FULL/LONG TITLE OF THE STUDY

The effect of glucagon like peptide-1 (GLP-1) on glycaemic profile and eating behaviour following gastrectomy

SHORT STUDY TITLE / ACRONYM

Gastrectomy, eating behaviour and GLP-1

- **This protocol has regard for the HRA guidance and order of content; OR**

RESEARCH REFERENCE NUMBERS

IRAS: 218762

CUH R&D: A094265

PROTOCOL VERSION NUMBER AND DATE

Protocol v1.1 24th November 2016

OTHER RESEARCH REFERENCE NUMBERS

University of Cambridge Insurance Ref: 609/M/C/1763

CO-SPONSORS

Cambridge University Hospitals NHS Foundation Trust

University of Cambridge

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IRAS Number:	218762
SPONSORS Number:	A094265
Clinicaltrials.gov	NCT02971631

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirement.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the study publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the Study Sponsor:

Signature: Date:

..../...../.....

Name (please print):

.....

Position:

.....

Chief Investigator:

Signature: Date:

..../...../.....

Name: (please print):

.....

KEY STUDY CONTACTS

Chief Investigator	Mr Geoffrey Roberts Metabolic Research Laboratories and MRC Metabolic Diseases Unit University of Cambridge WT-MRC Institute of Metabolic Science (Level 4) Addenbrooke's Site (B289), Cambridge, CB2 0QQ, UK Gpr25@cam.ac.uk Tel: 07740 782742; 01223 767176
Study Co-ordinator	Geoffrey Roberts, details as above
Sponsor	Cambridge University Hospitals NHS Foundation Trust and University of Cambridge Stephen Kelleher R&D Manager Cambridge University Hospitals 1 Hills Road Cambridge CB2 0QQ Tel: 01223 217418 Fax: 01223 34849 Email: r&denquiries@addenbrookes.nhs.uk
Funder(s)	Wellcome Trust Cambridge Biomedical Research Centre Seed Fund
Key Protocol Contributors	Professor Fiona Gribble Dr Frank Reimann Mr Richard Hardwick Professor Rebecca Fitzgerald Professor Paul Fletcher Dr Hisham Ziauddeen

STUDY SUMMARY

Study Title	The effect of glucagon like peptide-1 (GLP-1) on glycaemic profile and eating behaviour following gastrectomy
Internal ref. no. (or short title)	Gastrectomy, eating behaviour and GLP-1 (GaS)
Study Design	Double blind, randomised, crossover physiological study.
Study Participants	16 patients who have undergone total gastrectomy
Planned Size of Sample (if applicable)	16
Follow up duration (if applicable)	3 study visits (one screening, two intervention)
Planned Study Period	2 years
Research Question/Aim(s)	To investigate the role of GLP-1, an incretin gut hormone, on the altered eating behaviour and glucose homeostasis experience following gastrectomy.

FUNDING AND SUPPORT IN KIND

FUNDER(S) (Names and contact details of ALL organisations providing funding and/or support in kind for this study)	**FINANCIAL AND NON FINANCIAL SUPPORT GIVEN**
Wellcome Trust	**Part of the joint investigator award of Professor Gribble and Dr Reimann**
Wellcome Trust / NIHR Addenbrooke's Clinical Research Centre	**All participant facing work will be carried out in the core funded ACRC, and so benefit from the core grants awarded to this facility within Cambridge University Hospitals from the Wellcome Trust / NIHR**

ROLE OF STUDY SPONSOR AND FUNDER

The University of Cambridge and Cambridge University Hospitals NHS Foundation Trust are co-sponsors of this study. The sponsors provide oversight of study design and implementation, as well as providing the facilities required for the study and access to the necessary patient populations. The sponsors have no control over the final decisions regarding data analysis or interpretation, or publication of the research findings.

This study is funded through a Wellcome Trust joint investigator award held by Professor Gribble and Dr Reimann, for the study of the enteroendocrine system in health and disease. The funding bodies have no influence over data interpretation or dissemination of results.

ROLES AND RESPONSIBILITIES OF STUDY MANAGEMENT COMMITEES/GROUPS & INDIVIDUALS

This study has been designed by the CI with substantial contributions from a steering group made up of the named co-investigators. Oversight of the study, data analysis and publication will be the responsibility of the CI supported by this group.

Protocol contributors

The protocol was written by the CI, with the assistance of the named co-investigators.

It has been reviewed and approved by the sponsors prior to submission to the REC to ensure it meets local guidelines and regulations.

