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Metabolic Research Laboratories, Level 4, Institute of Metabolic Science

Box 289, Addenbrooke’s Hospital, Cambridge, CB2 0QQ

**Title: Investigating gut hormone levels in human health and disease “GutHHD”**

**Protocol B: Two Meal Study**

**Information Sheet for Volunteers**

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully. Talk to others about the study if you wish.

* Section 1 tells you the purpose of this study and what will happen if you take part.
* Section 2 gives you more detailed information about the conduct of the study.

Do ask us if anything is not clear or if you would like more information. Do take your time to decide whether or not you wish to take part.

**SECTION 1: AIMS OF THE RESEARCH**

**Who are we and what do we do?**

We are a team of doctors and nurses in Cambridge. We are interested in understanding how hormone levels released from the gut vary across different individuals. This will help us to further understand how these hormone levels vary in healthy volunteers and in patients with a particular metabolic or gastrointestinal disease. This will aid the development of new tests and new treatments for patients with different metabolic and gastrointestinal diseases.

**What is the purpose of this study?**

We wish to understand how hormones released from the gut vary before and after a meal. In particular certain hormones are associated with hunger and feeling full and are a particular interest of clinical research. These gut hormones are known to vary both before and after a meal.

Newer technique have been developed to measure gut hormones in humans. We wish to utilise these new techniques to measure how gut hormones and other metabolic markers vary both before and after a meal.

The long term aim of this work is to develop a technique for measuring gut hormones in clinical practice, and see how it varies across different metabolic and gastrointestinal diseases. This should aid diagnosis of such conditions, and help develop new treatments for these diseases.

**Am I eligible to take part?**

In this study we aim to assess how gut hormones vary both before and after a meal.

For this protocol we are currently recruiting patients with bile acid diarrhoea or bile acid malabsorption who are on treatment with bile acid sequestrants.

Bile is known to influence gut hormone release in the gut and we wish to assess in more detail how increased bile levels in the gut with this condition influence gut hormone levels.

You are eligible to take part if you are between the ages of 18 and 65.

A full exclusion criteria is included later in this information sheet.

If you have questions before the trial and are uncertain regarding your eligibility a virtual screening appointment can be arranged, at which consent to take part in the study can be taken also.

**Do I have to take part?**

Taking part in this study is entirely voluntary. You can take some time to decide whether or not you want to take part and you are free to withdraw at any time, without giving a reason. If you participate, we will ask you to sign a consent form and you will be given a copy of the form. If you do not wish to take part it will not affect the standard of care you receive regularly.

**What will happen to me if I take part?**

You will be invited to the Translational Research Facility (TRF) located in the Cambridge Centre for Clinical Research (CCRC) at Addenbrooke’s Hospital, Cambridge. The study takes place over two days.

During your first visit you will have some blood samples taken. You will then be provided with a meal and have further blood samples taken.

You will then be asked to stop taking your bile acid sequestrants and then return for a second meal study after at least 7 days.

During this period it is possible that diarrhoea symptoms may worsen whilst not taking sequestrants for usual symptom relief, similar to before your condition being diagnosed.  Loperamide (immodium) may be taken during this period for symptom relief, but cannot be taken in the 48 hours before either meal study due to the possibility of this effecting the results of the study

After this second meal study you can continue on your bile acid sequestrants as usual.

We will cover your travel expenses for travelling to the TRF both days in Cambridge and a fee of £50 for participating in the study.

If you are interested in the study, please contact us with the information at the bottom of the sheet and we can answer any questions you may have.

**SECTION 2: WHAT DOES THE STUDY INVOLVE?**

**What happens at the study visit?**

When you come to Cambridge, a doctor or senior research nurse will talk to you about everything to make sure you understand things and give you time to ask questions. If you agree to take part, you will be asked to sign a consent form.

If you have questions before the trial and are uncertain regarding your eligibility a virtual screening appointment can be arranged, at which consent to take part in the study can be taken also.

On the day of the study visit, you will need to arrive at 9am fasted from midnight the night before. The night before we will ask you to eat and prepare a standardised pasta meal. You will then have a blood sample taken, and a cannula inserted for taking further blood samples across the day. You will then continue to fast across the morning for 30 minsand have an additional blood test to measure for gut hormones and other metabolic markers. You can drink water up to 60 mins before the study.

You will then be given a liquid meal of known nutrient content and have further blood samples taken for **up to 4 hours.**

Following conclusion of the study you will have your cannula removed and will be free to go.

Each blood sample will only take a short period of time, allowing time to relax. TVs and wifi will be available at the TRF facility.

