Study Title: Food preference following bariatric surgery

Principle Investigator:
Prof Carel le Roux
Metabolic Medicine Research Group
Conway Institute of Biomolecular and Biomedical Research
University College Dublin
Belfield
Dublin 4
carel.leroux@ucd.ie

Co-Investigators
Dr Alan Spector
1107 W. Call St.
Florida State University
Tallahassee
FL 320306-4301
USA
spector@psy.fsu.edu

Mr Justin Geoghegan
Department of Surgery
St Vincent's University Hospital
Elm Park
Dublin 4

Prof Donal O'Shea
Department of Endocrinology
St Vincent's University Hospital
Elm Park
Dublin 4

Research Investigator

Dr Loai Shakerdi

Clinical Trial Co-ordinator

Metabolic Medicine Research Group

Conway Institiute of Biomolecular and Biomedical Research

University College Dublin

Belfield

Dublin 4

loai.shakerdi@ucd.ie

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1 Overview

1.1 Relevance

Obesity remains a significant public health problem with the prevalence world wide doubling and now standing at 600 million adults [1]. We are seeing direct rises in obesity related morbidity and mortality, particularly relating to type 2 diabetes, cardiovascular disease and obesity related cancers [2]. Treating Obesity remains a challenging prospect and the role of pharmacotherapies have been limited by their side effects with surgical interventions proving most effective [3]. Bariatric surgery has led the way in terms of effective therapies for obesity with 14-25% reduction in body weight as well as improvement in metabolic risk markers and reduced mortality compared to control groups [4]. Despite the dramatic effects on calorie intake, weight loss and metabolic health, our understanding of mechanisms through which bariatric surgery mediates these effects remains limited. The impact of the altered gut hormone milieu following Roux-en-Y gastric bypass (RYGB) has raised questions regarding the impact of these peptides on food avoidance and food reward patterns. To explore this relationship we will conduct a prospective study objectively measuring food preference and gut peptide responses in patients undergoing RYGB.

2 Study Objectives and Design

2.1 Objectives

The primary objectives of this study are

1. Determine the effect of Roux-en-Y gastric bypass (RYGB) surgery on food preference using a standardised Buffet meal.

2. Determine if the changes in food preference following RYGB are mediated through changes in gut peptide following surgery.

2.2 Design

The Study will be conducted in two parts. The first phase of the study is an observational component where participants who are due to undergo RYGB surgery in addition to a matched control group will have their food preference assessed using a standardised macronurtient self selection paradigm (MSSP). This process will be undertaken 1 months pre and 3, 12 and 24 months post surgical intervention (See figure 1). The control group will be studied at matched time points. This will allow determination of the primary outcome, whether RYGB surgery alters food preference. Phase two of the trial will focus on understanding potential mechanisms responsible for altered food preference. It will take the form of a randomised control study whereby subjects following RYGB and controls will be

invited to repeat the MSSP after randomly receiving octreotide or saline placebo in a blinded crossover fashion. This assessment will take place one year following surgery.

Figure 1: Schematic of Study Design

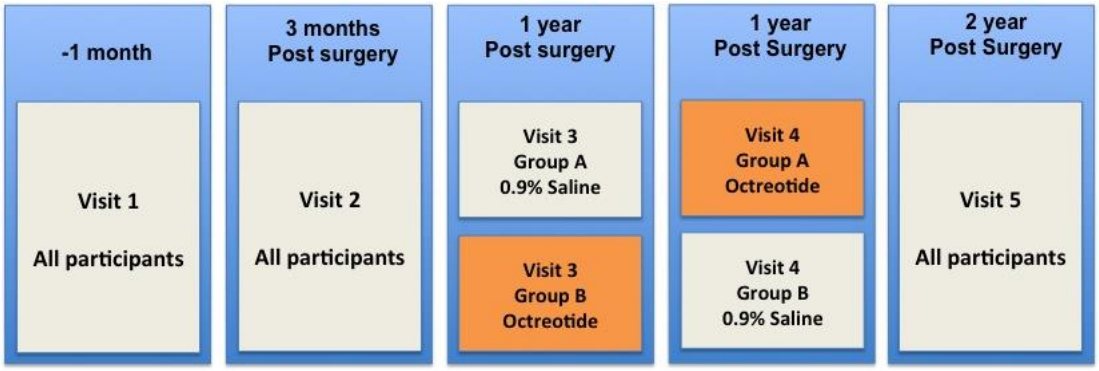

Figure 1. Each Study visit will include a Buffet lunch, macronutrient self-selection paradigm. Fasting and postprandial blood samples will be collected on all participants. Subjects will be randomised to either 0.9% Saline or Octreotide at the 1 year visit crossing over to the other therapy at their second visit.

