Participant Information Sheet
Mitochondrial DAMPs as mechanistic biomarkers
of m**u**co**s**al inflammation **i**n **C**rohn's disease and Ulcerative Colitis
MUSIC Study

You are being invited to take part in the MUSIC study. Before you decide whether or not to do this, it is important for you to understand what the MUSIC study is and what it involves. Please take time to read the following information carefully. Talk to others about the study if you wish. Contact us if there is anything that is not clear or if you would like more information. Take plenty of time to decide whether or not you wish to take part.

In Inflammatory Bowel Diseases, Crohn's disease (CD) and Ulcerative Colitis (UC), one of the most important goals in treatment is **complete mucosal healing** - the full return to normal and healthy gut lining with the healing of all ulcers seen during active disease or flare up. For IBD patients, full healing of the inflamed gut will lead to a good future prognosis, a return to normal bowel habit, energy levels and long-term remission.

Although we have strong medicines for IBD, doctors do not have good tests that can reliably show how well these powerful drugs are working. In general, 50% of patients who feel better on these drugs, continue to have gut inflammation when their bowels are examined using an internal camera test (such as an ileo-colonoscopy or flexible sigmoidoscopy). In other words, symptoms alone (for example, how you feel) are poor guides to whether the bowel wall has healed or not.

We need better tests to monitor gut inflammation. As patients who carry on with treatments that are not fully healing the inflamed gut wall may be unnecessarily exposed to the extra risks associated with these strongdrugs; potential long term bowel wall damage due to under-treated inflammation; and miss the opportunity to try a different treatment that might be better.

LAY SUMMARY POINTS: WHY TAKE PART IN THIS STUDY?

1. Settling an IBD flare-up can take time - it's like turning a ship around at sea. Being involved in a research study will be like having a **2nd pair of eyes on my condition** running in parallel with my NHS treatment. It will put me at the forefront of research that might improve how we treat IBD.

2. It will give me the opportunity to be more **actively involved** in my treatment and to engage more fully with the clinical team in monitoring the course of the flare.

3. I will be more **closely monitored** during the flare up, both in terms of symptoms and investigations.

4. There will be **objective evidence** sought to show how well my current drug treatment is working and this information maybe useful for my doctor to change my medications.

What is the purpose of the study?

The MUSIC Study aims to investigate a new approach by measuring damage-associated molecular patterns (DAMPs) or 'danger signals' in the blood and stools, as a useful new test to inform IBD patients (and their doctors) whether their affected and inflamed bowel gut linings have healed in response to their respective drug treatments.

Recently, we found that DAMPs arising from the mitochondria are increased in patients with active IBD. Mitochondria are the 'batteries' or 'powerstations' that are found in, and provide energy for living cells. They have evolved from bacteria around 2-3 billion years ago. As such the **mitochondria have many similarities with bacteria**.

Of interest, our on-going research suggests that DAMPs are released from the inflamed part of the gut that is affected by IBD. When our immune cells encounter these signals, they confuse them with bacteria, become activated and trigger a prolonged inflammatory response, which is destructive to the bowel wall and lining.

Typically, doctors find out how well a prescribed treatment for active flare of IBD has worked, by asking the patient whether he/she feels better and if bowel symptoms have improved. They also check blood or stool tests (C-reactive protein and calprotectin) for signs of inflammation. The current evidence showed that such approaches are not fully informative on whether the bowel wall has healed or not. The best way to find out whether the bowel wall has healed is by carrying out an internal camera test to examine the bowel lining of the lower small and large bowel. However, this is not always possible within the NHS due to lack of resources.

In the MUSIC study, we will investigate the role of DAMPs as a biomarker for inflammation. We will measure DAMPs and assess how well they reflect the state of inflammation within the gut lining at the start and during medical treatment for active IBD.

