# TRIAL PROTOCOL

East Lancashire Hospitals NHS Trust

# EFFECT OF A MODIFIED STARCH COMPARED TO STANDARD MALTODEXTRIN ON POST-OPERATIVE INSULIN RESISTANCE WHEN GIVEN PRE-OPERATIVELY FOR LAPROSCOPIC COLORECTAL SURGERY AS PART OF AN ENHANCED RECOVERY PROGRAM: (SUPERSTARCH STUDY)

Trial Registration: Controlled Trials ISRCTN TBC

Sponsor: East Lancashire Hospitals NHS Trust

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## 1. ROLES & RESPONSIBILITIES

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| **ERP Nurse** | Heather Coleman |
| **Dietician** | Fran Armstrong |

The CI will be responsible for the overall conduct of the study. The research fellow will be responsible for recruitment, consent and data collection. The ERP Nurse will provide outcome data collected by the ERP Database. The statisticians will be responsible for the sample size calculation, randomisation procedure and the statistical analysis of the study.

## 2. TABLE OF CONTENTS

# 3. GLOSSARY

- ASA = American Society of Anesthesiologists
- CRP = C-reactive Protein
  ERP = Enhanced Recovery Program
- GSD = Glycogen Storage Diseases
- GI = Glycaemic Index
- HbA1c = Glycated haemoglobin
- HPMS = Hydrothermally processed maize starch
- MAL = Maltodextran
- MDT = Multi-disciplinary team
- POD = Post-operative Day
- POMS =
- PONV = Post-operative nausea and vomiting
- POCT = Point of care test
- POAC = Preoperative Assessment Clinic
- PQRS =
- HOMA = Homeostasis Model Assessment
- VAS = Visual Analogue Scale

# 4. INTRODUCTION

## 4.1 BACKGROUND AND RATIONALE

The development of insulin resistance and hyperglycaemia following surgery is a well-documented phenomenon which is associated with increased morbidity and mortality.[1–3] Insulin sensitivity is reduced by approximately 50% following elective surgery and persists for at least five days postoperatively in the case of upper abdominal surgery. There is a dose-response relationship between the magnitude of surgery and the degree of insulin resistance postoperatively. In the case of colorectal surgery where the magnitude is variable the change is closely correlated with the duration of surgery. Blood loss is the other independent predictor of the degree of insulin resistance. Therefore this metabolic variable is governed by the degree of surgical trauma itself rather than any predisposing or associated factors.

It appears that endogenous glucose production (EGP) in the liver is unaffected by the suppressive effect of insulin per se, postoperatively. Thus the changes in insulin sensitivity following surgery are secondary to alterations in peripheral glucose uptake alone, and therefore reasonable to assume that the main site for this is skeletal muscle, being the largest organ involved.

The precise mechanism behind this loss of insulin sensitivity is unknown but it has been demonstrated that providing carbohydrates pre-operatively can attenuate this effect.[4–6] Pre-operative carbohydrate drinks were also found to reduce pre-operative anxiety and hunger.[7] There is also evidence that pre-operative carbohydrate drinks may decrease loss of post-operative muscle mass and function and attenuates protein catabolism. [6,8–11]

In addition, receiving a carbohydrate drink 2 hours before the start of anaesthesia does not significantly affect the gastric residual volume compared to patients fasted overnight.[2,4,7,12]

This practice, in conjunction with several other interventions, has now become routine with the introduction of Enhanced Recovery Protocols (ERP). These have been shown to reduce length of stay and complication rates for major surgery.[13-16] A recent ERAS cohort study showed that patients that were treated with preoperative carbohydrates, experienced a 44% reduction in the risk of postoperative symptoms.[17]

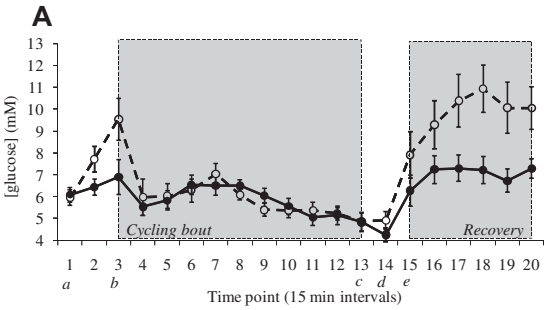
In the search for a treatment for the rare group of inherited, metabolic disorders known as Glycogen Storage Diseases (GSD), a hydrothermally processed maize starch (HPMS) was developed with the aim of providing overnight blood glucose stability with a lower glycaemic index (GI).[18] Two small trials led to the development of a high-amylopectin-containing cornstarch. This compound demonstrated a longer duration of action and a lower initial increase in blood glucose with lower peak concentration compared to standard uncooked cornstarch. [18,19]

Hydrothermally processed maize starches, or so-called *Superstarch*, have been used as an alternative to standard, maltodextrin (MAL) based drinks within sports nutrition. They are used to provide stable blood glucose concentrations over time and avoid a spike in insulin concentration, factors which are thought to be advantageous in endurance exercise. This was investigated in a comparison of *SuperStarch* to a standard MAL formulation in a randomized, controlled crossover trial in nine elite cyclists.[19] These participants' ingested 1mg/kg of either MAL or HPMS, rested for 30 minutes, exercised for 150 min at 70% peak VO2 and then at 100% peak VO2 until they fatigued. Following exercise another 1mg/kg of HPMS or MAL was taken and the participants then rested for 90 min. The researchers found that during exercise and recovery HPMS provided more stable blood glucose levels, blunted insulin release and increased levels of fatty acids and glycerol, suggesting increased lipolysis. There was also a reduced initial spike in blood glucose and insulin following ingestion of HPMS compared to MAL (Figures 1 and 4).

