Full Title

Investigating the acceptability and feasibility of a novel nutritional supplement on patients undergoing different treatment stages for cancer and emergency disease presentations.

Short Title

Feasibility of a novel nutritional supplement for surgical patients.

Protocol Version and Reference Numbers

Version 0.1

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IRAS Number : 280595

Sponsors Number:

KEY TRIAL CONTACTS

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i. LIST of CONTENTS

ii. LIST OF ABBREVIATIONS

Define all unusual or 'technical' terms related to the trial. Add or delete as appropriate to your trial. Maintain alphabetical order for ease of reference.

CI	Chief Investigator
GCP	Good Clinical Practice
ICF	Informed Consent Form
MHRA	Medicines and Healthcare products Regulatory Agency
NHS R&D	National Health Service Research & Development
PI	Principal Investigator
PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality Control

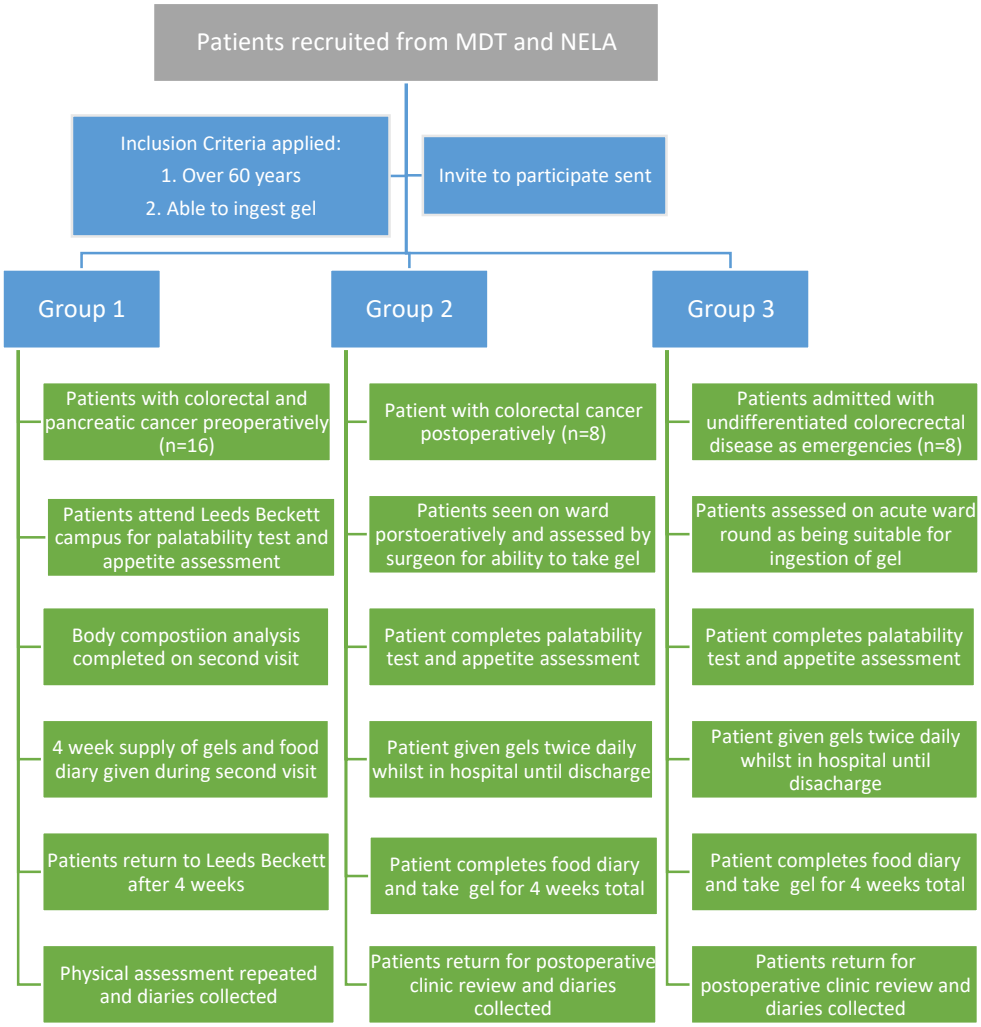
iii. TRIAL SUMMARY

Trial Title	Investigating the acceptability and feasibility of a novel nutritional supplement on patients undergoing different treatment stages for cancer and emergency disease presentations	
Internal ref. no. (or short title)	Feasibility of a novel nutritional supplement for surgical patients	
Clinical Phase	Pilot study	
Trial Design	Two parts to this pilot study: A) Palatability assessment of a novel nutritional supplement and impact of a nutritional supplement on appetite during a breakfast meal B) Supplementation regime compliance over a 4-week period with impact on appetite (groups 1, 2 & 3) and body composition (Group 1)	
Trial Participants	Preoperative elective colorectal or pancreatic cancer patients (Group 1, n=16) Postoperative emergency patients presenting with cancer (Group 2, n=8) General abdominal surgical emergencies (Group 3, n=8) All patients will be over 60 years of age and are able to ingest the nutritional supplement independently.	
Planned Sample Size	32	
Treatment duration	1 month	
Planned Trial Period	2 months	
	Objectives	Outcome Measures
Primary	To assess the palatability of a nutritional supplement for surgical patients	Whether patients can take the supplement
Secondary	To assess compliance to supplementation regime and impact on body composition	1. Whether the supplement impacts patient appetite (Groups 1, 2 & 3) 2. Whether supplementation affects body composition (Group 1)
Formulation, Dose, Route of Administration	Nutritional supplement gel to be taken orally.	

iv. FUNDING AND SUPPORT IN KIND

FUNDER(S) (Names and contact details of ALL organisations providing funding and/or support in kind for this trial)	**FINANCIAL AND NON FINANCIALSUPPORT GIVEN**
Vitrition UK Ltd	**65 gram nutritional supplement gel. Product specification QD27 V8.2.25.04.2017**

v. TRIAL FLOW CHART



Background

Surgical resection of colorectal and pancreatic cancer is usually undertaken as a curative procedure but these operations are major undertakings and approximately half of the patients can suffer with debilitating postoperative complications (van Rooijen et al., 2019). The physical impact of surgical intervention has been reduced, with modern surgical and anaesthetic techniques, reducing morbidity post operatively, but the patients presenting for cancer surgery tend to be in an older age group, with 50% being over 65 years of age. As people age they are more likely to become frail, and the presence of frailty syndrome (a multisystem disease process that reduces the ability of an individual to respond to stressors) is well documented to be associated with worse surgical outcomes (Tan et al., 2012). Complications, length of hospital stay, and mortality rates also increase with age and frailty (Makary et al., 2010), whilst the nutritional status of older patients is an independent predictor of survival rates (Ommundsen et al., 2014).