If you choose to take part, the MUSIC study will provide very close monitoring of your IBD over a 12-month period. We will monitor your reported symptoms, carry out standard blood and stool tests every 3-months and provide a follow-up ileo-colonoscopy or flexible sigmoidoscopy test to check whether your bowel wall has healed in response to medical treatment. **Importantly, all this information will be given to your NHS doctor who will decide whether to change your medical treatment depending on the findings.**

At each of these time-points, our research aims to study how well our mitochondrial DAMP measurements perform in monitoring gut inflammation. In the research samples obtained from you, we will carry out further scientific studies to understand how DAMPs activate inflammation in the gut in order to find new ways to block them as potential future treatment in IBD.

Why have I been asked to take part?

You have been asked to take part because you have IBD.

You are currently receiving your clinical care from NHS.

You have a flare or your current IBD is not well-controlled requiring new or a change in medical treatment.

Do I have to take part?

No, you do not have to take part or give a reason for not doing so. At your upcoming appointment, a member of your healthcare team will ask whether you would like to take part. If you would, our clinical research doctor will describe the study in detail and go through the information sheet with you. You will be asked to sign a consent form to show that you understand the risk and benefits of the study. **You can withdraw from this study at any time. Your decision will not affect your healthcare.**

What will happen if I take part?

If you agree to take part in the study, you will then be asked to sign a consent form. You should keep a copy of this Patient Information Leaflet and Consent Form for your records. In addition to your usual clinical care given by your doctor:

- You will see a research nurse or doctor who will explain the study in detail to you.
- Our research team will assess and record your symptoms at the start of the study
- We will ask you to provide a short report of your IBD symptoms every 3 months through a secure questionnaire, by telephone, email link or post. This will be explained clearly to you during your first visit
- We will ask you to provide one saliva sample for DNA analysis
- We will ask you to provide a blood sample every three months over a 12-month period. Here, we will also take standard blood tests required to monitor your IBD (such as full blood count, C-reactive protein) and research blood samples - 4 standard blood tubes (approximately 40mls)
- Blood sampling will be carried out on your first visit in clinic. Our team will arrange a convenient time for you to attend for future blood tests. These appointments can coincide with your usual NHS clinic visits (for example when you come to see your doctor, or during your drug infusion, or your camera tests), in dedicated appointments to the hospital OR our research team can carry out the blood tests in the community
- In a small selected group of patients, we may ask to take up to 100mls of blood (1/2 cup or 6 tablespoons) (Optional)
- We will also ask you to provide a stool sample every three months over a 12-month period. At each time point, we will provide you with stool containers to measure calprotectin (a test for gut inflammation), haemoglobin (qFIT – a marker for blood in the stools) and your gut bacteria (as part of research)
- We will provide these stool containers and special envelopes where you can send to dedicated research locations at your convenience
- We will arrange an ileo-colonoscopy or flexible sigmoidoscopy[1] at approximately 3 months' time from the start of the study to assess how well your bowel wall has healed in response to treatment. We will discuss with you during the first visit whether an ileo-colonoscopy or flexible sigmoidoscopy is a more suitable test for your follow-up. During

your camera test, we will take approximately 8-12 pinches of gut lining tissue, also known as biopsies (up to a maximum of 16 additional biopsies) from normal and affected parts of the small and large bowel for research. This will add an extra 5-10 minutes to your ileo-colonoscopy

- If you have not had a recent ileo-colonoscopy or flexible sigmoidoscopy to assess your IBD (i.e. within 6 weeks of consent) before the start of our study, we will arrange this test for you as part of our research study. Data from this test will be entered into the study

- If you have had a recent ileo-colonoscopy or flexible sigmoidoscopy within 6 weeks' of consent, where the level of gut inflammation has been carefully documented, **a further test is not necessary at the start of our study**

- **If your ileo-colonoscopy or flexible sigmoidoscopy at the 3 month time point shows continual inflammation in the gut, we will arrange a further test at the 12 month time point**

- If your usual NHS doctor requires an ileo-colonoscopy or flexible sigmoidoscopy during our study period, we can provide this test as part of our research study. For example, you may be admitted to hospital with an acute flare of your symptoms and a further camera test is needed. Data from this test will be entered into this study

- If you are admitted to hospital for further treatment of your IBD during the study period, we will record the information of your IBD activity and tests. We may also approach you again to give a blood and stool sample, which will be taken at the same time as routine tests requested by your doctor in the hospital