Gastric emptying is influenced by carbohydrate load and by osmolality, with increasing osmolality associated with prolongation of gastric emptying.[2,12,21-24] Therefore, it stands that increasing the complexity of the

carbohydrate source would increase speed of gastric emptying whilst providing the same calorific content. Indeed this is the case, with maltodextrin based carbohydrate drinks currently given pre-operatively as part of ERP having little effect on gastric residual volume at the start of anaesthesia, and actually result in less residual volume than a starved state. [4,7,12]

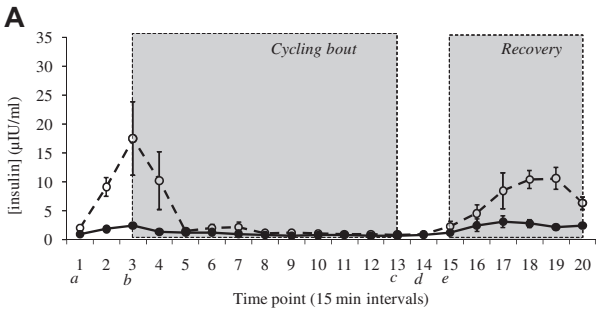





B

| Time (range) | Glucose (mM) | | |
|---|---|---|---|
| | HMS | MAL | p-value |
| PreEx + Ex (*185 min) | 1140 ± 60 | 1204 ± 68 | 0.22 |
| Recovery (*75 min) | ***608 ± 43*** | ***841 ± 80*** | ***0.001*** |
| Total (*260 min) | ***1747 ± 99*** | ***2045 ± 142*** | ***0.005*** |

**Fig. 1.** Serum glucose response to HMS (closed circles) versus MAL (open circles) before and after cycling bouts (A) and area under the curve analysis for different time ranges (B). Values are expressed as mean ± SE. (A) Intervals between time points spanned 15-min periods. a, Fasting blood before first drink ingestion (1 g/kg of body mass); b, onset of cycling bout; c, blood before time to exhaustion; d, blood immediately after time to exhaustion; e, blood 15 min after second drink ingestion (1 g/kg of body mass). (B) Between-trial values were compared using paired-samples *t* tests. Significant differences between trials ($P \leq 0.05$) are italicized. HMS, hydrothermally modified starch; MAL, maltodextrin; PreEx + Ex, before exercise plus exercise.




B

| Time (range) | Insulin (µIU/ml) | | |
|---|---|---|---|
| | HMS | MAL | p-value |
| PreEx + Ex (*185 min) | ***286 ± 41*** | ***827 ± 183*** | ***0.012*** |
| Recovery (*75 min) | ***240 ± 45*** | ***636 ± 119*** | ***0.002*** |
| Total (*260 min) | ***525 ± 79*** | ***1463 ± 296*** | ***0.005*** |

**Fig. 4.** Serum insulin response to HMS (closed circles) versus MAL (open circles) before and after cycling bouts (A) and area under the curve analysis for different time ranges (B). Values are expressed as mean ± SE. (A) Intervals between time points spanned 15-min periods. a, Fasting blood before first drink ingestion (1 g/kg of body mass); b, onset of cycling bout; c, blood before time to exhaustion; d, blood immediately after time to exhaustion; e, blood 15 min after second drink ingestion (1 g/kg of body mass). (B) Between-trial values were compared using paired-samples *t* tests. Significant differences between trials ($P \leq 0.05$) are italicized. HMS, hydrothermally modified starch; MAL, maltodextrin; PreEx + Ex, before exercise plus exercise.

*Preload®*, the pre-operative carbohydrate drink used in ERP across the NHS and in our institution, has an osmolality of 135mOsm/kg when mixed in the standard dilution (one 50g sachet is diluted with 400ml water). *Generation UCAN* is a powder-based sports energy drink mix, which makes use of *SuperStarch*, which has an osmolality of 89mOsm/kg when 60g, is diluted into 500ml water. This indicates that *Generation UCAN* will be emptied from the stomach more rapidly than *Preload®.*

The rationale for this pilot study is that HPMS drinks given pre-operatively may result in a further reduction in insulin resistance post-operatively compared with standard maltodextrin containing carbohydrate drinks due to a longer duration of action, a greater reduction in peak glucose concentration, a greater reduction in post-operative blood insulin levels and a greater lipid oxidation. This in turn may lead may lead to a greater reduction muscle loss and morbidity, specifically infectious complications, and in turn time to fitness for hospital discharge.

## 4.2 Objectives

The null hypothesis states that there is no difference in post-operative insulin resistance between patients who drink *Preload®* compared to those drinking *Generation UCAN* preoperatively.

## 4.3 Trial Design

Randomised controlled single-blinded (subject only) parallel group, 1:1 allocation ratio superiority framework study.

# 5. Methods: Participants, Interventions, and Outcomes

## 5.1 Study Setting

Royal Blackburn Hospital, a large district general hospital, and Royal Surrey County Hospital NHS Foundation Trust, a university hospital, which both perform high volumes of major abdominal surgery with well established Enhanced Recovery Programmes.

## 5.2 Eligibility Criteria

### Inclusion criteria

- Patients > 18 years of age
- Laparoscopic colorectal resection
- Included in Enhanced Recovery Protocol
- ASA 1-3
- Able to give consent

### Exclusion Criteria

- Non-English speaker
- Pregnancy
- Diagnosed diabetes mellitus (diet, drug or insulin controlled)
- Diagnosed impaired glucose tolerance (fasting glucose in POAC >5.5 mmol/l and/or HbA1C>5.7%)
- Decreased gastrointestinal motility (from medication or disease) or predisposition to reflux
- Diagnosis of Inflammatory Bowel Disease
- Allergy to either preoperative carbohydrate drink

## 5.3 Interventions

Following consent and randomisation at the Preoperative Assessment Clinic (POAC) visit one group will receive the current pre-operative carbohydrate solution, *Preload®* (a maltodextrin solution), and the other group will receive *Generation UCAN* (a hydrothermally modified starch solution) to take home.