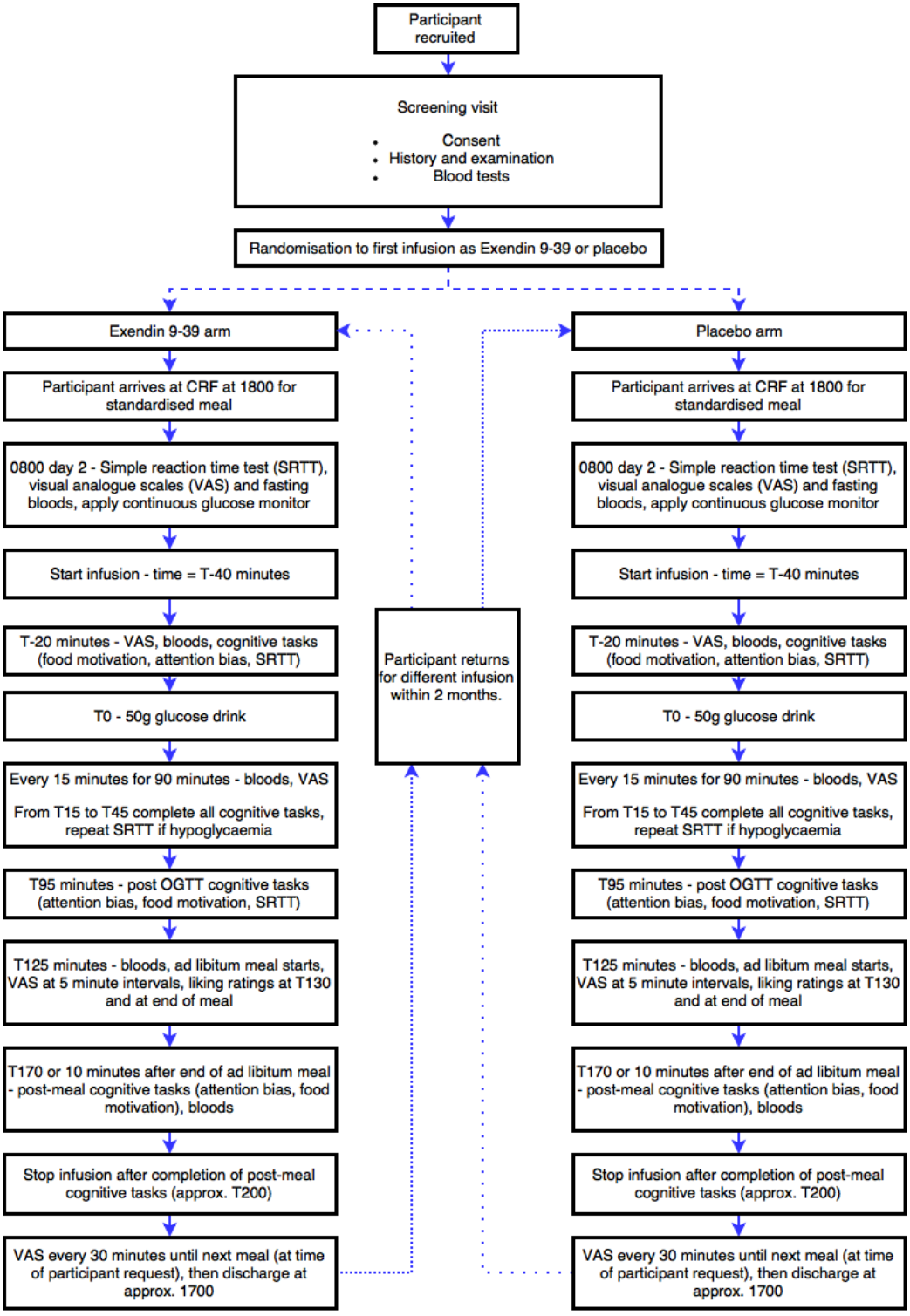
The sponsors and funders have no input to data analysis, interpretation, dissemination of results or manuscript writing.

We have engaged an interested local patient and his family to ensure this study is designed and performed in a fashion that is acceptable to our target population. They have reviewed our protocols and assisted with the final version.

KEY WORDS: Gastrectomy
GLP-1
Eating behaviour
Hypoglycaemia

LIST of CONTENTS

STUDY FLOW CHART



STUDY PROTOCOL

The effect of glucagon like peptide-1 (GLP-1) on glycaemic profile and eating behaviour following gastrectomy.