3 Methodology

3.1 Recruitment

3.1.1 Participants

1. Patients scheduled to undergo bariatric surgery will be recruited from existing clinics.

2. Healthy free-living individuals will be recruited through community and hospital based efforts.

3.1.2 Inclusion/Exclusion Criteria

The inclusion and exclusions criteria for the study are outlined below and in order to participate in the study patients must comply with these criteria.

Inclusion Criteria

- Age 18 or over
- Surgical and non-surgical groups:
    - Bariatric surgery
    - Controls with no history of bariatric surgery
- Independently mobile

- Capacity to consent to participate

Exclusion Criteria

- Age <18 years
- Pre-operatively: Factors impairing ability to consume meal
    - Significant dysphagia
    - Gastric outlet obstruction
    - Anything factor that prevents subjects from eating a meal.
- Post-operatively: Factors impairing ability to consume meal
    - Significant and persistent surgical complications or
    - Anything that prevents subjects from eating a meal.
- Systemic or gastrointestinal condition which may affect food intake or preference
- Pregnancy or lactation
- Active and significant psychiatric illness including substance misuse
- Significant cognitive or communication issues
- Medications with documented effect on food intake or food preference
- History of significant food allergy and certain dietary restrictions
- History of liver disease or pancreatitis (Exclusion from Octreotide)
- History of bradyarrythmia (Exclusion from Octreotide)
- Use of medications with potential serious interactions with Octreotide (Exclusion from Octreotide)

3.1.3 Recruitment procedure

Recruitment of RYGB group

- Subjects referred to the Bariatric surgery service at St Vincents University Hospital will be considered for recruitment.
- Subjects will be approached after it is confirmed that they are suitable candidates for RYGB. A member of the clinical team will provide potential participants with a letter inviting them to participate in the study.
- Volunteers will be asked to contact the research team if they are interested and a screening visit will be scheduled.
- Written information will be sent to individuals interested in taking part prior to the screening.

- At the study visit the participant will have the opportunity to address any concerns or questions prior to informed consent being obtained.

Recruitment of RYGB group (non affiliated)

Recruitment will be opened up to individuals scheduled to undergo bariatric surgery in centres other than those outlined above. Posters containing information about the study and contact details of the investigators will be distributed to external centres undertaking bariatric surgical procedures. Allowing members of the public undergoing bariatric surgery the opportunity to opt in to the study if they wish.

Recruitment of Control group

Recruitment of the control group will be focused on recruiting healthy free living individuals who did not have bariatric surgery. These subjects will include those recruited by the community and hospital based protocol.

Proposed Recruitment methods

1. **Community based campaign**

   Posters outlining the study initiative will be places in public areas including hospital waiting rooms, and universities contact information for the research investigator will be available. Study information will be circulated internally by email at University College Dublin as well as its affiliated hospitals St Vincents University Hospital. Potential participants identified through this method will be able to make contact with the research investigator and they will receive written information detailing the study and be invited to attend a screening visit. If required an open advertisment will be placed in national newspaper.

2. **Primary care campaign**

   Posters and information sheets relating to the study will be circulated to GP practices in the greater dublin area. We will offer to make a presentation at the UCD and the North Dublin City GP training meetings educting primary care physicians on the ongoing study initiative. GP/GP trainees will be given information supporting this presentation containing contact details for the research investigator that can be given to people ientified as potentially suitable in GP practices. Potential subjects identified through this method will be able to make contact with the research investigator, patients will be invited to attend the hospital for a screening visit.

3.2 Study Procedures

3.2.1 Food Preference Questionnaire

At the screening visit, volunteers will be asked to rate their preferences for 72 different food stuffs using a Likert scale. The items will be categorised into 6 different groups representing depending on their macronutrient content. They will be listed in no particular order. Participants will be asked to rate each individual item along the 9 point scale with the following anchors: 1 = dislike extremely; 5 = neutral; 9 = like extremely. Responses from the Screening Questionnaire will be used to select appropriate foodstuffs for use in a 18 item buffet spread, for each given subject, from the stock list of 72 items. The 18 items selected for the buffet spread will comprise high fat and low fat options combined with varying carbohydrate and protein content.