In both cases these will be dispensed as a powder in a clear plastic zip lock bag to ensure blinding of the patient (the research team will have decanted the appropriate dose of each supplement into these bags and will be aware of the allocated intervention). This will be a single sachet, in the case of *Preload®*, and an equivalent weighed and measured volume from a large tub, in the case of Generation UCAN. Both groups will be instructed to reconstitute the powder provided in 400mls of water on the day of surgery, and consume it between two and three hours before surgery, as per standard practice in the ERP.

Both groups will also be instructed to consume approximately 500mls (1 pint) of water with their evening meal the evening before surgery to remain well hydrated.

The *Control* group will receive 47.5g of carbohydrate in the form of *Preload®*.

The Intervention group will receive 56.55g of flavoured Generation UCAN (providing 47.5g of carbohydrate).

All other aspects of patient care will be standardized as per our ERP (see Appendices).

## 5.4 Outcomes

### Primary Outcome

- Change in insulin resistance from baseline on POD 1 measured using a technique called HOMA (see Appendices), which utilises serial fasting blood glucose and insulin measurements.

### Secondary Outcomes

- Change in insulin resistance from baseline on POD 2 and POD 3 measured using a technique called HOMA, which utilises serial fasting blood glucose and insulin measurements.
- Stress response following surgery, measured by sampling cortisol levels preoperatively, at the end of surgery, and at 24 hours post-operatively and the inflammatory response measured by CRP levels pre-operatively, and on POD 1,2 and 3.
- Ultrasound measurement of gastric volume pre-operatively (see Appendices for technique)
- Recovery profile including:
    - PQRS (see Appendices) score measured pre-operatively, at 2 hours after surgery, POD 3 and POD 7;
    - Muscle strength measured using a grip strength dynamometer pre-operatively, twice daily (morning and afternoon) on POD 1, 2 and 3, and then once daily on alternate days thereafter until discharge (the patient's dominant hand will be used for this measurement, and the best out of three consecutive strengths will be used with mean values analysed);
    - Time to surgical fitness for discharge (see Appendices for criteria) measured in hours (date and time of fitness for surgical discharge is recorded in the ERP database).
- Morbidity measured using the POMS score on POD 2 and POD 5 (see Appendices).
- PONV VAS score on POD 1.
- Sensations of thirst & hunger VAS score immediately pre-operatively and on POD 1.
- Caloric intake POD 1 and 2.
- Ambulation time POD 1 and 2.
- Adverse events i.e. aspiration and hypo- or hyperglycaemia (these are the only relevant safety assessments for these interventions) will be assessed on the operative day for the former & up to the end of POD 1 for the latter.
- Cost analysis: difference in cost between doses of Pre-Load & Generation UCAN and costs of respective hospital and critical care lengths of stay.

## 5.5 Participant timeline

| | Enrolment | Allocation | Close-out | | | | | |
|---|---|---|---|---|---|---|---|---|
| TIMEPOINT | Surgical OPD | POAC | Op Day | POD1 & POD2 | POD3 | POD5 | POD7 | D/C Hospital |
| ENROLMENT: | | | | | | | | |
| Eligibility screen | X | | | | | | | |
| HbA1C* | | | X | | | | | |
| Informed consent | | X | | | | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| PQRS score | | X | X | | X | | X | |
| Fasting glucose (POCT) | | X* | | | | | | |
| Allocation | | X | | | | | | |
| INTERVENTIONS: | | | | | | | | |
| *Preload®* | | | X | | | | | |
| *Generation UCAN* | | | X | | | | | |
| ASSESSMENTS: | | | | | | | | |
| Baseline Data Collection | | X | | | | | | |
| Outcome Data Collection | | | X | X | X | X | | X |
| Gastric Volume Measurement | | | X | | | | | |
| Blood samples | | | X | X | X | | | |
| Insulin Resistance (HOMA) Calculation | | X** | X** | X | X | | | |
| Hand Grip Strength** | | X | | X | X | X | X | |

*If a patient has a recent HbA1c result available on the laboratory results system this will be used for screening as opposed to point of care blood glucose.

** Measured twice a day first three postoperative days then alternate days until discharge from hospital.

***The baseline HOMA to be done on either of these 2 visits as long as the patient is fasted.

## 5.6 SAMPLE SIZE

The standard deviation for insulin resistance data was obtained from a previous study of pre-operative carbohydrate treatment in total hip replacement surgery (Soop 2001)[5]. Twenty patients in each group are needed based on 80% power for a two-sample t-test, detecting a minimal important difference of 15% in change of insulin resistance on the first postoperative day from baseline, with a standard deviation of 16% and a two-tailed significance level of 0.05. A minimal important difference of 25% was used in a previous study comparing pre-operative carbohydrate treatment with a placebo group for patients who had total hip replacement (Soop 2004) [6]. In this study two carbohydrate drinks are being compared, PreLoad with Generation UCAN. Therefore, a smaller minimal important difference of 15% was deemed appropriate. This sample size calculation allows for 10% attrition.

### 5.7 Recruitment

The colorectal specialist nurses will be asked to forward details of patients listed for eligible surgery following each Colorectal Cancer MDT Meeting. All of the surgeons who are part of this group, along with the Waiting List Clerks who book the operation dates, the Pre-operative Assessment Clinic staff (the CI also undertakes weekly Cardiopulmonary Exercise Testing Clinics in this area) and the Enhanced Recovery Nurse will all be aware of the study eligibility criteria and inform the research team as early as possible regarding such patients.

Patients requiring admission to a higher level of care and therefore arterial line monitoring will be preferred due to the ease of blood sampling.

