Fast Track Recovery Surgery with A Whey Protein Infused Carbohydrate Loading Drink Pre-Operatively and Early Oral Feeding Post-Operatively among Surgical Gynaecologic Cancer Patients: Study Protocol of an Open Labelled Randomised Controlled Trial

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Abstract

Introduction: There has been growing evidence on the favourable outcomes of fast tract recovery (FTR) surgery; expedite recovery, minimise complications, reduce length of hospital stay on surgical patients. However, there is lack of evidence on the effectiveness of FTR in surgical gynaecologic cancer patients. Most of previous study did not focus on feeding composition in FTR surgery protocol. This study aims to determine the effectiveness of FTR feeding with whey protein infused carbohydrate loading drink pre-operatively and early oral feeding post-operatively on post-operative outcomes among surgical gynaecologic cancer patients.

Methods and analysis: This open labelled RCT will randomly allocate patients into intervention and control group. Ambulated Malaysian aged over 18 years and scheduled for elective surgery for (suspected) GC, will be included in this study. Intervention group will be given whey protein infused carbohydrate loading drinks evening before operation and 3 hours before operation as well as started on early oral feeding 4 hours post-operatively. Control group will be fasted overnight pre-operation and only allowed plain water, and the diet transition fashion is followed when there is bowel sound post-operatively. Primary outcomes of study are length of post-operative hospital stay, length of clear fluid toleration, solid food toleration and bowel function. Additional outcome measures are changes in nutritional status, biochemical profile and functional status**.** Data will be analysed on an intention-to-treat basis.

Trial Registration Number: ClinicalTrials.gov, NCT03667755. Registered 12 September 2018 – Retrospectively registered, https://clinicaltrials.gov/ct2/show/NCT03667755

Protocol Version: Version 3 dated 27th September 2017

Strength And Limitations Of Study

- This is an open-labelled randomised controlled trial study
- Large number of participants (n=110 patients)
- This study is among the first few RCT focused on FTR surgery with pre-operative whey protein infused carbohydrate loading and post-operative early oral feeding on gynaecology oncology patients in South East Asian region.
- Limitation is post-operative observation is short, so long term effect of perioperative FTR surgery feeding with whey protein infused carbohydrate loading on wound healing could not be assessed.
- This is a single centre study and the protocol used might not be applicable to other hospitals

Background And Rationale

Fast track recovery surgery (FTR) (or known as Enhanced Recovery After Surgery (ERAS)) has been proposed and established since 1999 by Professor Dr Henrik Kehlet[1]. FTR is developed based on the

concept of multimodal post-operative recovery programs after it was realised that unimodal intervention was impractical to solve multimodal perioperative morbidity problem. Fast track recovery (FTR) surgery or also known as early recovery after surgery (ERAS) program are increasingly been practiced in colorectal surgeries [2], gastrointestinal [3]) and various fields [4 5 6]. One of the crucial parts in the FTR program is early perioperative feeding which is safe and beneficial in recovery postoperatively[7]. Many studies highlighted the general FTR program which includes providing patients with solely carbohydrate (CHO) loading preoperatively and allowing early oral feeding with clear fluid and followed by solid food after tolerated 500ml clear fluid postoperatively [7 8 9 10]. However, the effectiveness of providing whey protein infused carbohydrate loading drink as preoperative CHO loading drink remains unclear. Practical consideration for FTR surgery development in gynaecologic oncology surgical patients was started growing [11]. "The FTR program include evidence based items designed to reduce peri-operative stress, maintain postoperative physical function and accelerate recovery after surgery" [12]. Using multi-modal stress minimising approach has been shown repeatedly to reduce rate of morbidity, improve recovery and shorted length of hospital stay (LOS) after major colorectal surgery [13]. Updated consensus review of perioperative care of colorectal cancer, has highlighted the multimodal metabolic stress-minimizing approach was demonstrated repeatedly to shorten length of hospital stay, promote recovery and reduce morbidity rate after major colorectal surgery[14]. Clinical care of patients undergoing surgical gynaecology cancer (GC) are different between hospitals and countries, thus it is a need to understand the effectiveness of the FTR surgery perioperative feeding in Malaysia.