- We may also approach you again in the future to give a blood sample, which will be taken at the same time as routine blood samples requested by your doctor

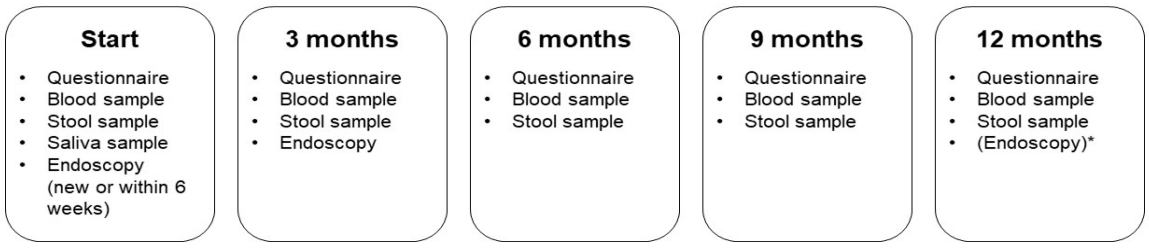
- If you have a bowel operation as a result of IBD, we will ask your consent to take additional small samples of your bowel for research

- We will ask for your permission for our approved members of the research team to access your medical records to obtain study specific clinical information pertaining to IBD

- The samples you provide and accompanying clinical data may be analysed to inform other related research projects.

We have detailed what will happen at each visit below:

Overview of involvement



*You will only have an endoscopy at 12 months if it is clinically advised

What are the possible risks of taking part?

Although generally regarded as safe, standard ileo-colonoscopy carries a small risk. This includes causing a tear in the bowel (1 in 1200 cases), unexpected reaction to sedation, excessive bleeding from biopsy site.

As there are extra research biopsies taken, there is a slightly higher risk of excessive bleeding (<1%). Most bleeding will settle spontaneously and if there is more bleeding than expected, this can usually be treated by cauterisation or clipping during the same procedure by the Endoscopist.

Your research endoscopy tests will be carried out by experienced doctors within NHS Hospitals with all the necessary support and facilities, like an usual NHS endoscopy appointment.

There is a possibility of some pain or bruising from giving an extra blood sample.

We acknowledge that 3-monthly blood tests may be inconvenient. Where possible, we will make all necessary effort to minimise this by arranging a flexible time and place for this to take place.

For most IBD patients with an active flare requiring medical treatment, regular blood monitoring is usually necessary. We will endeavour to coincide these appointments with our research blood tests to make things easier for you.

What are the possible benefits of taking part?

Due to the nature of this research, your participation will mean that your IBD will be very closely monitored.

This information may help your usual NHS doctor to make adjustments that might improve your current IBD treatment.

All the medical IBD information (your ileo-colonoscopy results and your routine NHS blood and stool tests to measure how active or well-controlled your IBD is) will be given to your NHS doctor who will decide whether to change your medical treatment depending on the findings.

Our research into DAMPs aims to identify a new way to monitor the actual level of gut inflammation, potentially replacing the need for subsequent repeated colonoscopies in IBD.

We will offer reasonable travel expenses to cover your hospital trip(s) for your ileo-colonoscopy or flexible sigmoidoscopy and additional hospital visits for clinic review.

Will my taking part be confidential?

Your participation in this study will be recorded in your medical notes and your usual IBD doctor and GP will be informed.

The information gathered for research purposes will be confidential. Only members of the research team will be able to identify you. They will abide by the Data Protection Act 2018 at all times and make sure your name, address, and any other information that would identify you are removed from your medical information before it is given to any researchers. The information held on computer will be kept secure, and all written information will be held in locked filing

cabinets within research offices, under the direct responsibility of the MUSIC study doctor in your area.

In order to monitor and audit the study we will ask your consent for responsible representatives from the sponsors and NHS institution to access your medical records and data collected during the study, where it is relevant to you taking part in this research. The Sponsors are responsible for overall management of the study and providing insurance and indemnity. With your consent we will inform your GP that you are taking part in our study.

Will my medical notes be used?