Local data for the past four years indicates an average of 50 eligible patients per year at the Royal Blackburn Hospital. The Royal Surrey County Hospital has a higher volume of eligible patients. Due to the non-invasive nature of the intervention and experience with current interventional RCT at both centres in a similar study population a high approach to consent ratio would be expected. Hence recruitment of 40 patients (20 patients per centre) is feasible in 6 months.

## 6. Methods: Assignment of interventions

### 6.1 Allocation

Sequence generation:

Patients will be randomised to groups using the online randomisation service (sealed envelope) allowing allocation concealment:

https://www.sealedenvelope.com

Implementation:

The CI and the Clinical Research Fellow will enrol participants and assign participants to interventions.

### 6.2 Blinding

This study will be single blinded (patients only). The primary end point is an objective physiological parameter which cannot be influenced by any observer bias.

## 7. Methods: Data collection, management, and analysis

### 7.1 Data collection methods

Data will be collected from patient notes (pre-operative assessment booklet, anaesthetic chart, operative note, notes made post-operatively) and the ERP Database. The research team will perform the blood sampling and record the measured results as described and collect the VAS scores.

#### Pre-Operative Assessment Clinic

- Fasting POCT blood glucose to confirm eligibility (or use of previous HbA1C result if available)
- Baseline demographics – Pre-op Blue Document
- Height and weight - Pre-op Blue Document
- Mid Upper Arm Circumference (MUAC)
- ASA score – ERP Database
- Co-morbidities - Pre-op Blue Document
- Baseline PQRS score - questionnaire
- Baseline hand grip strength measurement
- Baseline fasted blood samples (to be combined with routine blood sampling).
    - Fasting Glucose
    - Fasting Insulin (3 sample to be taken at 5 minute intervals)
    - Cortisol

- CRP
- HbA1c (if not recently measured)

### Operative Day Pre-surgery

- Confirm allocated drinks consumed as per instructions & document
- Thirst and hunger sensation VAS score
- Blood samples on morning of surgery fasted (before consuming the intervention) if not done in POAC.
  - Fasting Glucose
  - Fasting Insulin (3 sample to be taken at 5 minute intervals)
  - Cortisol
  - CRP
  - HbA1c (if not recently measured)
- Duration surgery (obtained from Theatreman system)
- Volume of blood loss
- Description of operation and type of primary analgesia - obtained from Theatreman system or ERP Database
- Calories consumed

### Post-Operative Data Collection

- POSSUM score from ERP Database
- Blood samples:
  - Fasting insulin (3 samples to be taken at 5 minute intervals and glucose on the morning of POD 1, 2 and 3
  - Cortisol (at end of operation and at 24 hours)
  - CRP (POD 1 and 3)
- PQRS score Theatre Recovery, POD 3 and POD 7.
- PONV and Thirst and hunger sensation VAS scores on POD 1.
- POMS score on POD 2 and 5
- Hand grip strength measurement twice daily on POD 1, 2 & 3 and then alternate days until discharge
- Calories intake POD1 and POD2
- Ambulation time (minutes) POD1 and POD2
- MUAC POD5 or Day of Discharge if earlier
- Adverse Events up to end POD 1.
- Date and time reached surgical fitness for discharge and actual discharge – obtained from ERP Database

## 7.2 Data management

Identifiable data including full name, date of birth and hospital number will be required by the research team for identification purposes during the post-operative phase. All patient confidentiality will be ensured. The trial team will not disclose or reproduce any information by which patients could be identified. All patient data collected will be entered on to a password-protected Microsoft Excell Spreadsheet. The CI will ultimately be responsible for data collection, quality and recording and handling however data collection will be delegated to the Clinical Research Anaesthetic Fellow and ERP Data Clerk. The R&D Quality Manager will undertake monitoring to assess data quality. A separate and secure log will be kept with consent form and identifiers to allow patient follow up. During the conduct of the trial all electronic patient data will be encrypted and all trial documents stored securely at East Lancashire Hospitals NHS Trust. Following completion of the trial all non-essential confidential documents will be destroyed and essential documents (paper and electronic) will be archived and retained securely for five years in accordance with ICH GCP guidelines. Essential documents are

those which enable both the conduct of the trial and the quality of the data produced to be evaluated and to show whether the unit complied with the principles of ICH GCP and other applicable regulatory requirements.

All archived documents should be available for inspection by appropriate authorities upon request.

#### END OF TRIAL

The end of the trial will be when the final patient has been discharged from hospital, at which point the 'declaration of end of trial' form will be submitted to the REC, as required.

### 7.3 STATISTICAL METHODS

#### STATISTICAL METHODS FOR ANALYSING PRIMARY AND SECONDARY OUTCOMES

Baseline demographic and clinical variables will be reported for the two groups using summary statistics. Categorical variables will be reported using frequencies and percentages. Quantitative variables will be reported using either the mean and standard deviation or the median and interquartile range depending on the skewness of the data.

In terms of the primary outcome, the mean difference in change of insulin resistance from baseline to POD 1 will be compared using either the Independent Samples T-Test or Mann-Whitney U Test. This will depend on the skewness of the data distribution.

Between-group comparisons of quantitative secondary outcomes including change of insulin resistance from baseline to POD 3, the PQRS score and time to surgical fitness will made using either the Independent Samples T-Test or Mann-Whitney U Test, depending on the skewness of the distribution of the data. Categorical secondary outcomes will be compared between groups using the Chi-square test.

#### METHODS FOR ANY ADDITIONAL ANALYSES (EG, SUBGROUP AND ADJUSTED ANALYSES)

If differences are observed in baseline demographic and/or clinical variables prognostic of outcome, then the analysis of the primary and secondary outcomes will be adjusted for using regression-based analysis appropriate to the type of outcome variable. The trial statistician will describe details of sub-group analysis in the statistical analysis plan if possible.