The primary modalities of cancer treatment are surgery, chemotherapy and radiotherapy; these may be used alone or in combination[15]. For those cancers which are well margined and operable, surgery is first treatments for GC[16]. Surgery, a like injury, causes catabolism which involve skeletal muscle tissue breakdown to release amino acids for wound healing. Optimal nutritional status peri-operation support speedy wound healing, improve immunity and ensure the better post-surgery outcome. Other than calories and carbohydrate, protein is crucial for post-operative recovery, promotes anabolism, slows down muscle catabolism and decreases the inflammatory phase[17]. Protein are divided into two classes: whey and casein. Whey protein is a high-quality protein that is easier to be digested and stimulates muscle protein synthesis if compared to casein. Fast digestion and absorption of whey protein is due to the high degree of branched-chain amino acids content which directly stimulates the early cellular process involved in protein synthesis called initiation translation[18]. However, this might not beneficial to people with allergic to milk as it might allergic to whey protein[19].

Conventional feeding strategy for pre- and post-operation whereby prolonged fasting or rest for both the patient and the gastrointestinal tract will delay the recovery of patients since the organic response to surgical trauma is enhanced by prolonged period of fasting. Inadequate oral intake due to delayed oral feeding caused depletion of nutrient storage in patient's body. This is because of utilisation of energy which converted from protein source of body (muscle) which promote catabolism. Thus, patients experienced weight loss and muscle mass loss post-operatively[20].

In order to overcome complication of conventional surgery approach, Kehlet and Wilmore[7] developed multimodal perioperative protocol, named Enhanced Recovery after Surgery or Fast Track Recovery Surgery program. One of key of fast track recovery (FTR) programs is metabolic strategy to reduce perioperative stress and improve outcomes. Nutrition intervention post-operatively is crucial. Studies of FTR program in gynaecology surgery had showed that FTR significantly reduce LOS and consequently have positive economic benefits without increasing readmission and complication rates[8 9 21]. Studies of FTR protocol in gynaecology surgery had showed that FTR with preoperative carbohydrate loading and postoperative early oral feeding significantly reduce LOS and consequently have positive economic benefits without increasing readmission and complication rates. FTR protocol focus primarily on reducing perioperative stress, achieving satisfactory pain control, resumption of normal gastrointestinal function and early mobilization[17 20 22].

While early oral feeding is preferred mode of nutrition, avoidance of any nutritional support therapy bears the risk of underfeeding during postoperative course after major surgery. To abbreviate preoperative fasting, beverage containing carbohydrates have been used and recommended in FTR protocol. Carbohydrate loading with solely carbohydrate drink was widely used and proven positive and beneficial outcomes[17 20 22]. Whey protein contains essential amino acids especially branch-chain amino acids, a high degree of digestibility and rapid absorption in the small bowel, which rapidly used by skeletal muscle during stress and highly stimulate protein synthesis[23]. Perrone, et al.[5] concluded that whey protein infused with carbohydrate drinks as carbohydrate loading drink prior to operation did improve post-operative muscle strength, reduce fatigue, anxiety and discomfort as well as lowering the endocrine-metabolic response to trauma. The study aims to determine the effectiveness of fast track recovery surgery with a whey protein infused carbohydrate loading drink and early oral feeding among surgical GC patients.

Method And Design

This study is an open labelled randomised controlled trial (RCT) conducted at National Cancer Institute, Putrajaya, Malaysia. Since this is an open labelled RCT study, blinding will not occur. Study is conducted in Surgical Gynaecologic Department which involved multidisciplinary clinic and female surgical ward. The RCT will conform to the Consolidated Standards of Reporting Trials (CONSORT) statement for reporting RCT with two arms comparing an intervention group to control group[24]. After consented to participate, subjects will be allocating into intervention and control group randomly. Randomisation will be done by computerised generated random number.

Subjects

One hundred and ten subjects fulfilling the eligibility criteria will be enrolled into study. Ambulated Malaysian aged over 18 years and scheduled for elective surgery for (suspected) GC, will be included in this study. Those who allergic to soy or whey protein, diagnosed with chronic renal disease, ischemic heart disease and diabetic mellitus or involved in other intervention study are excluded. Time of

enrolment will be started from admission day until discharged day (throughout hospitalisation for elective surgery).