3.2.2 Participant Information and Consent

In advance of the study volunteers will have received a copy of the participant information. Any questions and concerns that remain can be discussed with the investigator at the screening visit. If the volunteer meets the inclusion criteria and is satisfied to proceed with recruitment to the study they will be asked to sign the consent form prior to the initiation of any further elements of the study visit. As part of this process every participant will be advised of their right to refuse to participate or to withdraw at any time without impediment to their medical care in accordance with Good Clinical Practice guidelines. Withdrawal from the study can be done at any time by contacting the hospital or research team. If a participant chooses to participate, and subsequently withdraws their consent, all blood samples, records or footage in storage will be destroyed and the information stored will be deleted so it cannot be used again.

3.2.3 Study Screening Questionnaire

All volunteers attending who have attended and consented to the screening procedure will undertake a screening questionnarie with the assistance of the study doctor. This will outline medical history and inclusion and exclusion criteria for the study.

3.2.4 Anthropometric measures

In order to minimise variability in the measurements the same investigator will take all measurements. At the screening visit the following procedures for anthropometric measurement will take place

- **Weight measurement**

  Study participants will have their weight meaured on a digital eqilibrated scale. The measurements will be taken between 10.00 and 11.00 after the volunteer has been asked to void. Volunteers will be weighted in their clothing with their shoes off and in barefeet or socks . Measurements will be recorded to the nearest 0.1Kg.

- **Height measurement**

  Study participants will have their height measured using a stadiometer. This measuremet will be taken in bare feet or socks. Patients will be asked to stand upright with their heels, buttocks and occiput touching the backboard of the stadiometer. The measuring arm are of the stadiometer will be brought down to the top of the subjects head. Height is recorded to the nearest 0.1cm.

- **Waist Circumference**

  A non-stretch tape measure will be used to measure waist circumference. The measurement will be taken with the subject in a standing position with the abdomen relaxed, the arms at the sides and the feet together and breathing normally. The measurer faces the subject and places a measuring tape around the subject in a horizontal plane, at the mid-point between the lowest rib and the supra iliac crest. The measurement should be taken at the end of a normal expiration, ensuring the tape is taut around the subject's waist, without compressing the skin. Waist circumference measurements will be taken in duplicate and values will be recorded to the nearest 0.1cm. The mean value of both measurements will be recorded as the waist circumference.

3.2.5 Venepuncture

At the study visits bloods will be taken to evlauate both fasting and post prandial gut peptide levels.

- A blood sample will be drawn approximatley 10ml in total.
- They will be collected in the **fasting** state and **2 hours after meal initiation.**
- All samples will be acquired by a medical doctor with experience in phlebotomy.

    - 2x 5ml EDTA tube

Collected samples will be transferred to the laboratory and processed accordingly. Plasma samples will be centrifuged for 15 minutes at 2500g. The supranatent pipetted into aliquots. The aliquots will be labelled with the **subject recruitment number**, **visit number** and **"fasting"** or **"Post Prandial".** Samples will be stored within a -20 freezer at the clinical research centre until processing of the samples commencs. Waste will be disposed of in line with hospital was disposal policies.

3.2.6 Urinary pregnancy test

Urine specimens will be collected on all women with child bearing potential prior to the administration of any drugs which the investigator and participant are blinded to. A spot urine sample will be collected from participants, transferred to the biochemistry lab and analysed for βHCG according to standardised method in the laboratory. Samples will be labelled with the volunteers name, date of birth and medical record number where available. Volunteers with an unexpected positive pregnency will be informed by the investigator of the result, excluded from the study and referred to their primary care physician for further assessment.

3.3 Randomisation

For phase two, the randomised control trial. All subjects recruited will have be assigned an anonmysed study number. Randomisation of volunteers to the intervention or placebo group will be undertaken using a web based randomisation programme. Subjects will be randomised to receive treatment A or B. Treatment A or B will correlate to either Octreotide 1µg/Kg or 0.01ml/Kg of 0.9% Saline. The buffet meal will be undertaken 60 minutes following the administration of either treatment A or B. At the subsequent study visit subjects will receive the opposite treatment in a crossover manner. The research investigator and volunteer will be blinded to the treatment. Unblinding will only take place at the end of the intervention study and data on all subjects has been statistically analysed.

3.4 Study Drug preparation and administration

Octreotide (Sandostatin® 100µg/ml, Novartis Ireland)

- The drug will be stored in line with manufacturer instructions.
- As the study drug will be blinded to the research investigator, the research nurse will be charged with preparing the study drug.
- A dose of 1µg/Kg will be drawn up by the research nurse and labeled with the appropriate code **Treatment A** or **Treatment B**.