#### DEFINITION OF ANALYSIS POPULATION RELATING TO PROTOCOL NON-ADHERENCE (E.G., AS RANDOMISED ANALYSIS), AND ANY STATISTICAL METHODS TO HANDLE MISSING DATA (EG, MULTIPLE IMPUTATION)

All analysis will be performed according to the intention to treat principle. The primary analysis will be based only on data obtained; sensitivity analysis will explore sensitivity to assumptions around missing data and details will be included in the statistical analysis plan devised by the trial statistician.

## 8. METHODS: MONITORING

### 8.1 DATA MONITORING

As this is a non-CTIMP study measuring low risk interventions (nutritional supplements) a DMEC is not required. The trial will be stopped by the CI following any SAE deemed to be definitely or probably related to the new study intervention (the control arm is already standard clinical practice), however this is extremely unlikely given the nature of the intervention.

### 8.2 HARMS

#### ADVERSE EVENTS (AE)

Any untoward medical occurrence or effect in a patient treated with the trial protocol, which does not necessarily have a causal relationship with trial treatment. An adverse event (AE) can therefore be any

unfavourable symptom or disease temporarily associated with the trial treatment, whether or not it is related to the trial treatment.

#### SERIOUS ADVERSE EVENT (SAE)

An AE that:

- Results in death
- Is life-threatening
- Requires in-patient hospitalisation or prolongs existing hospitalisation
- Results in persistent or significant disability/incapacity
- Is otherwise considered to be medically significant by the investigator

#### REPORTING PROCEDURES

All patients undergoing this trial are having major abdominal surgery and there is a recognised high risk of morbidity, therefore they are at risk of frequent AE. These events are largely as a result of a patient's medical condition and consequences of major surgery and may not be related to the trial. Consequently any AEs occurring as a result of patient's condition will not be reported. All other AEs that occur during the trial period from treatment to hospital discharge must be recorded in the patient notes. Any AE will be reported to the CI directly. The CI will facilitate any local monitoring by the R&D quality manager, REC review and provide access to source data as required. Following any monitoring a report will be provided which will summarise the visit and documents, along with any findings. The CI will be responsible for ensuring that all findings are addressed appropriately. Additional monitoring will be scheduled where there is evidence of suspicion of non-compliance with the Trial protocol.

#### NOTIFYING THE REC

Any SAE causally attributed to the trial interventions will be reported to the REC by the CI in an expedited fashion. AEs that do not require expedited reporting will be reported in the annual progress report, which will be submitted by the CI to the REC annually. This will commence one year from the date of approval for the trial.

### 8.3 AUDITING

The R&D Quality Manager will audit the first patients recruited. The CI will facilitate any local monitoring by the R&D Quality Manager, REC review, audits and regulatory inspections, by providing direct access to source data/documents as required. Trial participants will be informed of this during the informed consent process.

Following any monitoring, a report will be provided which will summarise the visit and the documents reviewed, along with any findings. The CI will be responsible for ensuring that all findings are addressed appropriately.

## 9. ETHICS AND DISSEMINATION

### 9.1RESEARCH ETHICS APPROVAL

The SuperStarch Study will be conducted in accordance with the approved Trial Protocol, ICH GCP guidelines, the Data Protection Act 1998, the Mental Capacity Act 2005, and the Medical Research Council's (MRC) Guidelines for Good Research Practice, Guidelines for Good Clinical Practice in Clinical Trials and Procedure for Inquiring into Allegations of Scientific Misconduct. The ELHT R&D Department has developed its own policies and procedures, based on these MRC guidelines, for the conduct of all its research activities. Policies regarding alleged scientific misconduct and breach of confidentiality are reinforced by disciplinary procedures.

The trial has received a favorable opinion from the <<REC name to be inserted>> REC. The CI will submit annual progress reports.

The SuperStarch Study will only be conducted once all necessary local approvals for the trial have been obtained.

## 9.2 Protocol amendments

Any important protocol modifications will not be implemented until a protocol amendment application is approved by the REC.

## 9.3 Consent

Once the research team are informed about an eligible patient as described in the recruitment section they will meet them at their next hospital attendance & provide them with a written Patient Information Sheet (PIS) and a verbal description of the study along with contact numbers should they wish further information or clarification. They will be followed by telephone in the interim to gauge interest, and again at their pre-operative assessment clinical visit to ascertain if they wish to participate. Some patients may be encountered for the first time at this clinic and may be willing to participate after sufficient time to absorb the PIS, which will vary individually. If so, consent will be taken followed by randomisation in order to provide them with their allocated bags of *PreLoad*® or *Generation UCAN* to take home with them to take as directed in the intervention section.

No other aspect of care will be altered apart from that detailed in the study protocol (i.e. provision of different pre-operative drink in intervention arm). The conduct of anaesthesia and planned surgical technique will be at the discretion of the responsible clinicians.

### Withdrawal of a Patient

In consenting to the trial, patients are consenting to the trial intervention they are allocated, assessments, and data collection. However, patients can withdraw from the SuperStarch Study at any time during the trial. If a patient explicitly states that they no longer wish to take part or contribute further data to the trial, their decision must be respected. The patient's withdrawal from the trial should be recorded in the patient's medical notes and no further data collected. All data collected up to the point of withdrawal will be included in the trial analysis. However, if a patient withdraws consent for any of their data to be used, these will be confidentially destroyed immediately. If a patient is randomised and later found to be ineligible, or the responsible clinician feels that it is no longer appropriate for the patient to continue taking part, then they will be withdrawn from the study and the reason for withdrawal indicated in the medical notes. Patients withdrawn will not be replaced.

## 9.4 Confidentiality

Identifiable patient data, including full name, full postal address, date of birth and NHS number will be required by the CI and research team to maintain a screening and enrolment log and ensure follow up for detection of AE. This information will be kept together with all copies of consent forms in the Master Site File securely in the R&D Department. The trial team will not disclose or reproduce any information by which patients could be identified. Data will be entered and stored securely on a ELHT drive folder, with only the research team having access, within the SuperStarch Study excel spreadsheet, which will be password protected by the research team.