Recruitment procedure

Patients' perioperative feeding will be managed according to FTR surgery program[1]. Candidates who been referred to surgical gynaecologic department and complying with the inclusion criteria will be approached to participate in the RCT study. Oral and written information about the study procedures will be provided by gynaecologic surgeon or dietitian in an undisturbed consultation room. Gynaecologic surgeon and dietitians involved in recruitment have been trained and instructed in the recruitment procedure in order to maximize the recruitment rate. Patients are provided with patient information sheet and study consent form and given sufficient time consider and discuss participation with family members before decision making. Dietitian will contact the patient to confirm the participation in the study. Written informed consent form will be collected on the admission day. Subjects will be required to attend dietitian clinic to have anthropometry and dietary assessment on the day of admission.

Randomisation

Consented subjects will be randomised into two groups: The intervention (CHO-P) group and control group (CO) before baseline assessment. Randomisation is done by a computer-generated randomisation number which is prepared by independent statistician. Allocation randomised numbers will be concealed in sealed envelopes by study coordinator. The envelop will only be opened after consented and before baseline assessment.

Intervention Group (CHO-P)

Intervention group will receive a specific drink of a lactose-free clear tea-colour fruit flavoured fluid contains 14% whey protein, 86% carbohydrates and 0% lipids. Subjects in CHO-P group will be given 474ml evening drink which provides 500 kcal and 18g whey protein on the evening of a day before operation. Three hours prior to operation, subjects will be provided with 237ml drink with 250 kcal and 9g whey protein. Before operation, subjects fast for solids for 6 hours from the operation. Staff nurse in-charged will monitor anaesthetic risk of drinking whey protein infused carbohydrate drinks and ensured subject to finish specific drinks prior to surgery. Subjects will be provided with same specific clear fluid (474ml which provide 500 kcal and 18g whey protein) after 4 hours' post-operation (without present of bowel sound) and reviewed by dietitian. When they tolerated at least 500ml of specific clear fluids, they are given a regular solid diet.

Control Group

The subjects in control group fasting from 12 mid-nights on the day of operation with the last meal was minimal 12-hours before operation. On the day of post-operation day, subjects were reviewed by gynaecologist. They were allowed for clear fluid once there is bowel sound. After tolerated clear fluid, they

proceed for nourishing fluid then soft diet and they will only receive a regular solid diet after tolerating soft diet.

Discharged Criteria

Gynaecologic surgeon will determine time to discharge of subjects according to discharged criteria. Discharge was allowed based on pre-established criteria (oral pain management, independent mobilisation, sufficient food intake, gastrointestinal function, and the absence of a suspicion of complications)[13].

Criteria for withdrawal

The participation will be voluntary, and subject will be free to withdraw anytime from the study without giving any reason and this will in no way affect subject's future treatment.

Adverse events and data safety monitoring

There are no serious side effects identified and low anaesthetic risk of drinking whey protein 3 hours before operation (vomiting/nausea) in this study. If there is any adverse event during the study in subjects, it will be recorded in the electronic medical record. In the adverse event directly resulting from the study product or a medical procedure required for this study, subject will be referred to a medical doctor as soon as possible and the expenses involve will be paid by the sponsor. There is no additional medication/treatment involved in study. Staff nurse in-charged will monitor subjects if there are any adverse events after consuming study product. If there is any adverse events/inter-current illness, staff nurse in-charged will report to medical officer in-charged (gynaecology) immediately. Medical officer will initiate appropriate treatment. Study findings shall potentially improve treatment outcomes. The expected benefit outweighs the minimal risk to subjects and thus this study should be supported. If any injuries do occur as a direct result of participating in the study, treatment for such injuries shall be provided by the sponsors. There is not prorated payment for participation in this study.