- The weight used will have been recorded prior to drug administration
- This drug will be administered using a sterile technique to the participant's subcutaneous tissue.
- It will be given 60 minutes prior to the Buffet meal.
- A menstrual history and urinary pregnancy test will be completed on all females of child bearing potential prior to the administration of any drug.

0.9% Saline Placebo

- The drug will be stored in line with manufacturer instructions.
- As the study drug will be blinded to the research investigator, the research nurse will be charged with preparing the study drug.
- A dose of 0.01ml/Kg will be drawn up by the research nurse and labeled with the appropriate code **Treatment A** or **Treatment B.**
- The drug will be drawn up using a 1 or 2 ml syringe depending on the volume needed.
- The weight used will have been recorded prior to drug administration.
- This drug will be administered using a sterile technique to the participant's subcutaneous tissue.
- It will be given 60 minutes prior to the Buffet meal.
- A menstrual history and urinary pregnancy test will be completed on all females of child bearing potential prior to the administration of any drug.

3.5 Buffet Meal

The study will take place at the Clinical Research Centre at St Vincents University Hospital. The study methodology will follow the paradigm for food preference assessment developed and validated by Geiselman *et al* [1].

Subjects will be provided with a Food preference questionnaire prior to the study visit. This will ask patients to hedonically/by preference rate each of approximately 90 common foodstuffs of known macronutrient composition on a 9-point Likert scale with the following anchors: 1 = dislike extremely; 5 = neutral; 9 = like extremely. This assessment will be completed by subjects priot to their screening visit, the data sheet will the collected and evaluated by the research investigator. This food preference questionnarie will categorise the 90 food stuffs into each of the 6 cells highlighted in the table below and in no particular order.

Responses from the questionnaire will be used to select appropriate foodstuffs for use in an 18 item buffet spread, for each given subject, from the stock list of 90 items. The 18 items selected for the buffet spread will comprise high fat and low fat options combined with varying carbohydrate and protein content, as depicted in **Table 1**. We will endeavour to provide each subject with foods to which he/she had an intermediate hedonic response (5 – 7). High fat foods given to an individual subject will be paired with a low fat variation of the same food; eg high and low fat meat options, high and low fat cheese options. Stock list foods are all items which are commercially available and require minimal or no preparation (for example slicing fruit, bread or cheese). All food items will be stored and used according to manufacturer's instructions.

Table 1: Macronutrient self-selection paradigm

	High Simple Sugar	**High Complex CHO**	**Low CHO/High Protein**
High Fat	Three foods Fat > 40% Sugar >30%	Three foods Fat >40% Comp Carb >30%	Three foods Fat >40% Protein >13%
Low Fat	Three foods Fat <20% Sugar >30%	Three foods Fat <20% Comp Carb >30%	Three foods Fat <20% Protein >13%

Adapted from Geiselman *et al [1]*.

Subjects will be asked to fast from 22:00 the night before the study visit. Subjects may drink water during this period. Volunteers will be asked to abstain from alcohol consumption and strenuous exercise for the preceeding 24 hours. Medications may be taken as per usual, but this will be discussed with individual subjects in advance of the study day. Subjects will be asked to come to the CRC at 10:30 on the morning of the assessment. On arrival at the CRF, study documentation and body anthropometry will be completed.

Each subject will have access to their own individual buffet table, in separate rooms, such that subjects cannot observe the selections made by other subjects. Order of foods on the buffet spread will be randomised on each study visit. Containers of known weight of the 12 test foods will be provided to each subject. Subjects will be provided with written and verbal instructions prior to commencing the buffet meal. Volunteers will be instructed that they can now eat their meal and consume as much food as they wish in order to feel "comfortably

full". Patients will be made aware that gut hormone responses will not be optimal if they don't reach a state of being comfortably full, eat the foods they like or if they overeat and feel unwell. Subjects will be reminded that it is important that they understand and follow these instructions, as the blood test for gut hormones will be performed on completion of the meal. They may also eat as much of any particular food type they wish and that it is not a competition. All subjects will be provided with still bottle water to accompany the buffet meal.

Each subject will have access to their own individual buffet table. Subjects will be asked to place any mobile electronic devices that they have brought with them into a sealed container in their room, with all electronic devices switched off. Reading material and medica sources in the form of television or radio will be provided. Subjects will instructed to alert the research team when they have finished eating, or should they experience any problems. After providing these instructions and answering any questions the subject may have, the investigator will then leave the room.

