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

Protocol A: Fasting and Post Meal Study – Single Visit

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 in the fasted and fed state. In particular a hormone called motilin, released from the gut has been understudied to date in clinical research and is known to vary particularly in the fasted state. The hormone motilin

has been shown to promote motility and hunger within the gut. The hormone is known to vary in both the fasted state and in response to feeding.

A new technique has been developed to measure this hormone motilin in humans. We wish to utilise these new technique to measure how motilin varies in the fasted and fed state and in relation to other hormones and metabolic markers released from the gut.

The long term aim of this work is to develop a technique for measuring motilin 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?

We are currently recruiting volunteers with a range of gastro-intestinal conditions and healthy volunteers to take part in this protocol.

You are eligible to take part if you are between the ages of 18 and 75

To be an eligible healthy volunteer you will need to have not been previously diagnosed with a gastrointestinal or metabolic condition.

A list of full exclusion criteria for healthy volunteers is included later in this information sheet.

If you regularly see a gastroenterology doctor and/or have a condition we are also recruiting participants with a range of different conditions, including but not limited to chronic diarrhoea, gastroparesis, patients with altered stoma output, and participants with altered nerve innervation to the gut.

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 one day. During your visit you will have some blood samples taken across the morning whilst fasting. You will then be provided with a meal and have further blood samples taken.

We will cover your travel expenses (up to £50 per visit) for travelling to the **[TRF in Cambridge/participating site]** 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.

On the day of the study visit, you will need to arrive at 9am fasted from midnight the night before. 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 **up to 4 hours** and have a blood sample taken every 15 minutes to measure for gut hormones and other metabolic markers. You can drink water up to 90 mins before the study, but will not be able to have water during this fasted period.

In the unlikely event of having an episode of low blood glucose during the study whilst fasting, you will be given either fruit juice or a glucose drink and will be re-assessed if you can continue the study.

You will then be given a liquid meal of known nutrient content or a glucose drink and have further blood samples taken for up to a further **2 hours.**

The exact length of your fasting period and period of sampling post meal will be specified to you before the start of the study.

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.

For Healthy Volunteers:

Inclusion/Exclusion criteria

We are currently recruiting healthy volunteers into this study.

To be eligible to take part in the study you need to be aged between 18 and 75 and not have a previous diagnosis of a gastrointestinal or metabolic condition.

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

- Type 1 or 2 Diabetes
- Gastrointestinal motility disorders (eg gastroparesis, achalasia, Hirschsprung's disease, mixed connective tissue disease)
- Coeliac Disease
- Endocrine condition (eg Thyroid condition, Pituitary disorder, Polycystic Ovarian Syndrome, a condition requiring hormone replacement)
- BMI > 35 kg/m2
- Gastro-oesphageal reflux disease
- Inflammatory bowel disease
- Irritable bowel syndrome
- Bile acid diarrhoea
- Previous GI surgery (eg cholecystectomy, gastric band, gastric bypass, any surgery involving removal of section of GI tract) – 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), loperamide (decreases gastric motility), or other drugs with known effects on intestinal motility.
- 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.
- Any concerns regarding anaemia can be discussed with the clinical research doctor. 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.
- Pregnancy or currently breastfeeding

- 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).

Extra note:

- Dietary reason to be unable to take Ensure which contains Milk protein eg lactose intolerance; cow's milk protein allergy, vegan. These participants would only be able to receive an oral glucose solution.

For Participants with a gastrointestinal condition:

Inclusion Criteria

- Aged between 18 and 75
- Diagnosis of a gastrointestinal condition which causes altered motility/altered gut transit time
    - Within this we would aim to include (but not limit to) patients :
        - with altered nerve input to the gut,
        - patients with gastroparesis,
        - patients with a stoma
        - patients with previous surgery to the bowel including:
            - Gastrectomy
            - Bariartic Surgery
            - Removal of gall bladder
        - patients with chronic diarrhoea.
        - patients with dumping syndrome

Exclusion Criteria

- Pregnancy or breast feeding
- 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.
    - Any concerns regarding anaemia can be discussed with the clinical research doctor. If clinical investigator feels there is an additional clinical reason not mentioned above which would make them unsuitable for the study

- If clinical investigator feels there is an additional clinical reason not mentioned above which would make them unsuitable for the study

Study Day:

The following procedure will happen on the study day:

- On the day of the study you will need to arrive at the TRF facility for 9am following an overnight fast from midnight the night before. You will be able to drink water until 90 mins before starting the study. You will be advised on a controlled meal to prepare yourself the night before attending the unit.