Protocol Amendment

Any modifications to the protocol which may impact on the conduct of the study, potential benefit of the patient or may affect patient safety, including changes of study objectives, study design, patient population, sample sizes, study procedures, or significant administrative aspects will require a formal amendment to the protocol. Such amendment will be agreed upon by National Cancer Institute and Universiti Putra Malaysia and approved by the Medical Research and Ethics Committee (MREC) prior to implementation and notified to the health authorities in accordance with local regulations.

Data collection procedure

Data will be collected at baseline, during post-operative hospitalisation and upon discharged post-operation. Table 1 illustrates the framework for data collection procedures and the study outcomes.

Table 1 Data collection procedures and the study outcomes

Procedure/Parameters	Location	Baseline	Pre-Operation	Post-operation	Post-operative Hospitalization	Discharge	1-month post-discharged
Enrollment	Clinic						
Allocation	Clinic						
Data collection	Ward						
Age		√					
Ethnic		√					
Education level		√					
Employment status		√					
Marital status		√					
Diagnosis		√					
Other comorbidity		√					
Cancer stage				√			
ASA score		√					
Height		√				√	
Weight changes past 1-month		√					
Body composition (Weight, Muscle mass, FM, FFM and MUAC)		√				√	
Handgrip strength		√				√	
PG-SGA		√					
Diet recall		√			√	√	
Hemoglobin			√	√			
Glucose level			√	√			
C-reactive protein			√	√			
Albumin			√	√			
Length of post-operative stay						√	
Length of bowel function					√		
Length of solid food toleration					√		
Length of clear fluid toleration					√		
Post-operative complication (PONV, ileus & infection)					√		
Readmission within 1 month post-discharged							√
Reason of readmission (infection & wound debridement)							√

ASA: American Society of Anaesthesiologists; FM: Fat Mass; FFM: Fat Free Mass; MUAC: Mid Upper arm circumference; PG-SGA: Patient Generated Subjective Global Assessment; PONV: Post-operative Nausea & Vomiting

Outcomes measurement

Baseline characteristics

Subject characteristics such as socio-demographic data (age, ethnic, education level and marital status), clinical characteristic (diagnosis, other comorbidity and American Society of Anaesthesiologists (ASA) score), nutritional status (PG-SGA score, weight changes past 1-month, height, body composition and dietary intake), functional status (handgrip strength) and biochemical profile (haemoglobin, C-reactive protein, albumin and glucose level) will be collected.

Primary outcomes

The primary outcome will be the between-group difference in length of post-operative outcomes (length of post-operative hospital stays, clear fluid toleration, food toleration and bowel function return) between the intervention and control group. Length of post-operative hospital stay is defined as the time from operation end to discharge from the hospital. Length of clear fluid toleration is defined as the time from operation end to tolerate clear fluid. Length of food toleration is defined as the time from operation end to tolerate regular food. Length of bowel function return is defined as the time from operation end to flatus or bowel open. Primary outcomes will be assessed by gynaecologic surgeon and recorded on data collection form (progress in ward form) by nurse in-charged.

Secondary outcomes

Post-operative complications

Post-operative complications including post-operative nausea and vomiting (PONV), ileus and infection, will be monitored and recorded by surgical gynaecologic team. Overall complications were assessed during hospital stay; complication rates were defined per patient; a patient could have suffered from one or several complications[14].

Readmission within 1-month post-discharged

Readmissions of study subjects will be documented from the day of discharge until 1-month (30 days) postoperatively. Readmission complications will be described separately from complications during hospital stay.

Other outcomes measures

Nutritional status

The changes within group (pre- and post-operation) and between groups (intervention and control group) for body composition [weight and muscle mass] and mid upper arm circumference (MUAC) will be assessed. Calibrated TANITA body composition analyser will be used to assess body composition while calibrated SECA measuring tape for MUAC.

Biochemical profile

The changes within group (pre- and post-operation) and between groups (intervention and control group) for biochemical profile (haemoglobin, C-reactive protein, albumin and glucose level) will be measured. Result of biochemical profile of study subjects will be accessed from medical record system.

Functional status

The changes within group (pre- and post-operation) and between groups (intervention and control group) for functional status (handgrip strength) will be measured by using calibrated JAMAR® Hand Dynamometer. Record the scores of three successive trials for non-dominant hand tested. The average score of the three trials was used to interpret a grip strength performance.

