoring

Composition of the coordinating center and trial steering committee {5d}

A trial steering committee comprising the PI, and the study team assisting with the consent taking, recruitment of patients, and collection of data will be formed. This team oversees the day-to-day running of the trial. This committee will meet once every 2 months to ensure that

processes have been complied with, and to identify any difficulties in the organizational set-up of the trial.

Composition of the data monitoring committee, its role and reporting structure {21a}

A data monitoring committee (DMC) comprising the PI, and staff involved in the collection of data will be formed. This DMC will meet to review issues relating to the collection of data. This may include safety issues relating to the interventions, any missing data, or difficulties relating to the collection of data. This DMC is independent of the study sponsor, who will not be made known of the results until they have been wholly analyzed.

Adverse event reporting and harms {22}

All AEs occurring during the trial that are observed by the study team or reported by the participant will be recorded and reported to the DSRB overseeing the trial. An AE is defined by the DSRB as "any untoward or unfavorable medical occurrence in a patient or clinical investigation subject administered with a pharmaceutical product and which does not necessarily have a causal relationship with this treatment". The following information will be reported to this DSRB: description, date of onset and end date, severity, assessment of relatedness to trial intervention, other suspect drugs or devices, and action taken. Follow-up information should be provided as necessary. The severity of events will be assessed on the following scale: 1 = mild, 2 = moderate, 3 = severe. Again, we take direction from the DSRB on the grading of severity. A severe AE is defined as "any untoward medical occurrence which (a) results in or contributes to death, (b) is life-threatening, (c) requires inpatient hospitalization or prolongation of existing hospitalization, (d) results in or contributes to persistent or significant disability or incapacity, or (e) results in or contributes to a congenital anomaly or birth defect."

It will be left to the PI's clinical judgment to decide whether or not an AE is of sufficient severity to require the participant's removal from treatment. A participant may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable AE. If either of these occurs, the participant must be given appropriate care under medical supervision until symptoms cease and the condition becomes stable. This medical care will be provided by the medical team of the participant. The Investigator will arrange for follow-up visits or telephone calls with the participant.

Frequency and plans for auditing trial conduct {23}

In our institution, trial conduct is audited by the Research Office (RO). This RO is independent of the study investigators and the sponsor. The RO may conduct audits in an unplanned manner to ensure that there is constant compliance to the ethical responsibilities of the trial to its participants. The RO is headed by the institution's Director of Research, who is independent from this project.

The trial steering committee will also conduct further checks to ensure that protocols associated with informed consent taking, the administration of the intervention, as well as the collection of data, is adhered to. As discussed, the trial steering committee will once every two months. In addition, the Data Monitoring Committee meets to ensure that there are no safety issues related to the intervention and that if any safety issues are found, are reported to the regulatory authority, and remedied. This Data Monitoring Committee also meets once every 2 months. Should any breaches be found, this will be reflected in the trial's breach report form.

Plans for communicating important protocol amendments to relevant parties (e.g. trial participants, ethical committees) {25}

All protocol amendments must be made to the DSRB before such amendments can be realized in the running of the trial. The PI is responsible for communicating these amendments to the DSRB and for seeking approval for the amendments. Following approval by the DSRB to make the stated amendments, the PI will relay the amendments to the study sponsor and then to the study team. A copy of the newly amended protocol will be sent to the study site and filed for reference. The PI will reflect these amendments by updating the protocol's date and version. All amendments must also be elaborated in the protocol, and clinical trial registries will also be updated to reflect the amendments.

Dissemination plans {31a}

Results obtained from this study may be presented in scientific conferences, professional meetings, and may also be published in peer-reviewed journals. Results from this trial may also be disseminated via mass and social media to the public. All data presented would have undergone statistical analysis. No individually identifiable data will be disseminated.

Patient and public engagement

There was no patient or public engagement related to the design of this trial.

Discussion

Modalities to reduce postoperative ileus can directly improve patient outcomes, while reducing hospital bed utilization and healthcare costs associated with longer hospital stays. The principal strength of the experimental intervention in our trial is that the probiotic is

embedded within a readily available nutritional supplement. Should this trial be successful in demonstrating a reduction in postoperative ileus rates, providing patients with Boost Optimum would be easy to achieve, given the availability of Boost Optimum as a nutritional supplement in many hospitals within Singapore, and worldwide. Having the probiotic as a component of nutritional supplementation could also increase compliance, given that nutritional supplementation is itself a key component of perioperative optimization prior to major surgery [33]. Patients would therefore not be required to take an additional pill or tablet containing the probiotic. Such a modality could also be easily incorporated into existing ERAS protocols and therefore is both highly practical, as well as scalable.

In spite of this, we foresee that one major limitation of our experimental design is the need for participants to be responsible in consuming the nutritional supplement in the seven days preceding surgery. Therefore, a lack of efficacy in our interventional arms (Arms 2 and 3) could represent either a true lack of efficacy arising from the intervention or simply poor compliance to the protocol in the 7 days preceding surgery. It was for this reason that we introduced Arm 1. Arm 1 represents a control in which no nutritional supplement is provided. Given the strong evidence supporting the use of probiotics in reducing postoperative infective complications, we therefore conceived of Arm 1 as an internal check that would allow us to ascertain if compliance to our protocol was poor. Put differently, should the infective complication incidence in Arms 2 and 3 be insignificantly different from Arm 1, we might guess that compliance with our protocol was poor.

Other limitations that the authors acknowledge include limitations relating to the single-center design,

Assessing compliance with our protocol is a key factor in this trial. There exists significant heterogeneity regarding not only the probiotic strain, but also the various dosing regimens of the probiotic within the literature. This suggests that getting the dosing regimen right for patients in terms of convenience could help to improve compliance, and in turn, bring about a positive effect of the probiotic on postoperative outcomes. We have chosen to analyze our results in an intention-to-treat approach to reflect the real-world compliance to our proposed interventions.

The above challenges notwithstanding, we are optimistic that this trial will contribute to the literature by providing more evidence for or against the effectiveness of probiotics in reducing postoperative ileus.

Trial status

Recruitment is scheduled to begin on 15 July 2024, and we are expected to complete recruitment on 15 July 2025. The current protocol is Version 1.0, dated 6 July 2024.

Abbreviations

ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
AE	Adverse event
CI	Confidence interval
CRC	Colorectal cancer
CRS	Colorectal surgery
DCF	Data collection form
DMC	Data Monitoring Committee
DSRB	Domain-specific review board
ERAS	Early recovery after surgery
PI	Principle investigator
POD	Post-operative day
RC	Research coordinator
RCT	Randomized controlled trial
RO	Research Office
SGLT2	Sodium-glucose cotransporter-2

Acknowledgements

Not applicable.

Authors' contributions {31b}

DKHC is the Principle Investigator of this trial, conceived the study, and led the proposal and protocol development. BES, JL, NQP, and KKT contributed to the study design and development of the proposal. All authors read and approved the final manuscript.

Funding {4}

Nestle Singapore (Pte) Ltd will provide sponsorship of the nutritional supplements Isocal and Boost Optimum, which have been used in Arms 2 and 3 respectively. Nestle has no role in the design of the study and collection, analysis, and interpretation of data. Nestle also has no role in the writing of the manuscript.

Data availability {29}

All requests of data will be made available at reasonable request to the PI.

Declarations

Ethics approval and consent to participate {24}

The conduct of this trial has been approved by the National Healthcare Group Domain Specific Review Board (2024/00180). Written, informed consent will be obtained from all participants.

Consent for publication {32}

Not applicable.

Competing interests {28}

The authors declare that they have no competing interests.

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