Medical research is of more value if the researcher has information about the medical history of the person who donated the tissue. We would like your permission to use and store information from your medical notes now, and possibly in the future as a follow up. All information collected and stored will be kept strictly confidential. Your personal information like your name and address will be removed from your medical notes before being given to anyone for their research. Only the research team and your Healthcare team will be able to link your information to your research data.

What will we study on your research samples?

In your blood and stool samples, we measure the DAMP levels to see how well they are linked to whether your bowel inflammation has healed or not.

We will also carry out a number of protein and gene studies on your gut biopsies to understand how DAMPs are released in the bowel wall and the type of inflammation processes they cause.

We know that genetics play an important role in increasing your risk of developing IBD. We will carry out genetic testing of your DNA obtained from your saliva. These genetic variations may explain differences in the level of DAMPs and how they activate the immune system. This in turn helps in finding out who may benefit from future new drugs and treatments that block the effects of DAMPs.

The results of these tests cannot be traced back to you, and will only ever be used for research.

I have participated in the study…what happens next?

The clinical data obtained from your 1-year research follow-up will be passed to your usual consultant. Your doctor may adjust your medical treatment depending on the results of your tests. Following this, your clinical care of your IBD will continue as usual and be carried out by your consultant.

Where will my blood, stool and tissue samples be used?

We will recruit participants into our study for 3 years. The samples collected will be kept within the Gut Research Unit, Centre for Inflammation Research, Queens Medical Research Institute, University of Edinburgh and Wellcome Trust Clinical Research Facility, Western General Hospital under the oversight of the Lothian Gastroenterology Bioresource, University of Edinburgh and be processed every 2-3 months; or for certain experimental work, be used immediately in the Gut Research Unit, University of Edinburgh. Here, we will carry out new biomarker analysis from blood, stools and biopsies working together and in combination with our studies in Edinburgh.

Stool haemoglobin tests will be sent to University of Dundee for further analysis.

At the end of the study, your anonymised samples that are not directly used by our research will be transferred to South East Scotland SAHSC BioResource under the guardianship of NHS Lothian or disposed in accordance to the Human Tissue Authority Code of Practice. Your anonymised samples may also be used by clinical, academic or commercial researchers, and maybe used in countries out with the United Kingdom undertaking similar research in partnership with our group.

What will happen to the results of the study?

It is important for our participants to be fully informed about the progress and results from this study. The overall results of the project will be made widely available. They will be published in medical journals but anonymously so results cannot be traced back to individuals.

We will also provide fact sheets to communicate the most important research findings to the general public and patients.

We will set up a webpage for this study where we can update the participants of the progress and the publications that will come out from this work.

We have a very active Patient Public Involvement (PPI) program that is coordinated within the Edinburgh IBD Science Group with regular events with opportunities for participants to engage directly with the researchers. This information will be regularly posted in our webpage.

Who has reviewed the study?

All research in the NHS is looked at by an independent group of people called a Research Ethics Committee. The committee has the responsibility for scrutinising all proposals for medical research on humans, has examined and raised no objections from the point of view of research ethics. It is a requirement that your records in this research, be made available for scrutiny by monitors from NHS Lothian, whose role is to check that research is properly conducted and the interests of those taking part are adequately protected.

Identifiable Data for future research

University of Edinburgh and NHS Lothian are the co-sponsors for this study based in Scotland. The co-sponsors are responsible for any identifiable information about you for 5 years and are strictly governed by UK Policy Framework for Health and Social Care Research guidelines. In this study, we will use your Community Health Index (CHI) number, which uniquely identifies a patient within NHS in Scotland. Future information is provided in the accompanying leaflet Data Protection Information Sheet.

What if there is a problem?

If you have a concern about any aspect of this study please contact Dr Gwo-tzer Ho on Tel No: 0131 242 6653 who will do their best to answer your questions

In the unlikely event that something goes wrong and you are harmed during the research and this is due to someone's negligence then you may have grounds for a legal action for

compensation against the NHS but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you (if appropriate)

Further Information
If you have any further questions about the study please contact the MUSIC research team on: Tel No: 0131 537 1907 or 07929 784314. *If you would like to discuss this study with someone independent of the study team please contact:* Dr Alan Shand on: 0131-537-1770 or email: alan.shand@luht.scot.nhs.uk.