1 BACKGROUND

It is well established that surgery on the upper gastrointestinal tract profoundly alters appetite, weight and glucose homeostasis. This is harnessed in the treatment of obesity and type two diabetes[1] but can have significant deleterious effects in the lean population undergoing surgery for cancer[2]. At present, there is no adequate understanding of the pathophysiological basis of these changes, although it is suspected that gut hormones, bile acids and neuro-cognitive factors may play a role[3,4].

Approximately 2500 gastric and oesophageal resections are carried out annually in the UK for cancer, with a 50% five year survival rate. Long-term quality of life after gastrectomy is known to be poor, with a high prevalence of “dumping syndrome”, a poorly understood constellation of symptoms[2]. There is no effective treatment, or indeed understanding of the underlying cause, of these symptoms. This is a significant unmet need in the field of cancer survivorship.

The role of the (Glucagon-like-peptide-1) GLP-1 – insulin axis in the resolution of obesity and diabetes after bariatric surgery has been studied by several groups, and is suspected to play a role in the severe hypoglycaemias seen by some patients[5]. No one to date has assessed the role of GLP-1, a gut derived hormone responsible for potentiating the insulin response and suppressing appetite, in the symptoms seen after gastrectomy for cancer. A pilot study run by our group has demonstrated significantly elevated levels of GLP-1 and insulin, and altered appetite and satiety responses, in a cohort of five post-gastrectomy patients. The exact physiological effect of the GLP-1 elevation is however less clear, and temporary blockade of the GLP-1 axis will allow us to define the physiological changes resulting from GLP-1 secretion versus other altered physiological pathways in this group.

This study is a double-blind, crossover physiological study of the effects of excess GLP-1 secretion on glycaemic profile and cognitive eating behaviour factors in the post-gastrectomy population. Participants will attend for two study visits, on one occasion receiving an infusion of Exendin 9-39, a peptide antagonist of GLP-1 action, and on the other a placebo infusion. They will undergo a glucose tolerance test including serial blood tests and measures of hunger and satiety, and then have an ad libitum meal, with measurement of amount and speed of eating, as well as simple cognitive tasks to assess food / reward behaviour. These tasks include food-related attentional bias using a dot-probe task[6] and food-motivation behaviour using a validated grip-strength measurement task[7].

Exendin 9-39 is a peptide that has been used by several groups in the USA and Europe to investigate the effects of GLP-1 on physiological and cognitive factors, with no published serious adverse events. It has not previously been used in the gastrectomy population, but has been used in healthy volunteers and patients who have undergone bariatric surgery. It has an extremely short half-life and the effects cease within several minutes of cessation of the infusion. It is not at present a licensed medication, and is available for use as an investigative compound, manufactured to GMP standard by Bachem AG. Based on a review of the literature, and advice from a group at Stanford University who have used Exendin 9-39 infusions in the post-bariatric surgery population, the infusion will be commenced with a bolus of 7500pmol/kg and run at a rate of 500pmol/kg/minute.

The assessment of food and reward behaviour, and glucose homeostasis, requires controlling for confounding factors. These include diabetes and depression and will be assessed prior to study participation.

2 RATIONALE

At present, there is no physiological understanding of the altered glucose homeostasis and eating behaviour seen in patients after gastrectomy. There is a growing population of patients surviving long-term after surgery for gastric cancer, including some in their teens and twenties who have undergone prophylactic surgery for high risk genetic mutations. Our group works with the researchers leading the Familial Gastric Cancer Study, who provide clinical care, and research, for the familial gastric cancer population in the UK. This group has identified, through patient seminars, the need for further research into the long-term consequences of gastrectomy as a key priority.

This study aims to assess the role of one specific hormone, GLP-1, which is known from our pilot data to be excessively secreted in response to food in this population. Ultimately, a better understanding of this pathway may lead to novel investigative and treatment paradigms, for a condition presently lacking either.

3 THEORETICAL FRAMEWORK

We hypothesize that blockade of the GLP-1 axis using Exendin 9-39 in the post-gastrectomy population will:

1. Ameliorate the excessive post-prandial insulin response seen in this patient group, as evidenced during a 50g oral glucose tolerance test by:
    a. Increased nadir blood glucose
    b. Reduced total insulin secretion
2. Ameliorate the increased satiety signalling and consequent effects on food intake, hunger and satiety, and food motivation during and after an ad libitum meal, as evidenced by:
    a. Increased eating rate and food intake during ad libitum meal
    b. Increased hunger and decreased satiety ratings during and immediately after the ad libitum meal
    c. Increased attention to and motivation for food both prior to and after the ad libitum meal