At this point a member of the research team will record the exact quantity of each foodstuff chosen by each subject by determining change in test food container weight.

At each of the 12 month visits, patients eligible for randomisation will receive a subcutaneous injection of either 1µg/kg octreotide(Sandostatin® 100microgram/ml) or 0.01ml/Kg 0.9% saline, in a random sequence. The study meal will be initiated directly after the completion of the baseline blood test on study visits not requiring a subcutaneous injection. Where subjects have received an injection of octreotide or saline, the meal will be initiated one hour after injection to ensure adequate serum concentrations of octreotide have been achieved.

3.6 Clinical Nutritional Assessment

All participants will be have an assessment by a trained clinical nutritionist at the end of the first study visit. The session include a 45 minute consultation with all participants. It will include a review of current dietary preferences followed by a standardised dialogue guiding subjects on the priniciples of healthy eating.

4 Protocol Overview/Study visit and Event Schedule

Outlined below is a detailed overview of the study protocol. **Table 2** summarises the procedures that will be undertaken at each patient visit while **Table 3** outlines the basic schedule of a typical study visit.

Screening Visit

1. Informed consent
2. Food preference Qiestionairre
3. Screening Questionairre and Eligibility Assessment

Study Visit 1: Week -4

1. Anthropometric assessment: Height, weight, BMI and waist circumference
2. Fasting Bloods
3. Buffet Meal
4. Post prandial bloods
5. Clinical Nutrition education session

Study Visit 2: Week 12

1. Anthropometric Assessment: Height, weight, BMI and waist circumference
2. Fasting Bloods
3. Buffet meal
4. Post Prandial Bloods

Study Visit 3: Week 52

1. Anthropometric Assessment: Height, weight, BMI and waist circumference
2. Fasting Gut peptide level
3. Randomisation to treatment A or B (Saline or Octreotide)
4. Administration of blinded Study drug prior to buffet meal
5. Buffet meal
6. Post prandial bloods
7. Urinary Pregnancy test

Study Visit 4: Week 52

1. Anthropometric Assessment: Height, weight, BMI and waist circumference
2. Fasting Gut peptide level

3. Administration of blinded study drug prior to buffet meal(A or B determined by previous randomization)
4. Buffet meal
5. Post prandial bloods
6. Urinary Pregnancy test

Study Visit 5: Week 102

1. Anthropometric Assessment: Height, weight, BMI and waist circumference
2. Fasting Bloods
3. Buffet meal
4. Post Prandial Bloods
5. Discharge from study/Letter to General Practitioner

Table 2: Schedule of Study Visits and Events

	Screening Visit	Visit 1 Week -4	Visit 2 Week 12	Visit 3 Week 52	Visit 4 Week 52	Visit 5 Week 104
Informed Consent	X	X				
Height		X	X	X	X	
Weight		X	X	X	X	
Fat mass		X	X		X	
Blood pressure		X	X	X	X	X
Heart rate		X	X	X	X	X
Medical History		X				X
Fasting Gut Peptides		X	X	X	X	X
Post Prandial Gut Peptides		X	X	X	X	X
Pregnancy test		X	X	X	X	X
Administration of Study Drug				X	X	
Food preference Questionnaire	X					
Buffet meal			X		X	
Clinical Nutrition session		X				
GP letter	X					X

TABLE 3: General study visit schedule

Time	Action
10:30 to **12.00**	**Arrive at CRC** **Complete paperwork,** questionnaires and collection of anthropometric data
10.50	**Phlebotomy 1 (fasting pre-meal)**
11.00	**SC injection of octreotide or saline as randomised at 52 week visit**
12.00	**Commence *ad libitum* buffet meal** Upon completion of the *ad libitum* meal
14.00	**Phlebotomy 2 at 2 hours post meal initiation**
14.15	**End of Visit**

5 Adverse event program

5.1 Subject premature Withdrawl

If a study volunteer fails to complete the study protocol it will be documented in the individual case report form. The reason for failure to complete the study will be included in the CRF. Study Subjects may be withdrawn for the following reasons

- Adverse Event(s) (AEs)
- Abnormal laboratory value(s)
- Protocol violation
- Subject withdrew consent
- Lost to follow-up
- Death

All patients who withdraw early from the study will have their GP informed in writing that their participation in the study is complete. In the event of adverse event, GP's will be informed and arrangements will be made for subjects who have a requirement for ongoing medical follow-up as a consequence of an adverse event.