- 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 have further heart rate and blood pressure checks during the day.

- You will then be given a bowel symptom diary to complete starting and including the study day and for 7 days post the study day. Diary can either be returned in person, by post or by email (preferred option) (cuh.guthormonestudies@nhs.net).

- 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.

- 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.

- Samples will be collected every 15 minutes for up to 4 hours in the fasted state from the cannula in your arm.

- You will then be given a liquid mixed meal (Ensure meal) or a glucose drink and will have blood samples collected following this for up to a further 2 hours. The length of study and number of time points will be confirmed to you before starting the study.

- **To assess absorption of the meal, the clinical researcher may ask you to take a standard dose of paracetamol (1g) alongside the meal.**

- At up to every time point a blood sample is taken you will be given a questionnaire to assess your feeling of hunger.

- Before or after the study you will be given some questionnaires to perform which will ask questions regarding your mood, anxiety, eating behaviour and measures of impulsivity.
    - Some of these questions can raise sensitive topics– if you have any distress or wish to discuss anything further you can discuss this with the study psychiatrist (Prof Paul Fletcher - paul.fletcher13@nhs.uk)

- During the study you will be asked some questions regarding how full you feel and feelings within your gut and a questionnaire on your day to day gut symptoms.
- You may also be provided some questionnaires regarding your hunger and fullness and to mark this on a scale throughout the study.

- Blood glucose may be tested using a glucometer at the bedside during the study. It would also be tested if you develop symptoms suspicious of hypoglycaemia. In the unlikely event you experience low blood glucose during the study, this will be treated with either 200ml fruit juice, 60ml "Glucojuice" or 2 tubes of Dextrogel as per local trust guidelines. Your blood glucose will be re-checked 15 minutes later and assessment performed to see if you can continue in the study, or if the study day should be terminated.

- **If you are someone who has the potential to have low blood sugar after eating; (eg** if you have previously had gastrectomy/bariatric surgery and have dumping syndrome) your blood glucose will be checked regularly throughout the study:

- Note if you are at risk of low blood sugar after eating you are only eligible to have the Ensure mixed meal during the study – you will not be given an oral glucose drink.

- You will have your blood glucose checked regularly:
  - Every 15 minutes for the first hour after the Ensure mixed meal
  - Then every 30 mins for up to 4 hours after the Ensure mixed meal.
  - The team may perform additional glucose checks as deemed necessary.
  - Additional snacks, food and drink as per your requirements can be provided before leaving, and you will not be discharged until you feel ready and able to travel home.
- If you have an episode of hypoglycaemia it will be treated as per local guidelines

- At the end of the day, the cannula will be removed and you will be offered further food and drink before leaving.

- No follow up should be required, but you will be able to contact the research team if you have any further questions.

- 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 (max 14ml per time point). If there are any concerns eg concerns around anaemia, the protocol can be altered to minimise the amount of blood to around 200ml per visit – this can be discussed with your clinical researcher.

- This is less than the volume taken during blood donation which is about 500ml. For a healthy person 250ml is less than 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.

- Saline flushes or a slow saline infusion will be given through the cannula during the study to ensure it remains patent.

- Your collected research samples will immediately be frozen, and stored in [participating site] and Cambridge University hospitals before being analysed at a later date.

What if I am taking a medication that effects gut transit (such as loperamide, ondansetron, codeine, bile acid sequestrants).

This will depend on the medication.

If you take loperamide, ondansetron or codeine (or other opioids) you will be asked to avoid these medications for 24 hours prior to the study if possible. That is because these medications can slow down gut transit and it is unknown how they would affect the results.

If you cannot avoid these medications for 24 hours, discuss this with your researcher; you may still be able to take part at the investigator's discretion and decision.

If you take bile acid sequestrants you will have different options. You can either:

- Take as normal up to the visit.
- Pause for 72 hours prior to the visit. – This will be discussed with you clinical investigator prior to the study day and a decision will be made.