4 RESEARCH QUESTION/AIM(S)

4.1 Objectives

1. To identify the role of the excessive GLP-1 secretion experienced by post-gastrectomy patients in the physiological and behavioural symptoms seen after gastrectomy:
    a. Post-prandial hypoglycaemia
    b. Altered hunger / satiety scores
    c. Altered food attention bias and reward behaviour
    d. Altered food motivation and intake at ad libitum meal

4.2 Outcome

The key outcome of this study is the understanding of the physiological effects of excessive GLP-1 secretion seen in the gastrectomy population. To this end, Exendin 9-39, which is an antagonist of GLP-1 activity, will be used to block GLP-1 activity. This is a physiological study of the actions of GLP-1, not an investigation of the effects of Exendin 9-39.

5 STUDY DESIGN and METHODS of DATA COLLECTION AND DATA ANALYIS

Each participant will attend for three visits – a screening visit and two study visits (matched visits, one with placebo infusion and one with Exendin 9-39 infusion).

Screening visit

The purpose of this visit is to ensure there are no comorbidities which may be exacerbated by, or confound, the study protocol. The participant will have the study explained to them, be asked to consent to participation and then be asked a full medical and surgical history, and receive blood and cognitive screening tests as detailed:

Blood tests – Full blood count, thyroid function, renal function, HbA1c (diabetes screen).

Validated questionnaire tools – Three factor eating questionnaire, Barratt's impulsivity scale, PHQ9 and GAD7 for anxiety and depression, Dumping severity score

Demographic measures – Age, past medical history, details of gastrectomy and other associated treatments (chemotherapy or radiotherapy), current medications, family history, height, weight, waist / hip circumference.

Symptomatic measures – free discussion of participant reported post-gastrectomy consequences, changes in eating behaviour and food preference and behavioural adaptations.

Study visit

Participants will be admitted to the Clinical Research Facility at Addenbrooke's Hospital the night prior to each study visit, to allow for provision of a standard meal and commencement of the study soon after waking the following morning. Participants will receive an infusion of either placebo (1% human albumin in sterile water) or Exendin 9-39 (dissolved in 1% human albumin in sterile water), with an initial bolus of 7500pmol/kg and at a rate of 500pmol/kg/minute. Participants and investigators will be blinded to the infusion contents, with the infusion schedule randomised by sealed envelopes prepared in advance. We will use a balanced randomisation protocol, with half of participants undergoing placebo at their first visit. Visit schedule and interventions are as the table below, with discharge at approximately 1700, after the post-infusion meal. Participants will be provided with a symptom diary during and for twenty four hours after the visit to monitor for any adverse events.

All female participants of child-bearing age are to receive a urinary pregnancy test on each infusion visit.

Key study measures are:

1. Continuous glucose monitor – a Dexcom G4 continuous subcutaneous glucose monitor will be used to measure interstitial glucose levels at 5 minute intervals. This is a key outcome measure, as well as a safety measure to monitor for hypoglycaemia during the OGTT. The device is CE marked for the monitoring of glucose profile and in widespread use.
2. Blood tests – blood will be collected and centrifuged, and plasma assayed for hormonal mediators of glucose homeostasis (including insulin, glucagon and GLP-1). Maximum volume of blood collected across 3 visits will be 250ml.
3. Simple reaction time task – a straightforward measure of reaction time wherein a participant clicks a key in response to a stimulus on a computer screen, will act as a control / baseline measure to identify between and intra-participant variability in response times that may influence other cognitive tasks.

4. Visual analogue scales – participants will be asked to mark how hungry, sated or nauseous they feel on a 10cm visual analogue scale.
5. Sigstad score – a validated measure of post-gastrectomy symptoms, to be completed on a tick box sheet during the OGTT.
6. Attention bias task – participants will be asked to fixate on a central mark on a computer screen, and will then be shown two images conflicting as to their depiction of food (i.e. food vs not food, or high energy vs low energy food), under one of which appears a dot. The speed with which they indicate the side of the dot, with regard for the associated image, identifies their degree of food attention bias.
7. Food motivation task – a validated measure of food motivation, using grip strength as a measure of degree of work the participant will undertake to receive particular food related rewards and stimuli.
8. Eating rate / food intake – a universal eating monitor (a set of hidden scales placed beneath a meal) will examine rate and amount of consumption of a standard ad libitum meal.
9. Liking ratings – visual analogue scales of how much the participant likes the meal.

All questionnaires and tasks are validated.