Complaints

If you wish to make a complaint about the study please contact:

Patient Experience Team
2 – 4 Waterloo Place, Edinburgh, EH1 3EG
feedback@nhslothian.scot.nhs.uk
0131 536 3370

Thank you for taking the time to read this Information Sheet and for considering taking part in this study.

Data Protection Information Sheet

The EU General Data Protection Regulation (GDPR), along with the UK Data Protection Act, governs the processing (holding or use) of personal data in the UK.

You are receiving this as you are considering being a participant on this clinical research study. The information below details what data will be held about you and who will hold or store this.

University of Edinburgh and NHS Lothian are the co-sponsors for this study based in Scotland. We will use information from you and/or your medical records in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. The co-sponsors will keep identifiable information about you for 5 years.

As a University and NHS organisation, we use personally-identifiable information to conduct research to improve health, care and services. As a publicly-funded organisation, we have to ensure that it is in the public interest when we use personally-identifiable information from people who have agreed to take part in research. This means that when you agree to take part in a research study, we will use your data in the ways needed to conduct and analyse the research study. 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.

Providing personal data directly e.g. verbally, in a questionnaire or from your care provider

An NHS organisation will use your name, Community Health Index (CHI) number, contact details, and medical details to contact you about the research study, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study. Individuals from University of Edinburgh and NHS organisations and regulatory organisations may look at your medical and research records to check the accuracy of the research study. NHS organisations will pass these details to University of Edinburgh along with the information collected from you and your medical records. The only people in University of Edinburgh and the NHS who will have access to information that identifies you will be people who need to contact you to if further samples or follow-up clinical data are required or audit the data collection process. The people who analyse the information will not be able to identify you and will not be able to find out your name, NHS/ CHI number or contact details.

University of Edinburgh and NHS Lothian will keep identifiable information about you from this study for 5 years.

Providing personal data indirectly e.g. from your medical records

University of Edinburgh will collect information about you for this research study from you and your hospital medical files. This information will include your name/ NHS/ Community Health Index (CHI) number/contact details and health information, which is regarded as a special category of information. We will use this information solely for research purposes specific to the

MUSIC study.

Use of data for future research

When you agree to take part in a research study, the information about your health and care may be provided to researchers running other research studies in this organisation and in other organisations. These organisations may be universities, NHS organisations or companies involved in health and care research in this country or abroad. Your information will only be used by organisations and researchers to conduct research in accordance with the UK Policy Framework for Health and Social Care Research**.**

Your information could be used for research in any aspect of health or care, and could be combined with information about you from other sources held by researchers, the NHS or government.

Where this information could identify you, the information will be held securely with strict arrangements about who can access the information. The information will only be used for the purpose of healthcare research, or to contact you about future opportunities to participate in research. It will not be used to make decisions about future services available to you, such as insurance.

Where there is a risk that you can be identified your data will only be used in research that has been independently reviewed by an ethics committee and/ or the sponsor.

Contact for further information

You can find out more about how we use your information and our legal basis for doing so in our Privacy Notice at www.accord.scot.

For further information on the use of personal data by NHS sites, please link to the Health Research Authority (HRA) website; https://www.hra.nhs.uk/information-about-patients/.

If you wish to raise a complaint on how we have handled your personal data, you can contact our Data Protection Officer who will investigate the matter. If you are not satisfied with our response or believe we are processing your personal data in a way that is not lawful you can complain to the Information Commissioner's Office (ICO) at https://ico.org.uk/.

Data Protection Officer contact information:

University of Edinburgh
Data Protection Officer
Governance and Strategic Planning
University of Edinburgh
Old College
Edinburgh
EH8 9YL
Tel: 0131 651 4114
dpo@ed.ac.uk

NHS Lothian
Data Protection Officer
NHS Lothian
Waverley Gate
2-4 Waterloo Place
Edinburgh
EH1 3EG
Tel: 0131 465 5444
Lothian.DPO@nhs.net