## 9.5 Declaration of interests

The CI has no financial or competing interest to disclose regarding this study.

## 9.6 Access to data

Only the CI, co-investigator, the Clinical Research Fellows and the Trial Statistician will have access to the final trial dataset, which will be anonymised.

### 9.7 Ancillary or Post-Trial care

East Lancashire Hospitals NHS Trust holds professional liability insurance to meet the potential legal liability of the sponsor and employees for harm to participants arising from the design and management of the research for trial participants at East Lancashire Hospitals NHS Trust.

Indemnity to meet the potential legal liability of investigators/collaborators for harm to participants arising from the conduct of the research is provided by the NHS indemnity scheme or through professional indemnity.

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Blackburn BB2 3HH

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### 9.8 Dissemination policy

We anticipate the results of this study to be published by peer-reviewed journals and presented at international surgical, anaesthetic and perioperative medicine conferences.

Ongoing progress of the trial will be disseminated locally within the hospital trust via newsletters, emails and updates at divisional and department meetings as well as ERP Operational Meetings. All patient data will be anonymised before publication.

## 10. Appendices

### 10.1 ERP

#### Pre-operative:

- Pre-operative assessment, planning and preparation with CPET assessment if ≥60 years or <60 years with cardiorespiratory co-morbidity.
- Provide ERP pack: information leaflet, patient diary and *allocated pre-operative carbohydrate intervention to be consumed as detailed in the intervention section*.
- Bowel preparation: Upper GI resection and right sided colonic resections – none; Left sided colonic resections, rectal resections and radical cystectomies – phosphate enemas on the morning of surgery.
- Paracetamol 1gm and Gabapentin 300mg orally.

#### Intra-operative:

- GA and regional analgesia techniques preferred.
- Multimodal anti-emesis
- Nasogastric tube insertion avoided.
- Surgical drains minimised.
- Goal directed fluid therapy.
- Hotline® iv fluid warmers and Bair Hugger™ external warming blanket with temperature monitoring to maintain normothermia.

POST-OPERATIVE:

- Maintenance of regional analgesia.
- Multimodal oral analgesia: paracetamol 6 hourly PO or IV if not tolerating oral; Ibuprofen 400mg 8hrly PO once tolerating full oral diet and gabapentin 100mg 8hrly PO.
- Buccastem 3mg 8hrly buccal for 48 hrs.
- 4 x 60m walks per day from Day 1 postoperatively.
- Minimise/avoid iv fluid and promote 2 litres/day oral fluid.
- Removal of urinary catheters on day one unless an epidural in situ in which case at discontinuation of epidural.
- Encourage full oral diet from day 1 postoperatively.

## 10.2 SURGICAL FITNESS DISCHARGE CRITERIA:

- ability to pass flatus,
- open bowels,
- tolerate oral diet,
- pain control adequate with oral analgesia
- and the patient willing to go home.

## 10.2 BLOOD SAMPLING & HOMA CALCULATION OF INSULIN RESISTANCE

### BLOOD SAMPLING

The HbA1C will be collected in an EDTA sample (both centres will analyse these samples using TOSOH HPLC analysers), 1.5mls blood for cortisol in a serum gel tube (both centres will analyse these samples with Advia Centaur analysers), insulin with 5-10ml of blood in a lithium heparin (orange) tube. The insulin samples need to be received in laboratory within 30 minutes, then centrifuged and frozen for transport to Central Manchester Foundation Trust laboratory in the case of Royal Blackburn Hospital. The Royal Surrey County Hospital will perform this test in-house. Both sites use Mercoda insulin ELISA kit. Serum Glucose samples will be collected in a yellow topped tube. Royal Blackburn Hospital uses an Ortho Vitros analyser and the Royal Surrey County Hospital uses Siemens Advia. However external proficiency testing data shows that on average the methods perform within 2.5% of each other, which is acceptable.

### CALCULATION OF INSULIN RESISTANCE

Insulin resistance will be calculated using the University of Oxford Diabetes Trial Unit HOMA calculator (freely available from https://www.dtu.ox.ac.uk/homacalculator/index.php). Although the Clamp method is considered the "gold standard" for assessing insulin sensitivity this is limited to small-scale intensive physiological investigations and not pragmatic for anything larger i.e. our proposed study.

The homeostatic model assessment (HOMA 1) of pancreatic β-cell function was first described by Matthews et al in 1985[24]. This technique uses basal glucose and insulin or C-peptide concentrations to calculate β-cell function and insulin sensitivity. Insulin resistance is calculated as the inverse of sensitivity (%IR = 100/%IS).

The University of Oxford calculator is based upon the updated HOMA 2 computer model. This model is accurate across a range of insulin (1-2200pmol/l) and glucose (1-25mmol/l). This non-linear model is optimised to calculate insulin sensitivity from fasting glucose and insulin levels. This method is shown to correlate well with the 'gold standard' euglycaemic ($R_s$ = 0.85 to 0.88, $p < 0.0001$) and hyperglycaemic ($R_s$ = 0.61, $p < 0.01$)

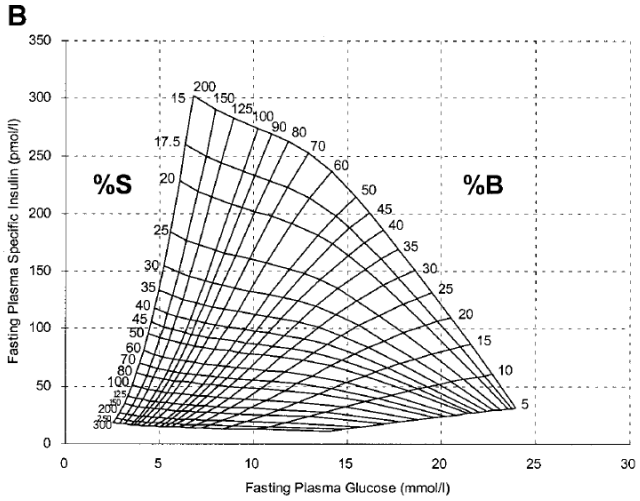
clamp methods of calculating insulin sensitivity and has been used as a measure of insulin resistance in over 500 publications to date[25] .