**Inclusion/Exclusion criteria**

We are currently recruiting patients with bile acid diarrhoea/bile acid malabsorption into the study

To study has the following requirements to be eligible to take part currently:

**Inclusion Criteria**

* Volunteers between the age of 18 and 65 can be included.

AND

* Have a diagnosis of bile acid diarrhoea confirmed with SEHCAT <15% retention and on treatment with bile acid sequestrants –

Note: both primary (idiopathic) bile acid diarrhoea and secondary (terminal ileum loss) bile acid diarrhoea patients are suitable for recruitment.

OR a diagnosis of bile acid diarrhoea following a trial of bile acid sequestrants and successful improvement of symptoms

OR a diagnosis of bile acid diarrhoea due to terminal ileum resection on treatment with bile acid sequestrants

Note: At this stage we will not be recruiting patients with bile acid diarrhoea purely due to cholecystectomy (gall bladder removal).

Having a diagnosis of the one of the following conditions makes you ineligible to take part:

Exclusion Criteria:

* Additional gastrointestinal motility disorders (eg gastroparesis, achalasia, Hirschsprung’s disease, mixed connective tissue disease)
* Coeliac disease
* Additional GI surgery (eg cholecystectomy, gastric band, gastric bypass) – appendectomy is not an exclusion criterion. If doubt regarding eligibility decision to be made by clinical researcher.
* If taking erythromycin (known to stimulate motilin receptors)
* Current diagnosis of anaemia
	+ If you have had a recent blood test showing moderate anaemia (men <110 haemoglobin g/l, female <100 haemoglobin g/l) you would not be able to take part.
	+ During the study you will have a full blood count taken at a time point. If this incidentally shows mild anaemia during the study day (female 100-109 haemoglobin g/l, male 110-130 haemoglobin g/l) you can still continue provided you are well. If it is incidentally found to be lower than this, then the clinical researcher will assess you, pause the study day and will inform your GP to further investigate it.
* Pregnancy or breastfeeding
* Taking insulin injections or GLP1 analogue therapy.
* Taking diabetic medications including SGTL2 inhibitors (eg Dapagliflozin) or DPP4 inhibitors (eg linagliptin), sulphonylureas (Gliclazide) and metformin as all are known to influence gut hormone levels.
* Dietary reason to be unable to take Ensure which contains Milk protein eg lactose intolerance; cow’s milk protein allergy, vegan.
* If clinical investigator feels there is an additional clinical reason not mentioned above which would make them unsuitable for the study (eg other bowel/gastroenterological condition or endocrine condition not listed above; needle phobia etc).

**Study Day:**

The following procedure will happen on and before the study day:

* The night before you will be asked to prepare yourself a standardised pasta meal and fast from midnight prior to attending the study unit. You will still be able to drink water during this time, but we would ask you to avoid caffeine and calorie containing drinks.
* On the day of the study you will need to arrive at the TRF facility for 9am following an overnight fast. You will be able to drink water until 1 hour before starting the study.
* We will require you to take your bile acid sequestrant tablets as normal up to meal study day, but we would ask you to not take loperamide in the 48 hours before the meal study.
* We will ask you to take your morning bile acid sequestrant with the meal at the study day.
* On arrival at the facility you will have initial observations taken including a brief medical history, heart rate, blood pressure and temperature and body measurements including BMI, weight and waist circumference.
* You will be given a bowel symptom diary to complete. This will be for up to (if possible) 7 days prior to the first study day, each study day and for 7 days post each study day. Diary can either be returned in person, by post or by email (preferred option) (GutHHD@addenbrookes.nhs.uk).
	+ 7 day diary prior to meal visit 1 would only occur if consented to take part in the study more than 7 days prior to first study visit day.
* You will then have a cannula inserted into a vein in the forearm for the study day. A primary blood sample will then be taken at this point for standard clinical measurements for reference. This will include your full blood count, kidney function, liver function tests and metabolic markers such as your HbA1c and lipid levels at visit 1 (and if felt necessary also at visit 2).
* The sited cannula will then be used for the blood samples for the rest of the day. If the cannula fails during the day it will need to be re-sited.
* You will have a further fasting blood test taken 15 minutes later and then be given a liquid (Ensure) meal. You will take your bile acid sequestrant with the meal.
* You will then have blood samples collected for up to 4 hours post the meal. The number of time points and length of study will be confirmed to you before starting the study.
* The maximum number of time points would be -30, -15, 0, 15, 30, 45, 60, 90, 120, 150, 180, 210 and 240 mins post meal.
* Hunger scores will also be taken at some time points using a visual analogue scale.
* Blood glucose will be tested before starting the study. In the unlikely event of your blood glucose becoming low, the study will be halted and this will be treated.
* At the end of the day, the cannula will be removed and you will be offered further food and drink before leaving.
* After conclusion of the first meal study, you will then be free to go. We will then ask you to not take your bile acid sequestrant for 7 days until your follow up meal study. You will still be able to take loperamide, but not in the 48 hours before the next meal study.
* 7 days later you will then follow the same meal study again, but this time without taking your bile acid sequestrant. If not possible to have the second study exactly 7 days later it will be at least 7 days later and as close to 7 days as possible.
* After the second meal study, you will be able to return to taking your bile acid sequestrants as normal.
* In the unlikely event that the baseline blood tests we measure show any abnormalities we will communicate these findings to your GP.
* The gut hormone tests we will be performing are not regularly performed in clinical practice. In the unlikely event that these tests appear abnormal and merit further investigation we will communicate these findings to your GP.
* From the number of time points up to 250ml will be collected from you.
* This is less than the volume taken during blood donation which is about 500ml. For a healthy person 250ml is about 5% of your total blood volume and should not constitute harm. You will be offered further food and drink before discharge in case you feel faint.
* Your collected research samples will immediately be frozen, and stored in Cambridge University hospitals before being analysed at a later date.
* Note – either saline flushes or a slow saline infusion with be used to ensure cannula patency during the study day.