Data will be collected in paper format, stored in a locked cabinet in a secure area of Addenbrooke's Hospital, and transcribed in anonymous fashion to a database on a secure University of Cambridge server. Data storage and analysis will be carried out using Microsoft Excel and R.

Exendin 9-39 will be sourced from Bachem AG, who produce GMP grade Exendin 9-39 with appropriate supporting documentation and guarantees. It will be stored as per supplier guidance in the Addenbrooke's pharmacy, or another appropriate secure storage area, and made up to a standard dilution in 1% human albumin in 0.9% sterile saline. Randomisation will be administered by means of sealed envelopes, with each visit provided with either an infusion of Exendin 9-39, or placebo (1% human albumin in 0.9% sterile saline). Both infusions will be at a rate determined by the weight of the participant and stock concentration of Exendin 9-39, and provide a 7500pmol/kg (25.27µg/kg) bolus of Exendin 9-39 followed by a 500pmol/kg/minute (1.685µg/kg/minute) infusion. Infusions will be administered through an appropriately maintained clinical infusion pump on the CRF.

Approximate time	Task	Test	Infusion
0800	Insert continuous glucose monitor and venous cannula		
0820	Fasting bloods and cognitive measures	Blood sample, simple reaction time task, visual analogue scales (VAS) for hunger, satiety, nausea, Sigstad	
0840	Start infusion		
0900	Fasting / blockaded measures	Blood sample, simple reaction time task, attention bias, food motivation, VAS, Sigstad	
0910	50g oral glucose drink (OGTT)		
0925	OGTT measures	Blood sample, VAS, Sigstad, attention bias	
0940	OGTT measures	Blood sample, VAS, Sigstad, food motivation	
0955	OGTT measures	Blood sample, VAS, Sigstad, simple reaction time task	
1010	OGTT measures	Blood sample, VAS, Sigstad	
1025	OGTT measures	Blood sample, VAS, Sigstad, (SRTT if hypoglycaemic)	
1040	OGTT measures	Blood sample, VAS, Sigstad	
1045	Post-OGTT cognitive tasks	Attention bias, food motivation, simple reaction time task	
1115	Bloods then ad libitum meal, VAS at 5 minute intervals, liking ratings twice (5 minutes into meal, and at completion of meal)	Blood sample, universal eating monitor, VAS, liking ratings	
1200 OR 10 minutes after completion of meal	Post meal bloods and cognitive tasks, then stop infusion (approx. 1230)	Attention bias, food motivation, bloods	
1230 until next meal (appr 1700)	Hunger / satiety scores every 30 minutes, meal then discharge	VAS	

Study visit timeline

6 STUDY SETTING

The study will be performed in the Wellcome Trust-NIHR Clinical Research Facility at Addenbrooke's Hospital. The staff and infrastructure of the CRF bring considerable expertise and experience in research involving metabolic factors and infusion of blinded agents. Each study visit will be supported by at least a dedicated nurse and doctor for the duration of the visit.

7 SAMPLE AND RECRUITMENT

7.1 Eligibility Criteria

7.1.1 Inclusion criteria

Participants must be:

- At least 3 months post completion of treatment for gastric cancer, or prophylactic gastrectomy
- Aged at least 18 years
- Able to tolerate an oral glucose tolerance test
- Able to understand and retain all information regarding the study and give informed consent.
- Willing to receive an infusion of human albumin solution

7.1.2 Exclusion criteria

Participants must not:

- Have a diagnosis of diabetes
- Have a history of untreated anaemia in the last 3 months
- Be aged under 18 years
- Have active gastric cancer
- Be pregnant or attempting to conceive

7.2 Sampling

7.2.1 Size of sample

Up to sixteen participants will be recruited for this study, each to complete one screening and two randomised study visits (placebo and Exendin 9-39). Previous data shows a between visit correlation of glucose measurement of 0.52, with standard deviation of 0.5. Salehi et al demonstrated mean nadir blood glucose of 3.9mmol/L (standard deviation 0.6) with GLP-1 blockade and 2.6mmol/L (0.6) with placebo in post-bariatric surgery patients[5]. Based on this data, we have conservatively estimated an effect size of 0.5 (based on mean change in nadir glucose of 0.5mmol/L. To detect this change with 90% power at a 5% significance level requires a sample size of 13. The recruitment of sixteen participants will allow for drop outs, and for the possibility that more data will be required to reach significance in the previously unstudied (in this group) outcomes of food motivation and reward behaviour.