Sarcopenia is the loss of muscle mass and function. Sarcopenia can be an acute process (less than 6 months) or a chronic process. It is linked to significant morbidity and mortality (Dodds and Sayer, 2016) and is more prevalent in aging populations. Muscle mass and function have emerged as key contributors to surgical outcomes, with surgical complications higher in patients with muscle weakness (Tamagawa et al., 2018, Limpawattana et al., 2018). Older surgical patients presenting as frail with associated sarcopenia who require major surgical intervention for pancreatic or colorectal cancer, pose a growing problem in healthcare systems that cater for an increasing elderly population (Lin et al., 2016). There is therefore an opportunity for these patients to maximise their physical health in order to optimise the outcome of surgery (van Rooijen et al., 2019).

The recent addition of potential SARS CoV2 infection for the elderly population places a preoperative surgical group under increased risk of postoperative complications (Doglietto et al., 2020). There are known protective effects against SARS CoV2 for vitamin supplementation, particularly Vitamin D (Grant et al., 2020). Promoting the immune response in this manner may have benefits in elective surgical patients (Kakodkar et al., 2020). Therefore, methods replacing depleted vitamin stores may reduce postoperative complications.

Cancer and patients with bowel disease patients often have reduced appetites and cannot simply increase volumes of food to achieve reasonable nutritional intakes perioperative. Ispoglou et al. (2017)and Butterworth et al. (2019) have demonstrated that older people, who are more likely to

suffer from frailty and sarcopenia, are able to consume novel gel and protein-based nutritional supplements without reducing their appetite. Preliminary data also showed that nutritional supplementation over a three-month period improved functional performance (Ispoglou et al., 2017, Butterworth et al., 2019) and body composition (Ispoglou et al., 2016) of older people. This approach, using a novel nutritional supplement, is potentially an ideal way to improve protein and energy intake in these patients. However, this approach has not been tested in patients with intestinal cancer. We do not currently know whether the nutritional supplement is acceptable to, and can be taken by, these patients as means to enhance protein and energy intakes. We therefore wish to investigate a group of elective preoperative cancer patients, a group of post-operative cancer patients, and a group of emergency patients. This latter group often present in a frail condition, and do not have the opportunity to improve their health before they undergo emergency surgery. In addition to measuring the acceptability of the supplement to patients, we plan to use non-invasive techniques (bioelectrical impedance, hand grip strength and a 'get up and go test") before and after a short-term supplementation period (4 weeks) to gather evidence of its efficacy

Aims and Objectives

The research team aim to investigate the feasibility and acceptability of novel nutritional supplementation in bowel/pancreatic cancer patients preoperatively and patients who have emergency bowel surgery or planned colorectal cancer surgery postoperatively.