5.2 Adverse Events (In accordance with the ICH)

An adverse event (AE) is defined as "any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment". The principal investigator (PI) will be informed of any adverse events affecting participants within 24 hours of the research investigator becoming aware of them. The suitability of the participant to continue with the study will be determined by the PI. All adverse events will be recorded in the CRF and the adverse events log contained within the site file. A data safety monitoring committee will be establish consisting of a senior physicians. All events will be reported within 7 working days and decisions to progress or stop the study will be made in conjunction with the Ethics committee.

5.3 Serious Adverse Events

A serious adverse event (SAE) or reaction is defined as any untoward medical occurrence that:

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect.

The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. The principal investigator (PI) will be informed of any adverse events affecting participants within 24 hours of the research investigator becoming aware of them. The suitability of the participant to continue with the study will be determined by the PI. All adverse events will be recorded in the CRF and the adverse events log contained within the site file. A data safety monitoring committee will be establish consisting of a senior physicians. All events will be reported within 7 working days and decisions to progress or stop the study will be made in conjunction with the Ethics committee.

6 Insurance and Indemnity

Clinical staff will be covered under the institutional Clinical Indemnity Scheme (CIS)

7 Reimbursement

All participants will be reimbursed for travel and parking expenses incurred while

participating. Volunteers will not be paid to participate in this study.

8 Data management

Data will be collected and stored in both paper and electronic format. Paper data will be filed and stored in a locked office at the Clinical Research Centre, St Vincents University Hospital. Electronic data will be password encrypted. All data will be handled in line with data protection legislation.

9 Statistical analysis

Data will be analysed using GraphPad Prism (version 6.0) for Windows, GraphPad software (San Diego, CA, USA) and SPSS® (version 20.0) software (SPSS, Chicago, IL, USA). Central tendencies for patient and control group demographics, anthropometric data, caloric intake and macronutrient intake will be calculated and expressed using arithmetic mean ± standard error of the mean or median (range), as appropriate. Differences in continuous variables between surgical and control groups will be calculated using the Student's *t* test or Mann-Whitney U test for parametric or non-parametric data, respectively. Correlative analyses will be performed using the Spearman Rho rank correlation to assess the relationship between *ad libitum* caloric intake and macronutrient intake with peri-operative weight loss and anthropometric data. Univariate analysis of factors associated with perioperative and post-surgical weight loss will be performed using Student's *t* test or one-way ANOVA for categorical variables or simple logistic regression for continuous variables. For the multivariate analysis, independent variables which were significant on univariate analysis, including standard demographic, food intake and food preference, will be entered into a multiple logistic regression model with a forward stepwise selection procedure to assess their impact on perioperative and post-surgical weight loss. All statistical analyses will be two-tailed with the threshold of significance set at $P < 0.05$.

Although the patients will be tested at all of the time points. Sample size has been estimated based on Gregersen *et al.*[2] who suggest that 35 patients will be required per group in an unpaired study design to detect a 300kJ difference in overall caloric consumption between two groups with a power of 0.8. We anticipate that single-sitting food intake after upper GI surgery will be approximately 60-80% that of matched controls. Given a control ad libitum caloric intake of approximately 600kcal, this would equate to a 120 – 240kcal difference in caloric intake. In addition, differences in preferred food types will be studied.

10 Duration of Project

The estimated duration of the study will be 36 months. Screening and recruitment will begin in February 2016. Completion of the study is planned for February 2019.

11 Administrative considerations

11.1 Changes to the conduct of the study/Amendments to study protocol

Any and all amendments to the protocol must be agreed upon by the named investigators of the study. All protocol amendments must submitted to the institutional ethics committee for approval. Informed consent documents must be updated with amendments appropriately and submitted with application for protocol revision. Changes to the protocol may not be implemented prior to ethical approval unless it is intented to eliminate and immediate hazard to the study subject. In this case study sponser and ethics committee must be informed as soon as possible of the deviation.

11.2 Premature termination of the study

The principal investigator reserves the right to terminate the study at any time. Adequate consideration must be given to the protection of all study volunteers on termination of the investigation. Subjects will be informed in writing immediately and appropriate follow-up is assured.

References

1. Geiselman, P.J., et al., *Reliability and Validity of a Macronutrient Self-Selection Paradigm and a Food Preference Questionnaire.* 1997. **63**: p. 919-928.
2. Gregersen, N.T., et al., *Reproducibility and power of ad libitum energy intake assessed by repeated single meals.* Am J Clin Nutr, 2008. **87**(5): p. 1277-81.