- **Optional additional tests:**

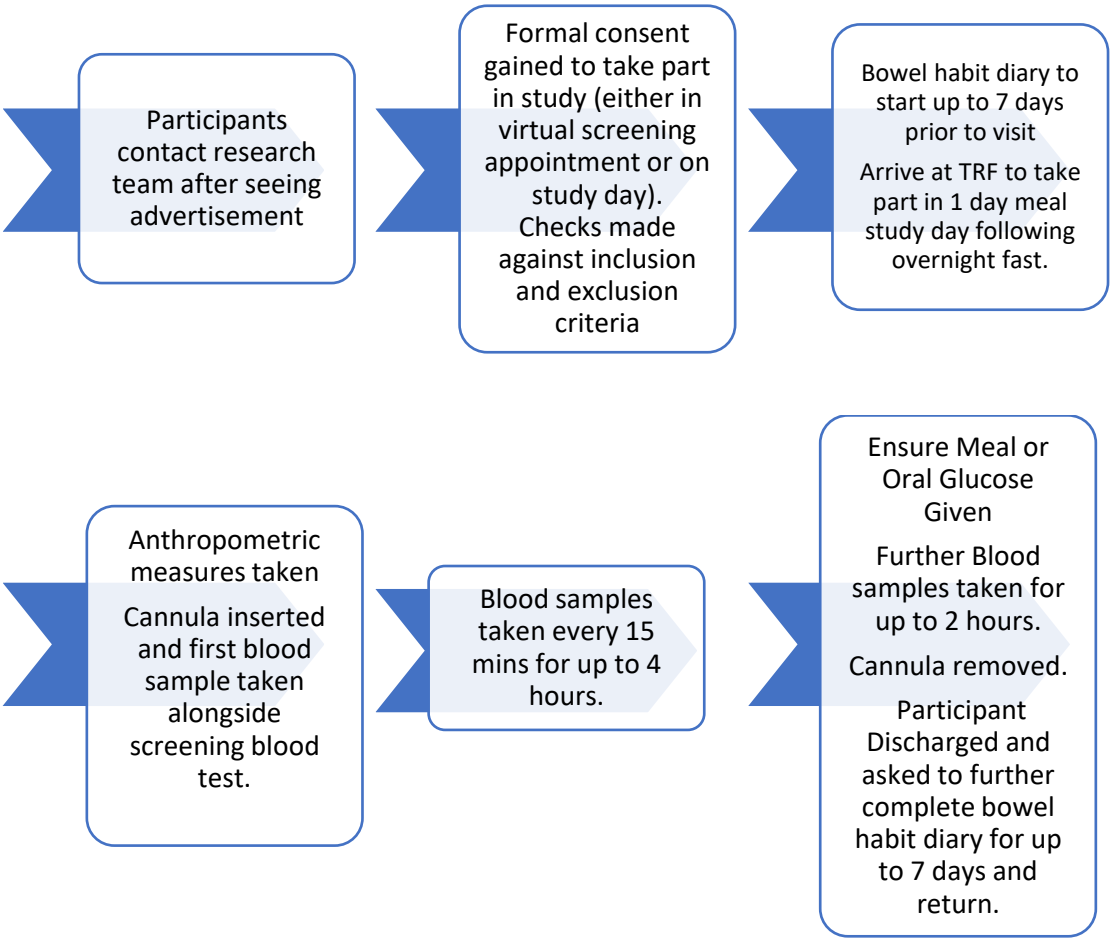
- At the study day there will be the option of providing a stool sample.

- The purpose of this will be assess the faecal bile acid levels, fatty acid levels, other metabolic markers 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 day:



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. Your samples will be given a unique anonymized research ID.

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 for markers of metabolism that your samples need to be analyzed at another NHS or University laboratory.

Only clinical researchers named on this project (Dr Chris Bannon, Dr Jeremy Woodward and Prof Fiona Gribble, Dr Htar Hlaing, Prof Paul Fletcher, Dr Philip Wild and Dr Agatha Van Der Klaauw and your referring doctor and regular doctor) 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 (cuh.guthormonestudies@nhs.net).

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 cuh.guthormonestudies@nhs.net). 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, Prof Paul Fletcher, Dr Jeremy Woodward, Dr Htar Hlaing, Dr Philip Wild and Dr Agatha Van Der Klaauw) 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 end of the study.
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 with an anonymous research ID after the study for up to 10 years 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/patient-privacy/, or email the Data Protection Officer at: cuh.gdpr@nhs.net

For University of Cambridge, please visit: https://www.information-compliance.admin.cam.ac.uk/data-protection/medical-research-participant-data, or email the Information Governance team at: research_governance@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 be accessed by a clinical researcher on the team. This will be for the purpose of checking your baseline blood results in the study, check previous blood results, past medical history and other test results relevant to the study and to inform your GP if there are any abnormalities to check you met the inclusion and exclusion criteria and anything else relevant to the study. 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 (cuh.guthormonestudies@nhs.net) 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: cuh.pals@nhs.net

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 (cuh.guthormonestudies@nhs.net) (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.