The project will be conducted in two parts: part A and part B. In part A of the feasibility study the key research question the research team will aim to answer is:

"Does consumption of a nutritional gel (65 ml) before an 'ad libitum' breakfast (eat as much as someone can eat) negatively affect appetite and energy intake compared to a breakfast alone (control)?"

The key outcomes measured will be nutritional intakes, appetite and palatability perceptions at the breakfast.

In part B of the feasibility study the key research question the research team will aim to answer is:

"Can participants (who also completed part A) consume two supplements daily over a longer period of time without compromising their ability to eat food?"

The key outcomes measured will be habitual nutritional intakes and monitoring compliance to the supplementation regime.

A secondary question for participants in part B will be:

"Can short-term supplementation improve body composition and aspects of physical fitness?"

The secondary outcomes measured will be fat mass and fat free mass as measured by bioelectrical impedance, handgrip strength test and a get-up and go test.

Design

A) Participant Recruitment

There are three main groups of participants who will be included in the study, who will be male and female patients over the age of 60, are:

1) Bowel (n=8) or pancreatic cancer patients (n=8) planned to undergo (elective) surgery. Part A and B will need to ideally be completed before surgery. These planned surgical patients, once they have completed part A of the feasibility study, will complete part B (i.e. they will be asked to take a nutritional supplement twice a day for 4 weeks and as preparation for their impending surgery).
2) Bowel cancer patients who have undergone elective surgery (n=8). Part A and B will be completed after surgery. After they complete Part A, these surgical patients will be asked to take part in part B of the study (i.e. take the supplements for 4 weeks) once they have a return of bowel function and have begun tolerating diet and fluids as assessed and documented by a surgeon during daily post-operative review.
3) Patients undergoing emergency surgery from a range of clinical conditions (n=8). Part A and B will be completed after surgery as these patients cannot be assessed pre-operatively due to the urgent requirement for surgery. After they complete Part A, these emergency surgical patients will be asked to take part in part B of the study (i.e. take the supplements for 4 weeks) once they have a return of bowel function and have begun tolerating diet and fluids as assessed and documented by a surgeon during daily post-operative review.

B) Methodology

The two parts of the feasibility study are as follows:

- Part A of feasibility study (Palatability and Appetite Assessment)

The experimental trial will involve consumption of an ad libitum breakfast and consumption of a 65 g essential amino acid based nutritional prototype 10 minutes before the ad libitum breakfast (intervention) or no additional gel supplementation(control). All patients will complete a control and an intervention visit. The patients will complete an appetite assessment for intervention and control visits (2 separate visits) and a palatability assessment for the intervention visit.

The outcomes we will be measuring in all three groups are nutritional intakes, appetite and palatability perceptions at the breakfast.

The gel is the intervention and is manufactured by Vitrition UK Ltd (Product specification QD27 V8. 2. 25. 04. 2017.) See below composition per 65 grams gel:
Energy = 113.65 kcal, Carbohydrates = 21.936 grams, Protein: 7.5 g and all in the form of essential amino acids, Sugars = 13.36 grams, Fats = 0 grams, Salt = 0.026 grams, 500 iu of vitamin D3 .

The ad libitum breakfast will have an energy density of 4.9 kJ/g and a macronutrient composition of 59% carbohydrate, 18% protein and 23% fat. Meal preparation will involve mixing of 54 g of porridge oats (Oatso Simple Original, Quaker Oats) with 292 ml semi-skimmed milk. The mixture will then be cooked in a microwave for two and a half minutes at 700 W. Patients will need to consume the breakfast in isolation to avoid any social influence on food intake. A bowl of the breakfast meal will be provided by one of the investigators or a trained nurse and patients will be instructed to eat until 'comfortably full', with no time limit set for eating. This bowl will be replaced before the participant empties it. Food intake will be calculated as the weighted difference in food before and after eating. Appetite perceptions (hunger, satisfaction, fullness and prospective food consumption) will be measured using 100 mm visual analogue scales with descriptors anchored at each end. A composite appetite score will be calculated as the mean value of the four appetite perceptions after inverting the values for satisfaction and fullness. Palatability ratings (visual appeal, smell, taste, aftertaste and pleasantness) will be obtained for the supplements and the ad libitum breakfast. A composite palatability score will be calculated as the mean value of the palatability subscales.