Confidentiality, Handling and storage of data documents

Subject's names will be kept anonymous and will be linked only with a study identification number for this research for confidentially purposes. The identification number instead of patient identifiers will be used on subject data sheets. Digital documents and data will be kept in a password protected applications and folders. The hardcopy documents will be stored in a locked office of the investigators and maintained for a minimum of five years after the completion of the study. Subjects will not be allowed to view their personal study data, as the data will be consolidated into a database.

Sample size calculation

The study will be powered to detect difference between intervention and control group in the primary outcomes (post-operative outcomes). Sample size of study is calculated by using formula which was proposed by Woodword[25]. According to result of previous study by Balayla et al.[20], study needs about 33 subjects per group. After adjustment with 80% respond rate and 90% expected eligible rate (power = 80%, alpha level = 0.05), study plans to recruit a total of 110 subjects (55 subjects each group) to account for 20% dropped-out rate.

Statistical analysis

All randomized RCT subjects will be included in analysis as an intention-to-treat (ITT) basis. ITT analysis includes every subject who is randomised according to randomised treatment assignment. According to Gupta[26], ITT analysis reflects the practical clinical scenario because it admits noncompliance and protocol deviations, maintains prognostic balance generated from the original random treatment allocation as well as gives an unbiased estimate of treatment effect.

The analyses will be performed using IBM SPSS (version 23.0). Descriptive statistics will be utilised for described subjects' characteristics. Data normality will be checked by using Shapira-Wilk test and reconfirmed by visual inspection of histogram and stem-leaf plots. Categorical data will be presented in

mean ± standard deviation or median (interquartile range) as appropriate while categorical data in frequency and percentage.

Comparison of numerical data, which is normally distributed between two groups, will be analysed using the Independent t-test while Mann-Whitney test will be used if not normally distributed. Pearson's Chi-square test to study association between Categorical Data and Categorical Data while Fisher's exact test will be used if assumptions of Pearson's Chi-square test for Independence are not met. Multi-linear regression test will be used to determine factors related to POHS among surgical gynaecologic cancer patients. All probability values will be used two-sided and a level of significance of less than 0.05 (p-value < 0.05) was considered as statistically significant[27].

Dissemination

This study will be conducted according to the principles of the latest Declaration of Helsinki, the Medical Research Involving Human Subjects Act (WMO) and the Good Clinical Practice standard (GCP). The study is investigator-initiated. We used the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist when writing this report[28].

Discussion

FTR surgery program mostly been conducted in gastroenterology (upper gastrointestinal and lower gastrointestinal) surgery even hepato-biliary surgery in Malaysia[29]. All of the post-operative outcomes in FTR studies are very convincing whereby shorten LOS, faster food toleration and lower readmission rate Although impact of FTR on nutritional status, anti-inflammatory effect and functional status among surgical gastric cancer had been published by Makuuchi, et al.[30], but impact of FTR among surgical GC patients remain unknown. Effectiveness of FTR in surgical GC patients is remained unexplored especially in Malaysia.

Most of available FTR surgery studies [7 8 9 10] investigate the effectiveness of solely carbohydrate contained solution as carbohydrate loading formula. Available study by Perrone, et al. [11] showed positive impact of whey protein-carbohydrate loading among cholecystectomy patients. However, formula containing whey protein infused with carbohydrate drink is not widely been implemented as carbohydrate loading drink among surgical GC patients. To our best knowledge, this is the first study that use formula containing whey protein infused with carbohydrate drink as carbohydrate loading drink among surgical GC patients in Malaysia.

Pre-operative overnight fasting has been doubted recently as in fact the incidence of aspiration is very little and clinically important consequences of aspiration are even rare [31]. Moreover, appropriateness of overnight fasting has been raised because carbohydrate reserves will be depleted and cause change in

metabolism and metabolic response [32]. Both nutritional compromise going into surgery and prolonged pre-operative overnight fasting state worsen glycogen and muscle mass depletion [33].