7.2.2 Sampling technique

Participants will be sampled from all patients under follow up after total gastrectomy by the Cambridge Oesophago-gastric centre at Addenbrooke's Hospital, or known to the service through the Familial Gastric Cancer Study (provided they have indicated an interest in being contacted regarding future research). We will select participants with suspected or proven post-prandial hypoglycaemia based on oral glucose tolerance tests performed as part of clinical care or other research projects administered by our study team.

7.3 Recruitment

Participants will be identified as having post-prandial hypoglycaemia (based either on symptoms or a previous glucose tolerance test) and initially approached by clinicians or clinical researchers involved in their care. If they are interested in receiving further information regarding the study, they will be contacted by a member of the study team. They will be provided with written information on the study, and if they wish to proceed, be invited to attend the CRF for a screening visit, at which time they will be formally consented by a member of the study team.

Participants will be paid an honorarium of £30 for each infusion visit (in line with current practice in our unit), and be fully reimbursed for travel costs.

7.3.1 Sample identification

Participants will be identified as meeting the inclusion / exclusion criteria by a clinician involved in their care, if necessary in discussion with the CI, who is a member of the clinical team of the Cambridge Oesophago-Gastric centre.

7.2.2 Consent

Participants will be asked to give written consent using a standard consent form at the time of the screening visit. They will be provided with written literature regarding the study prior to this occasion, and will have adequate time to ask questions, and withdraw consent should they wish. Only participants able to give fully informed consent will be recruited to this study, with capacity assessed by a clinically trained member of the study team.

8 ETHICAL AND REGULATORY CONSIDERATIONS

8.1 Assessment and management of risk

This is a physiological study, using a well described test (oral glucose tolerance test) with a blinded infusion of a peptide or placebo.

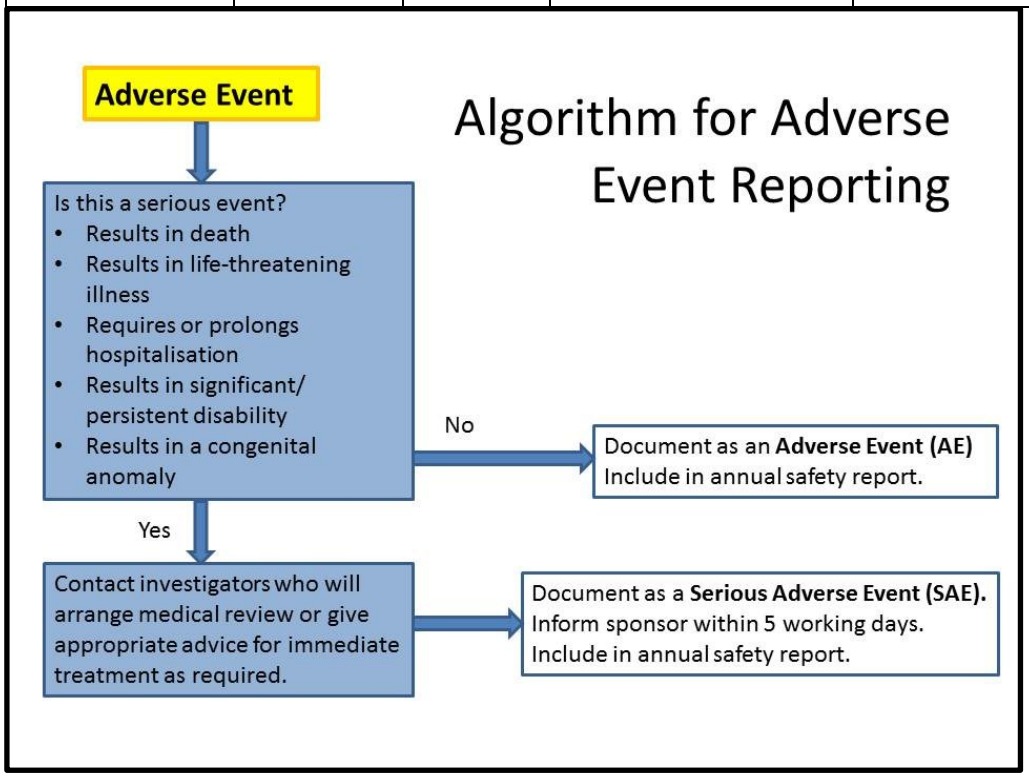
Oral glucose tolerance testing (OGTT) in this group has been carried out by our and several other groups. There is a risk of hypoglycaemia developing during the test period, for which the participant will be closely monitored using a continuous subcutaneous glucose monitor. A robust protocol is in place for the management of hypoglycaemia during an OGTT in this population, including the administration of intravenous glucose, or glucagon, should this be necessary (in our experience, this has never occurred). Other risks of the study visit and OGTT include pain and bruising at the cannulation site.