**Optional additional tests:**

At each study there will be the option of providing a stool sample, from the first stool passed on the meal day.

The purpose of this will be assess the difference in faecal bile acid levels between meal visits and also gut bacteria levels "the faecal microbiome" within the sample at each meal study.  A stool sample will be subject to the Human Tissue Act, and will be given a unique research ID and be tracked and stored as per the Human Tissue Act.

This is also an optional part of the study and declining this part would not exclude you from taking part in the study.

**Diagram of research days:**

**Consent to take blood samples and what will happen to my blood samples?**

If you agree to take part in the study you will complicate a formal consent form.

You will have some baseline blood tests performed which will be standard tests used in hospitals and general practice including your full blood count, kidney function, liver function tests, markers of glucose metabolism and thyroid function. These will be processed in the regular clinical laboratories at Addenbrookes hospitals and as they are performed in a regular NHS laboratory the results will be added to your medical records.

Other tests will be more specialized and more common to research rather than regular clinical use and will include gut hormones and other metabolic markers.

The blood samples you provide for these purposes will immediately be processed to remove any cells and genetic material. The remainder of the blood sample will then be frozen and stored at the University of Cambridge. Your samples will be given a unique anonymized research ID. Only clinical researchers named on this project (Dr Chris Bannon, Dr Jeremy Woodward and Prof Fiona Gribble) will have access to the identity of the samples, and to all other processing the sample they will only see a unique research ID.

If you agree to provide a stool sample these will be stored in accordance with the Human Tissue Act.

The majority of analysis will take place in the University of Cambridge and University of Cambridge Hospitals laboratories, however it may be necessary for specialized tests that your samples need to be analyzed at another NHS or University laboratory. If stool samples are analyzed at an alternative site it will again be in accordance with the Human Tissue Act.

**What if some of the tests show that I have a particular problem?**

If any of the tests show anything that might require further medical assessment, these results will be discussed with you and appropriate follow-up will be arranged through the doctor at your local hospital or your GP. If you would like further details about any of the tests we would be happy to provide this.

**What are the possible benefits of taking part?**

This research study is aimed at advancing knowledge only and may not result in any direct medical benefit to you or specific patients. It will help us to learn more about levels of gut hormone motilin and other metabolic hormones and markers with the aim of developing new clinical diagnostic tests and new treatments.

**Can I withdraw from the study?**

You can withdraw from the study at any time without giving a reason. You will be asked if you wish for your research data and samples collected to that point to remain in the study or if you would like them to be removed from the study​.

If you wish to withdraw from the study, before the visit this can be done via email to the research team (GutHHD@addenbrookes.nhs.uk).

On the study day this can be performed verbally to one of the research nurses or research doctors and this will be documented and a withdrawal form provided to you.  If you wish to withdrawal after the study day, this can be done by contacting the research team by email or by post (email GutHHD@addenbrookes.nhs.uk​).  A withdrawal form will be provided to sign to state if you would like your data and or samples additionally removed as well.  If a form is not returned but you have stated in writing you wish for samples and data to be removed this will be acted upon.

**Will my taking part in the study be kept confidential?**

Yes. All information collected will be anonymised and kept confidential and be kept separate from your medical records; any information which can identify you, for example your name and address, will not be revealed. Anonymous data will be stored on both paper and electronic format and can only be traced back to you with a coded crib sheet.