After major operation, conventional post-operative care usually included restrict oral intake to prevent sign of postoperative ileus and protect surgical anastomoses[34]. The other reason to nil-by-mouth post operation is to allow anastomoses time to heal before being stressed by food[35]. In fact, one to two litres of fluid is secreted by stomach and pancreas then absorbed in small intestine daily[36 37]. Hence, patient actually tolerated high volume of fluid[38]. Moreover, within 24-hours, starvation changed body metabolism by increasing insulin resistance and depleting muscle function[39]. Early oral feeding postoperatively was demonstrated to fasten bowel function return, improve oral toleration and shorter LOS [21 40]. Based on these studies finding, nil-by-mouth postoperatively does not seem to be reasonable or beneficial.

We hypotheses that FTR program with whey protein infused carbohydrate drinks as carbohydrate loading drink preoperatively and early oral feeding postoperatively can result in positive post-operative outcomes including shorten hospital stay, minimise catabolism in order to preserve muscle mass or functional status and promote anabolism among surgical GC patients. In Malaysia healthcare system, there is an immense advantage that may be achieved by the accomplishing execution of an FTR surgery program at an institutional level.

Trial Status

This study protocol version 3 dated 27th September 2017, received ethical approval by the MREC, Ministry of Health, Malaysia on 27th September 2017. The protocol was retrospectively registered in ClinicalTrials.gov on 12 September 2018. The data recruitment started on 3rd October 2017 and completed on 27th September 2019. This study protocol was submitted well for publication on 21st May 2019 while the recruitment was ongoing and before last patient/last visit.

List Of Abbreviations

ASA	American Society of Anaesthesiologists
CHO	carbohydrate
CHO-P	intervention group
CO	control group
CONSORT	Consolidated Standards of Reporting Trials
ERAS	Enhanced Recovery After Surgery
FTR	fast tract recovery
GC	gynaecology cancer
ITT	intention-to-treat
LOS	length of hospital stay
MREC	Medical Research Ethics Committee
MUAC	mid upper arm circumference
PONV	post-operative nausea and vomiting
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
RCT	randomised controlled trial

Declarations

Data monitoring and Auditing

Independent personnel from investigator and sponsor will monitor and audit protocol conduct in every three months' basis.

Ethics approval and consent to participate

This study was conducted with approval of Medical of Health Research Ethics Committee with reference number NMRR-17-1070-36021 (IIR) with protocol version 3 dated 27092017. Trial Registration Number in ClinicalTrial.gov is NCT03667755 (Pre-results). All subjects will be briefed on the objectives and procedures of the study and written consent will be obtained prior to the study.

Consent for publication

Not applicable.

Availability of data and material

The current database/materials for the study available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Patient and Public Involvement

This study protocol was designed without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this study protocol for readability or accuracy.

Funding

This trial was conducted with no external funding and was instead internally funded by the National Cancer Institute, Malaysia. The funder has no role in the design of the study and will not have any role in data management, analysis and interpretation or on the decision to submit results for publication.

Authors' contributions

HCY conceptualised and design the study. ZI, ZAZ, ZAMD and NBMY provided supervision in design and execution of the study. HCY wrote the first draft of study protocol. ZI, ZAZ, ZAMD and NBMY reviewed and edited the manuscript. All authors read and approved the final manuscript.

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Appendix

Participant Information Sheet and Informed Consent Form

(for adult subjects and intervention studies)

1. **Title of study:**

Fast Track Recovery Surgery with A Whey Protein Infused Carbohydrate Loading Drink Pre-Operatively and Early Oral Feeding Post-Operatively among Surgical Gynaecologic Cancer Patients

2. **Name of investigator and institution:**

Name and Institution of Principal investigator:

Ho Chiou Yi, Dietitian at National Cancer Institute, Putrajaya,

Postgraduate research student at Universiti Putra Malaysia

Name and Institution of Co-Investigators:

Dr. Zuriati Binti Ibrahim, Senior lecturer and dietitian Universiti Putra Malaysia

Dr. Zalina Binti Abu Zaid, Senior lecturer Universiti Putra Malaysia

Dr. Zulfitri 'Azuan Bin Mat Daud, Senior lecturer Universiti Putra Malaysia

Dr. Nor Baizura Binti Md Yusop, Senior lecturer Universiti Putra Malaysia

3. **Introduction:**

This study is an open labelled randomized trial study. There is experimental intervention being administered.