Exendin 9-39 has been used by multiple groups in Europe and the USA, with published results from 259 infusions in 240 participants[4,8-22]. No serious adverse events have been ascribed to the use of Exendin 9-39, which is unsurprising given it is a highly selective blocker of the GLP-1 receptor with a very short half-life. It is however possible that the participant may manifest an allergic reaction to the peptide, or to the human albumin in which it is dissolved. To facilitate early diagnosis and appropriate treatment should this occur, all participants will be closely monitored by dedicated nurse and doctor during the infusion. The study will take place on a clinical research ward within Addenbrooke's Hospital, with full resuscitation equipment and access to the hospital's emergency medical team should it be necessary. The CRF has experience in running phase 1 clinical trials, including first in human studies, which carry a greater burden of risk than this proposed study.

All adverse events (AEs) will be recorded as per the table and figure below. During study visits, participants will be questioned regarding adverse symptoms, and asked to keep a symptom diary for 24 hours post visit to ensure all AEs are recognised. All non-serious AEs will be documented and submitted in the annual safety report.

All SAEs will be reported to the sponsor within 5 working days of the investigative team being made aware of the event. SAEs will also be included in the annual safety report. The participants will have 24 hour contact details for the investigators in case a suspected SAE occurs following the study visit. In the event of a potential SAE occurring, the investigators will arrange for the participant to be reviewed promptly. Depending upon the severity of the event, the participant will be reviewed in the Wellcome Trust Clinical Research Facility (WTCRF) or will be advised to go straight to A&E (for example, if anaphylaxis is suspected).

	Expected events	**All events recorded?**	**All events reported?**	**Timescale for reporting**
Non-serious Adverse Event (AE)	Documented in protocol	Yes	Reported in annual study report only.	Annually in study report.
Serious Adverse Event (SAE)	Documented in protocol	Yes	Reported to sponsor within 5 working days. Reported in annual study report.	Reported to sponsor within 5 working days.



8.2 Research Ethics Committee (REC) review & reports

- Before the start of the study, approval will be sought from a REC and the HRA for the study protocol, informed consent forms and other relevant documents.
- Substantial amendments that require review by REC will not be implemented until the REC and HRA grant a favourable opinion for the study and full R&D approval is in place
- All correspondence with the REC and HRA will be retained.
- It is the Chief Investigator's responsibility to produce the annual reports as required.
- The Chief Investigator will notify the REC and HRA of the end of the study.
- An annual progress report (APR) will be submitted to the REC and HRA within 30 days of the anniversary date on which the favourable opinion was given, and annually until the study is declared ended.
- If the study is ended prematurely, the Chief Investigator will notify the REC and HRA, including the reasons for the premature termination.
- Within one year after the end of the study, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC and HRA.

8.3 Peer review

Peer review has been sought from two researchers independent to the research team.

8.4 Patient & Public Involvement

A patient representative has advised on the design of this study, including acceptability of the study protocol. The concept of this study was raised at a patient and family event for the Familial Gastric Cancer population, with positive feedback on the concept of studying the causes of post-operative symptoms. The research findings will be disseminated to the interested patient groups through the bi-annual Familial Gastric Cancer workshop, and directly to any participant interested in the results.

8.5 Regulatory Compliance

- Before any site can enrol patients into the study, the Chief Investigator/Principal Investigator or designee will apply for NHS permission from the site management organisation, HEI or NHS Research & Development (R&D).
- For any amendment that will potentially affect a site's NHS permission, the Chief Investigator/ Principal Investigator or designee will confirm with that site's R&D department that NHS permission is ongoing
- The MHRA has reviewed this protocol and confirmed it does not require a clinical trial authorisation
- This study will be registered with clinicaltrials.gov for the purposes of public reporting of a study involving human participants.

8.6 Protocol compliance

Protocol compliance will be monitored by the CI, with any accidental deviations being immediately reported to CI and sponsor. Frequent deviations will be investigated by the research team and

sponsor, and if necessary the study paused for review, notification of the REC and HRA and amendments.