Part B of Feasibility study (Supplementation regime compliance and body composition)
Following completion of Part A, patients will be given 56 gels (to cover 4 weeks of supplementation, twice daily (one gel alongside breakfast and one alongside their lunch meal). The patients will also be given a 1 x3 day food diary to complete at home in week 3 of the supplementation intervention.
Outcome measures include:

- Nutritional intakes in a food diary.
- Monitoring compliance to the supplementation regime.
- Body composition assessment (measured by bioelectrical impedance) at the start and end of the intervention.
- Functional capacity at the start and end of the intervention.
- Handgrip strength test

The preoperative group (group 1) and postoperative groups (2&3) will follow the feasibility study on different pathways:

GROUP 1(Preoperative):

Patients will need to visit our laboratories at Leeds Beckett campus on three occasions in total (each visit will last ~30-60 min). The preoperative group of patients will eat a breakfast meal only on one visit (condition 1 - control) and then a breakfast meal alongside a gel supplement (condition 2 - intervention) on a second visit. On each occasion the patients will complete an appetite assessment and be asked to complete a palatability assessment when they take the gel during the intervention visit The patients will all complete an intervention (condition 2) and non-intervention (condition 1) at random - ensuring they complete both conditions.

The two visits for the two conditions (1&2) will take place a week apart after an overnight fast for which they will be given pre-test instruction leaflet to describe the preparations for the visit. Patients or carers will be asked to record all food and fluid consumed in the 24 h prior to the first experimental trial and replicate this for the next trial. Patients will also be asked to avoid alcohol and intensive physical activity during the same time period.

During the second visit to Leeds Beckett campus the patients will have body composition assessment (measured by bioelectrical impedance) and functional capacity will be measured by assessment of handgrip strength test and a 'get up and go' test. These physical assessments will be measured twice during the study; at the start during the second Leeds Beckett campus visit (Day 1 of supplementation) and at the end of the supplementation intervention (after 4 weeks). During the second visit to Leeds Beckett campus the patients will be given the food diary with explanation about completion and a 4-week supply of gels to be taken at home twice daily alongside their breakfast and lunch therefore starting Part B of the study.

Part B will focus on compliance with daily nutritional gel supplementation during a breakfast and lunch time meal for 4 weeks. The patients will be asked to complete a paper food diary for 3 days during the third week. The patient will return to the laboratory after 4 weeks (for their third and final visit to Leeds Beckett campus) bringing their completed food diary and any spare gels on this visit. They will repeat the physical assessments described above on this final return visit.

GROUP 2 & 3 (postoperative cancer patients and postoperative emergency patients):

These two groups will complete Part A - palatability test and consume an ad libitum breakfast following their surgery during their hospital stay. They will not complete a second breakfast meal assessment. They will be assessed by a senior member of the surgical team who will decide if their bowel function has returned sufficiently to begin eating and drinking before they commence in part A.
These two groups will not be required to perform an overnight fast before the palatability test and will only complete the palatability/appetite test once.
No physical health assessments will be undertaken by group 2&3.

They will then enter Part B of the study and be given gel supplementation at breakfast and lunch each day whilst they are recovering in hospital. They will continue the supplementation at home for a total of 4 weeks and will complete a 3 day food diary during week 3 of the study. When these patients return for their postoperative outpatient review at 4 weeks following their procedures, the food diaries and spare gels will be collected by the research team.

Compliance to the regime will be monitored by counting any gels that have not been consumed. The food diaries will be collected in both groups and stored on site at St James's University Hospital. The diaries will be transcribed onto an electronic document that will be stored securely on Leeds Teaching Hospitals Trust servers in a password protected hard drive area. The paper diaries will be destroyed via the confidential waste system as per NHS protocols for information governance.

Eligibility

The elective patients presenting with cancer, will be identified and selected at the multidisciplinary meetings by the colorectal and pancreatic consultant surgical team. The patients to be included in the study will all be over 60 years old and will be subject to the following inclusion criteria:

- Patient has capacity to understand the study and give informed consent
- Patient is capable of ingesting the oral supplement

A senior member of the surgical care team will approach the patient either after diagnosis has been discussed with the patients for the planned colorectal/pancreas cancer patients. The emergency patients will be identified by the National Emergency Laparotomy Audit (NELA) team within the hosting organisation (Leeds Teaching Hospitals Trust). A senior clinician will assess the suitability of the patient to inclusion into the study whilst an inpatient on the surgical ward at least 48 hours following emergency surgery.
Patients will be excluded from the study if they meet the following criteria:

- Patient is incapable of understanding the study and giving informed consent
- Patient is incapable of ingesting the oral supplement
- Patients with the very rare potential complication of an allergy to nutritional supplement (sodium benzoate or sodium metabisulphites).