We would like to invite you to take part in our research study because you have gynaecology cancer. Before you decide we would like you to understand why the research is being done and what it would involve for you. One of our team members will go through the information sheet with you and answer any questions you have. We'd suggest this should take about 5-10 minutes. Ask us if there is anything that is not clear. After you are properly satisfied that you understand this study, and that you wish to participate, you must sign this informed consent form.

Your participation in this study is voluntary. You do not have to be in this study if you do not want to. You may also refuse to answer any questions you do not want to answer. If you volunteer to be in this study, you may withdraw from it at any time. If you withdraw, any data collected from you up to your withdrawal will still be used for the study. Your refusal to participate or withdrawal will not affect any medical or health benefits to which you are otherwise entitled. There is no prorated payment for participation in this study.

A total of 110 subjects from multidiscipline outpatient clinic in National Cancer Institute, Putrajaya will be participating in this study. The whole study will last about 8 months. The participation duration for each subject is minimum 1 week until patient is discharged. Probability for randomization into group A and group B are the same. If you agree to participate in the study, you will be assigned into either group A or B.

The product used in this study does not contain porcine and bovine ingredient and has been certified HALAL by Singapore Authorities. This study has been approved by the Medical Research and Ethics Committee, Ministry of Health Malaysia.

4. **What is the purpose of the study?**

This study is to determine the impact of fast track recovery feeding with a whey protein plus carbohydrate drink among surgical gynaecologic oncology patients in National Cancer Institute

5. **What will happen if I decide to take part?**

a. In this study, we will collect information on your nutritional status, physical function and hospitalization record
b. At first, we will collect information about your medical condition from your medical record at the time of follow up in medical outpatient clinic, including your blood laboratory investigations. All blood laboratory investigations are extracted from your medical outpatient record and not taken specific to the purpose of this study. This trial does not involve collecting biological specimens for storage. There will be no biological specimens collected for genetic or molecular analysis in this trial and future use in ancillary studies.
c. A dietician will assess your nutritional status in diet clinic. Your nutritional status will be assessed using a questionnaire; dietary recall and measurements of your height, weight, body fat percentage and handgrips at the arm will be assessed. Weight, height and body fat percentage will be measured using a special scale that requires you to stand on the scale.
d.Upon admission, you have to attend to diet clinic to assess of your height, weight, body fat percentage and handgrips.

- If you are assigned to group A, you need to be fasting at 12 midnight and only allowed to take water till 3 hours before operation.
- If you are assigned to group B, you are allowed to take solid food as hospital served 6 hours before operation. 3 hours before operation, you will be provided 1 pack supplement (a lactose-free clear tea-colour fruit flavoured fluid contain 14% whey protein, 86% carbohydrates and 0% lipids).

Upon discharge from ward, you have to attend to diet clinic to assess of your weight, body fat percentage and handgrips.

e. After completion of study, continuous treatment (diet intervention & oncological treatment) will be given as routine care. Study product will not be continued. But high protein fluid will only be given if indicated (malnutrition) after dietary assessment.

6. **What are my responsibilities when taking part in this study?**

It is important that you answer all of the questions asked by the study staff honestly and completely as well as compliance to diet advice and oral supplement as planned.

7. **What are the potential risks and side effects of being in this study?**

You may feel slight tired during the measurement of handgrip strength at the arm, which will resolve spontaneously after the measurement is completed. During admission to ward, branula will be set as routine care & which will cause discomfort.

Others potential risk and side effects of being in this study (group B) is intolerance towards whey protein plus carbohydrate drink provided such as nausea, diarrhoea or vomiting. If such intolerance occurs by the subjects, these steps will be taken into measure:

- To substitute with carbohydrate drink only and to ask subjects to withdraw from the study
- To stop the prescription of whey protein plus carbohydrate drink and to ask subjects to withdraw from the study
- Referral to doctor if necessary

8. **What are the benefits of being in this study?**

There may or may not be any benefits to you. This study does provide a better understanding of the disease/condition studied. It may provide benefit for surgical gynecologic oncology patients in the future in terms of development of new dietary intervention protocol in cancer patient ongoing for surgery treatment.