8.7 Data protection and patient confidentiality

The data custodian is the CI. The study and all investigators will comply with the Data Protection Act 1998 with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles. Data will be managed to a written policy, with participant identifiable information stored in paper format in a locked cabinet in a secure area within Addenbrooke's Hospital. All electronic records will be anonymised and held on secure servers within the University of Cambridge, with the key held by the CI and access only granted to key clinical members of the research team. Identifiable data will be held for up to 20 years following the completion of the study (MRC guidance), with fully anonymised results uploaded to the University of Cambridge Data Repository for at least 20 years, in line with current open access requirements.

8.8 Indemnity

1. *What arrangements will be made for insurance and/or indemnity to meet the potential legal liability of the sponsor(s) for harm to participants arising from the management of the research?*

   As the co-sponsor is Cambridge University Hospitals NHS Foundation Trust, indemnity will be provided through NHS indemnity schemes

2. *What arrangements will be made for insurance and/ or indemnity to meet the potential legal liability of the sponsor(s) or employer(s) for harm to participants arising from the design of the research?*

   As the research has been designed by a substantive employee of the University of Cambridge, insurance will be sought through the University insurance policy (Ref: 609/M/C/1763).

3. *What arrangements will be made for insurance and/ or indemnity to meet the potential legal liability of investigators/collaborators arising from harm to participants in the conduct of the research? Note that if the study involves sites that are not covered by the NHS indemnity scheme (e.g. GP surgeries in primary care) these investigators/collaborators will need to ensure that their activity on the study is covered under their own professional indemnity.*

   As the research is with NHS patients on a NHS site, indemnity will be provided by NHS schemes.

No arrangements have been made for payment of compensation in the event of harm to the participants where no legal liability arises.

8.9 Amendments

Application for any future amendments will be made by the study team in line with study requirements and developments in the scientific background to the study. Amendments to the protocol will be written by the CI or a delegated study team member in discussion with the sponsor's R&D department. The decision about whether an amendment constitutes a substantial amendment will be made by the study team and

sponsor's R&D department. Amendments will be submitted to the REC and HRA through the IRAS system with all necessary amended versions of the protocol or paperwork.

All versions of study paperwork will be stored on secure University of Cambridge servers, with an amendment record stored in the appendix of the active protocol version.

8.10 Access to the final study dataset

The final dataset will be available to the study team, which is based entirely on one site. Specific consent will be sought from participants for persistent anonymous storage and analysis of study data and publication of the basic data with associated metadata through an open access information repository.

9 DISSEMINATION POLICY

9.1 Dissemination policy

The data will be owned by the Gribble / Reimann group within the Institute of Metabolic Science, University of Cambridge. On completion of the study, the final results will be tabulated, presented to the REC and HRA as a final report, presented to scientific meetings and submitted for peer-reviewed publication. There are no time limits on publication of this work.

The work is being undertaken within a research group supported by the MRC, Wellcome Trust and NIHR BRC, who will be acknowledged in publications accordingly. Equally, some aspects of the research will be undertaken through hub facilities (e.g. the NIHR BRC Phenotyping hub), which will be acknowledged for their role as per local guidelines.

Participants will be able to request their individual results, which will be provided once analysis and quality assurance have been performed. This will be provided with a detailed explanation of the findings and the opportunity to answer questions.

The full study outcome will also be made available to participants on request, following completion of the study.

The anonymised dataset, metadata and any code for analysing the results will be published with open access on a data repository (e.g. the University of Cambridge Data Repository). This will be done on completion of the study and after publication of the research findings.

9.2 Authorship eligibility guidelines and any intended use of professional writers

Authorship of the final report and generated peer reviewed papers will follow ICMJE criteria, to include researchers making a substantial contribution to study design, data collection or analysis, or writing or editorial oversight.

10 REFERENCES

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11. APPENDICIES

11.1 Appendix 1- Required documentation

Protocol v1 22/11/2016

GaS PIS v2 17/11/2016

GaS Consent form v2 17/11/2016

CVs – CI and academic supervisor

GaS GP letter v1 03/11/2016

GaS hunger / satiety / nausea v1 07/11/2016

GaS likings ratings v1 07/11/2016

GaS Sigstad score v1 07/11/2016

GaS participant invitation letter v1 11/11/2016

GaS PHQ9 v1 11/11/2016

GaS GAD7 v1 11/11/2016

GaS DSS v1 11/11/2016

GaS TFEQ v1 11/11/2016

GaS study card v1 17/11/2016

GaS symptom diary v1 20/11/2016

13.2 Appendix 2 – Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made

List details of all protocol amendments here whenever a new version of the protocol is produced.

Protocol amendments must be submitted to the Sponsor for approval prior to submission to the REC committee.