The Clamp techniques reflect the stimulated state and the HOMA technique reflects the basal state. The Clamp allows differentiation between liver EGP and peripheral tissue (primarily skeletal muscle) glucose uptake regarding insulin sensitivity whereas HOMA does not differentiate between the sources of insulin resistance.

Fortunately this will not be an issue in our study as it has been shown by Soop et al[6] that postoperative insulin resistance shifts from exclusively peripheral tissue insulin resistance, with a very minor role from the splanchnic tissues, in the first 24 hours, to a substantial role from liver EGP at the third postoperative day onwards. Therefore any insulin resistance measured in our study will be assumed to align with the respective tissues depending on the postoperative timing.

Insulin secretion is pulsatile so three separate blood samples will be taken for insulin at five-minute intervals at each time point and the mean value along with a measure of dispersion. This improves the coefficient of variation from 10% for one sample to 5.8% for three samples.

The samples will be very carefully handled as haemolysis degrades insulin.




**HOMA2 MODEL**
**FROM: WALLACE, T. M., LEVY, J. C., & MATTHEWS, D. R. (2004). USE AND ABUSE OF HOMA MODELING**

## 10.3 Postoperative Quality of Recovery Scale (PQRS)

(http://www.pqrsonline.org)

| **Physiological Factors** |
|---|
| Blood Pressure |
| Heart rate |
| Temperature |
| Respiration |
| Oxygen use to maintain Sp02 |
| Airway |
| Agitation |
| Consciousness |
| Responsiveness |
| **Noiciceptive Factors** |
| Pain |
| Nausea and vomiting |

| **Emotional Factors** |
|---|
| Depression |
| Anxiety |
| **Cognitive Factors** |
| Orientation |
| Memory |

## 10.4 ASA Score (ASA Physical Status Classification System)

ASA Physical Status 1: A normal healthy patient
ASA Physical Status 2: A patient with mild systemic disease
ASA Physical Status 3: A patient with severe systemic disease
ASA Physical Status 4: A patient with severe systemic disease that is a constant threat to life
ASA Physical Status 5: A moribund patient who is not expected to survive without the operation
ASA Physical Status 6: A declared brain-dead patient whose organs are being removed for donor purposes