This crib sheet encoding your identity to your research id will be stored on paper in a locked file cabinet in the Institute of Metabolic Science, and electronically on an encrypted spreadsheet kept on Addenbrooke’s clinical computer network. Only named clinical researchers (Dr Chris Bannon, Prof Fiona Gribble, Dr Jeremy Woodward) will have access to this crib sheet.

Non-anonymised data such as the crib sheet will be kept for up to 3 years after the study has concluded.

Other researchers will only have access to the anonymised data which will be stored electronically and on paper. Anonymised data will be stored long term after the study and will be used for publication.

To ensure adherence to Good Clinical Practice, our research will be monitored by the NHS Trust; however, all information will remain confidential. Our data management is in compliance with the Data Protection Act.

It is anticipated it will take up to a year to recruit all required volunteers for the study and up to another year to analyse the blood samples.

Blood samples will be stored after the study for up to 10 years with an anonymous research ID for potential analysis with newer techniques for measuring gut hormones and other metabolic markers in the future. If you wish for your blood samples to be removed please contact the team and they will be removed and destroyed.

After this any remaining blood samples will be disposed of and destroyed.

**Further information on data collection**

Cambridge University Hospitals NHS Foundation Trust (CUHNFT) and the University of Cambridge are joint sponsors for this study based in the United Kingdom.

CUHNFT and the University of Cambridge will be using information from you and/or your medical records in order to undertake this study and will act as joint data controllers.

This means that both organisations are responsible for looking after your information and using it properly.

The University of Cambridge will keep identifiable information about you for 3 years after the study has finished.

CUHNFT will keep identifiable information about you for 3 years after the study has finished.

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate.

If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible.

You can find out more about how we use your information using the following links:

For Cambridge University Hospitals NHS Foundation Trust, please visit: <https://www.cuh.nhs.uk/corporate-information/about-us/our-responsibilities/looking-after-your-information>, or email the Data Protection Officer at: gdpr.enquiries@addenbrookes.nhs.uk

For University of Cambridge, please visit: <https://www.medschl.cam.ac.uk/research/information-governance/>, or email the Information Governance team at: researchgovernance@medschl.cam.ac.uk

<https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/data-protection-and-information-governance/gdpr-guidance/templates/transparency-wording-for-all-sponsors/>

**Will my doctor be informed?**

Should you decide to take part in this study, with your agreement, your GP will be informed of your involvement.

**Will my medical notes be accessed by the research team**

With your consent your medical notes will only be accessed by a clinical researcher on the team. This will for the purpose of checking your baseline blood results in the study and to inform your GP if there are any abnormalities, and if required to check you met the inclusion and exclusion criteria. All aspects will remain anonymised within your research data which are kept separate from your medical notes.

**What will happen to the results of the research study?**

We also intend to publish the results in relevant medical journals as they are likely to be of considerable benefit to both the scientific and medical community. Nothing that can be directly traced back to you will be published, everything will be in an anonymised format only.

A copy of the results can be obtained by contacting the research team (GutHHD@addenbrookes.nhs.uk) with any questions and to obtain a copy of the results when published in scientific journal.

Newly published research will be also published on the IMS-MRL webpage (https://www.mrl.ims.cam.ac.uk/) where results of studies are advertised once published.

**What if there is a problem?**

If you have a concern about any aspects of this study, you should ask to speak to the clinical team who will do their best to answer your questions. If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure.

As a point of reference the Patient Advice and Liaison Service (PALS) service contact details for Addenbrookes hospital are:

Email: pals@addenbrookes.nhs.uk

Phone: 01223 216756

The risks of participants suffering harm as a result of taking part in this study are minimal, but insurance (provided by the University of Cambridge and the NHS indemnity scheme) will provide compensation for any negligent harm caused by participation.

**Who is funding the research?**

The funding for this study comes from a grant to Prof Gribble from Wellcome to measure gut hormones in human blood samples using new techniques. The salary for Dr Bannon working on the trial also comes from this grant.

**Who has reviewed the study**

All research in the UK is reviewed by an independent group of people, called a Research Ethics Committee, in order to protect your safety, rights, wellbeing and dignity. This study has been reviewed and given a favourable opinion by the [ethics committee name giving approval to be inserted here] research committee.

**Contact details:**

Additional information or questions regarding this study can be obtained by contacting the following research team members at the above address and telephone numbers (01223 762634)

* + Professor Fiona Gribble
	+ Doctors: Christopher Bannon (GutHHD@addenbrookes.nhs.uk) (main contact)

**This is the end of the information sheet. We would like thank you for taking the time to read this sheet. If you wish to participate, do let us know.**