Data Analysis

Part A

Appetite perceptions (hunger, satisfaction, fullness and prospective food consumption) will be measured using 100 mm visual analogue scales with descriptors anchored at each end. A composite appetite score will be calculated as the mean value of the four appetite perceptions after inverting the values for satisfaction and fullness. Palatability ratings (visual appeal, smell, taste, aftertaste and pleasantness) will be obtained for the supplements. A composite palatability score will be calculated as the mean value of the palatability subscales.

Part B

Group 1 patients will have body composition assessment (measured by bioelectrical impedance) and functional capacity will be measured by assessment of handgrip strength test and a 'get up and go' test. These physical assessments will be measured twice during the study; at the start during the second visit (Day 1 of supplementation) and at the end of the supplementation intervention (after 4 weeks).

Part B will focus on daily supplementation during a breakfast and lunch time meal for 4 weeks. The patients in all three groups will be asked to complete a paper food diary for 3 days during the third week. The Group 1 patients will return to the laboratory after 4 weeks bringing their diaries and any spare gels on this visit. Group 1 patients will repeat the physical assessments described above on this final return visit. The Group 2 & 3 patients will bring unused gels and food diaries with then to the post-operative clinical review at St James's University Hospital.

Data Management

The research is sponsored by the University of Leeds and the researchers will undertake research activity at two sites:

- Leeds Beckett University, Headingly Campus
- St James's University Hospital, Leeds Teaching Hospitals Trust

Any clinical data will be reviewed by the clinical team only and no clinical data will leave the St James's University Hospital site. The clinical information required will be sex, gender, height, weight

planned surgery or surgical intervention undertaken. Data generated will be stored on secure servers which will be password protected will be anonymised with a unique identifier following identification of participants from the Multidisciplinary Team Cancer meetings and the National Emergency Laparotomy Audit. Only members of the research team will have access to any data generated. All data generated will then be sent electronically to Leeds Teaching Hospitals Trust NHS servers for storage and analysis. Paper food diaries will be transcribed and then destroyed securely at St James's University Hospital. Complete consent forms will be stored in a locked cupboard at St James's University Hospital.

Ethical Considerations

All participants will be given information about the study and will be part of an informed consent process. Consent will be sought by a senior member of the surgical care team. Participants will be given a written information leaflet and will be asked to complete a consent form. All participants will be able to review confidentiality policies and a summary of the planned study. Participants will primarily be approached through the colorectal/pancreas cancer MDT and via the NELA Team. No personal information will be known about potential participants until the time of the initial approach. The research team will use a screening log to monitor who is approached, how and how it progressed to ensure we can reassess our methodology should this be necessary at a later date. All participants will be given a unique identifier which will be held in a secure location on the Leeds teaching Hospitals NHS server and all patient data will be anonymised.

All participants will be given as long as is necessary for them to decide to participate in the pilot study. The planned surgical patients have a timeframe attached to planned surgery which will dictate a decision window. However, the research team would like to complete 4 weeks nutritional intervention before surgery in order to assess the benefit of the supplement. The post-operative and emergency patients will begin nutritional supplementation 48 hours following surgery and will be allowed to decide whether they want to participate during their inpatient stay, usually approximately 7 days if there are no postoperative complications. Assessment of the ability to tolerate oral fluids and therefore begin nutritional supplementation will be recorded in the patient records.

Potential unpalatability and intolerance of the oral supplement may arise but initial studies have been completed for the prepared nutritional supplements. Initial data show that the oral

supplement has been well tolerated so far. The nutritional supplement has been discussed with the Medicines and Healthcare Regulatory Agency and is not regarded as a medicinal product; therefore, a clinical trial of an investigational medicinal product is not required.

It is not anticipated that there will be any serious adverse events during the pilot study but in the event of occurrence then then a safety report form will be completed by the chief investigator and sent to the Research Ethics Committee as per the standard operating procedure of the Health Research Authority.

Time Schedule

It is anticipated that this feasibility study will be conducted over a 4-5 week period and will form the basis of a pilot study that will influence a clinical trial at a later stage.

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