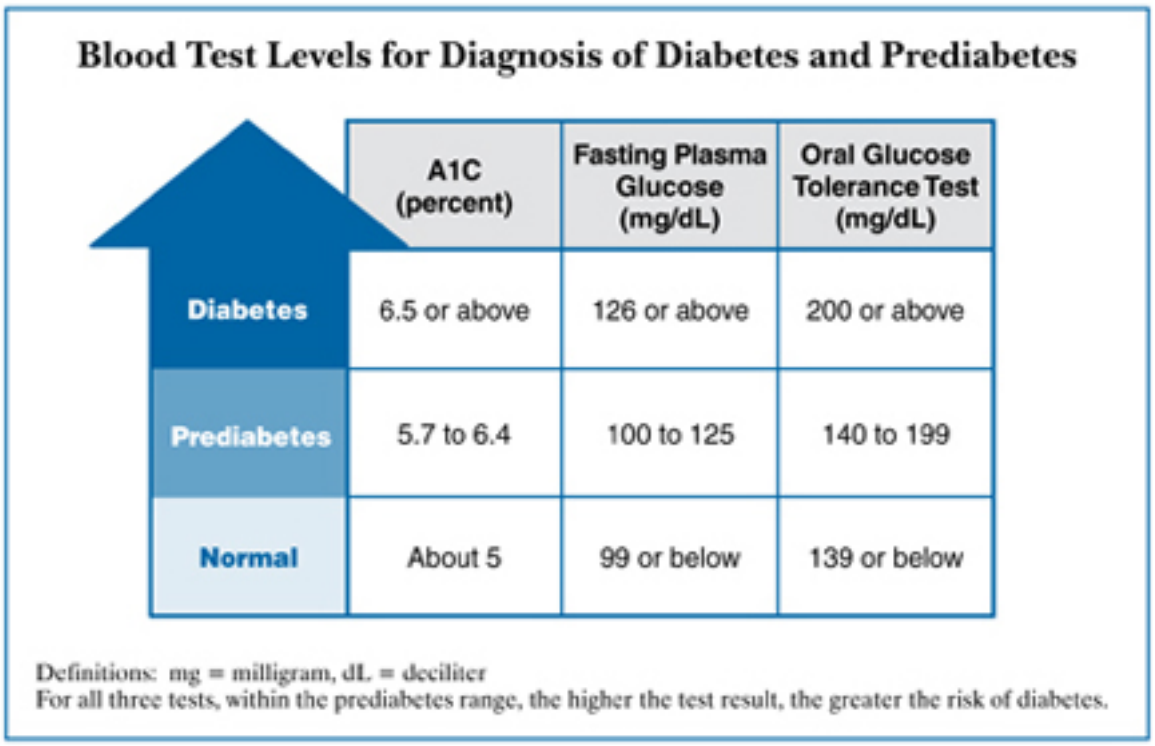
## 10.5 POSSUM Score

see http://www.riskprediction.org.uk

## 10.6 Postoperative Morbidity Survey (POMS) Score

| **Morbidity type** | **Criteria** |
|---|---|
| Pulmonary | De novo requirement for supplemental oxygen or other respiratory support (e.g. mechanical ventilation or CPAP) |
| Infectious | Currently on antibiotics or temperature >38$^0$C in the last 24h |
| Renal | Presence of oliguria (<500mls/day), increased serum creatinine (>30% from preoperatively), or urinary catheter in place for non-surgical reason |
| Gastrointestinal | Unable to tolerate an enteral diet (either by mouth or via a feeding tube) for any reason, including nausea, vomiting and abdominal distension |
| Cardiovascular | Diagnostic tests or therapy within the last 24h for any of the following: de novo myocardial infarction or ischaemia, hypotension (requiring pharmacological therapy or fluid therapy >200ml/h), atrial or ventricular arrhythmias, or cardiogenic pulmonary oedema |
| Neurological | Presence of a de novo deficit, coma, or confusion/delirium |
| Wound complication | Wound dehiscence requiring surgical exploration or drainage of pus from the operation wound, with or without isolation of organisms |
| Haematological | Requirement for any of the following within the last 24h; packed erythrocytes, platelets, fresh frozen plasma or cryoprecipitate |
| Pain | Surgical wound pain significant enough to require parenteral opioids or regional analgesia |

## 10.7 Reference Ranges for Diagnosing Pre-Diabetes and Diabetes




### 10.8 Ultrasound measurement gastric volume

In the anaesthetic room the head of the anaesthetic trolley will be elevated to 45° and the cross sectional area (CSA) of the gastric antrum will be measured at the level where the abdominal aorta and left lobe of the liver are visible using real-time ultra-sonography (Sonosite Micromaxx™, Sonosite Titan™ or Sonosite S-Nerve portable ultrasound machine with a 3.5 MHz linear transducer) followed by the same measurements in a right lateral decubitus (RLD) position. See Fig 1. for technique. Measurements need to be taken with the antrum at rest, between peristaltic contractions. The CSA must be measured from serosa to serosa, including the full thickness of the gastric wall.

The following equation is used to calculate Gastric Volume (GV):
GV (ml)=27.0+14.6×right-lat CSA −1.28×age (for RLD position)

GV (ml)=− 215+57 log CSA ($mm^2$) − 0.78 age (yr) − 0.16 height (cm) − 0.25 weight (kg) (for semi-sitting position)

Gastric antral ultra-songraphy measurement has shown adequate sensitivity to measure volumes of 25mls. The cutoff value of antral CSA of 340 $mm^2$ for the diagnosis of risk gastric reflux is associated with a sensitivity of 91%, a negative predictive value of 94%, an acceptable specificity of 71%, and a positive predictive value of 63%. Measurements of gastric emptying rate are highly reproducible, with an inter-observer systematic measurement error of 0.3% and a random measurement error of 10.9% between different observers, with intra-observer variability similar to inter-observer variability. A minimum of 200 ml of gastric fluid volume is considered necessary to induce passive regurgitation and pulmonary aspiration.

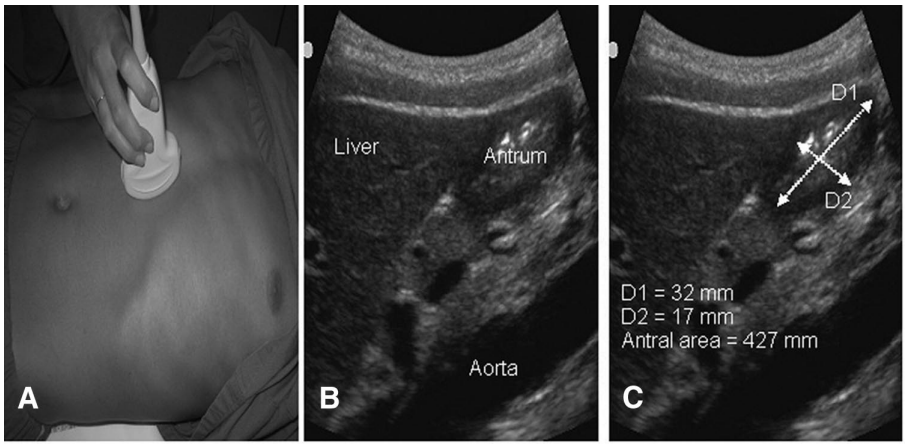



**Fig. 1.** (*A*) Transducer position to scan the gastric antrum. (*B*) Example of a gastric ultrasonographic image. (*C*) Example of measurement of the antral area.

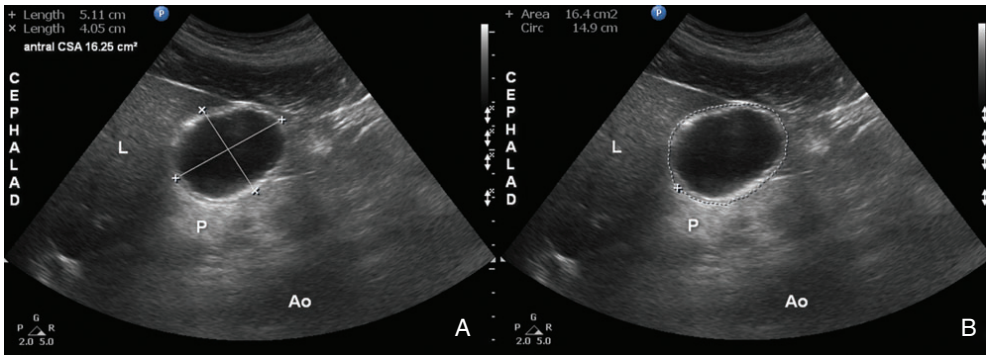



**Fig 5** Two alternate methods to measure antral CSA. (A) illustrates a method based on two perpendicular diameters (cranio-caudal and antero-posterior). (B) illustrates a free-tracing method following the outer border of the antrum at the level of the gastric serosa.

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