9. **What if I am injured during this study?**

If you are injured as a result of being in this study, you should contact your investigator. In the event of a bodily injury or illness directly resulting from the study product or a medical procedure required for this study which is very minimal, you will be referred to a medical doctor as soon as possible and the expenses involve will be paid by the sponsor. The sponsor is not responsible for medical expenses due to pre-existing medical conditions, any underlying disease, any ongoing treatment process, your negligence or wilful misconduct, the negligence or wilful misconduct of your investigator or the study site or any third parties. You do not lose any of your legal rights to seek compensation by signing this form.

10. **What are my alternatives if I do not participate in this study?**

You do not have to participate in this study to get treatment for your disease or condition. Alternative treatments of routine care in dietary interventions post-surgery are available in Institut Kanser Negara and most of government hospitals. You always can get diet intervention post-surgery and usage of high protein nourishing fluid will be depending on your daily energy and protein requirement to support post-surgery wound healing and optimize nutritional status.

11. **Who is funding this research?**

There is no funding involved in this research.

12. **Can the research or my participation be terminated early?**

The research officer may due to concerns for your safety, stop the study or participation at any time. If the study is stopped early for any reason you will be informed and arrangements made for your future care. You may be asked to attend a final follow up visit.

13. **Will my medical information be kept private?**

All your information obtained in this study will be kept and handled in a confidential manner, in accordance with applicable laws and/or regulations. Principal investigator and co-investigator in this study only are allowed to assess to medical records and data. The identification number instead of patient identifiers will be used on subject data sheets. All data will be entered into a computer that is password protected. When publishing or presenting the results, your identity will not be revealed without your expressed consent. Individuals involved in this study and in your medical care, and governmental or regulatory authorities may inspect and copy your medical records, where appropriate and necessary. With your permission, your family will be informed that ypur participation in this study. You will not be informed of study findings. You will be informed if new information becomes available relevant to consent. All data of study might be sent to overseas for analysis but your identity will not be exposed all the time.

14. **Who should I call if I have questions?**

If you have any questions about the study or you think you have a study related injury or you want information about treatment, please contact the researcher as below:

Ho Chiou Yi

Dietitian U 41, Dietetic and Food Service Department, National Cancer Institute

03-88923406

dtho@nci.gov.my

If you have any questions about your rights as a participant in this study, please contact: The Secretary, Medical Research & Ethics Committee, Ministry of Health Malaysia, at telephone number 03-2287 4032.

INFORMED CONSENT FORM

Title of Study: Fast Track Recovery Surgery with A Whey Protein Infused Carbohydrate Loading Drink Pre-Operatively and Early Oral Feeding Post-Operatively among Surgical Gynaecologic Cancer Patients: Study Protocol of an Open Labelled Randomized Controlled Trial

By signing below I confirm the following:

- I have been given oral and written information for the above study and have read and understood the information given.
- I have had sufficient time to consider participation in the study and have had the opportunity to ask questions and all my questions have been answered satisfactorily.
- I understand that my participation is voluntary and I can at any time free to withdraw from the study without giving a reason and this will in no way affect my future treatment. I understand the risks and

benefits, and I freely give my informed consent to participate under the conditions stated. I understand that I must follow the study doctor's instructions related to my participation in the study.

- I understand that study staff and government or regulatory authorities have direct access to my medical record in order to make sure that the study is conducted correctly and the data are recorded correctly and the data are recorded correctly. All personal details will be treated as STRICTLY CONFIDENTIAL.
- I will receive a copy of this subject information/ informed consent form signed and dated to bring home.

Subject:

Signature: I/C number:

Name: Date:

Investigator conducting informed consent:

Signature: I/C number:

Name: Date:

Impartial witness:

Signature: I/C number:

Name: Date:

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- 28.05.2019Fundingdisclosure.pdf
- SPIRITchecklistFTR28052019.pdf
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