[Site Logo and Details]

Defining microbial predictors of responsiveness to biologic therapies in Crohn's disease and ulcerative colitis

Participant Information Sheet

INVITATION

We would like to invite you to take part in IBD-RESPONSE.

Before you decide if you would like to take part, it is important to understand what taking part will involve for you. Please read the following information to help you decide if you would like to take part. You don't have to decide straight away. You may wish to take this leaflet away and discuss it with friends or family first. If you decide not to take part, this will not affect the care that you receive. A member of the research team will go through this information sheet with you and answer any questions you may have. If anything is unclear, or you need more information, please ask us.

Thank you for taking the time to consider being part of the study.

STUDY SUMMARY

- We are inviting you to take part in this study as you are soon to start, or likely soon to start a biologic (an injectable medication used to control inflammation in inflammatory bowel disease e.g. infliximab, adalimumab, vedolizumab or ustekinumab), a JAK inhibitor (tofacitinib) or other advanced therapy medication as treatment for Crohn's disease ('Crohn's') or ulcerative colitis ('colitis').
- There will be no changes in the care and treatment you receive, no extra visits to hospital, and we will only collect information about how you respond to your usual treatment.
- We are trying to find out why some people respond better than others to these treatments and if it may be possible to predict this response.
- We will ask you to complete questionnaires and collect stool samples at three different time points over the next year, and blood samples will be taken at two of these time points where possible.
- The majority of this study, including the consent form and questionnaires can be done on a mobile device at home. The stool samples can also be collected at home and sent back to us in the post. Bloods will only be collected if you visit the hospital for your routine care appointment.
- Stool samples are collected at three time points: (1) before you start your new treatment, (2) around 14 weeks after starting treatment, and (3) around 54 weeks after starting treatment.
- Blood samples are collected at two time points: (1) before you start your new treatment, and (2) around 14 weeks after starting treatment.
- If you are booked in for a colonoscopy or flexible sigmoidoscopy by your clinical team as part of your hospital care whilst you are taking part in the study, we will also ask for your permission for additional biopsy samples to be taken at the time of the procedure. These samples will be used for research. However, taking part in the study does not routinely involve or require you to have any additional colonoscopy or flexible sigmoidoscopy.

If you are interested in taking part, please read on for further details.

STUDY ASSESSMENTS

Assessment 1 - Baseline, prior to starting treatment

- Opportunity for you to discuss the study with a member of the research team and complete study consent form
- Complete questionnaires online
- Collect stool samples at home and send to research team at Newcastle University
- Blood samples will be collected when you next attend a clinical appointment (approx. 4 teaspoons)

Assessment 2 - 14 weeks after starting treatment*

- Complete questionnaires online
- Collect stool samples at home and send to research team at Newcastle University
- Blood samples will be collected when you next attend a clinical appointment (approx. 4 teaspoons)

Assessment 3 - 54 weeks after starting treatment**

- Complete questionnaires online
- Collect stool samples at home and send to research team at Newcastle University

*If you stop treatment before your first follow-up at week 14, we will ask you to complete questionnaires/provide samples required for Assessment 2 at the time of stopping treatment. If you start a new treatment within 10 weeks after this, the planned follow-up timeline will restart at Assessment 2, 14 weeks after starting the new treatment.

** If you stop treatment after first follow-up but before second follow-up, we will ask you to complete questionnaires/provide samples required for Assessment 3 at the time of stopping treatment. If you start a new treatment within 10 weeks after this, the planned follow-up timeline will restart at Assessment 2, 14 weeks after starting the new treatment.

WHAT IS THE IBD-RESPONSE STUDY?

There are two main types of inflammatory bowel disease ('IBD'); Crohn's disease and ulcerative colitis. The number of patients affected by Crohn's or Colitis is rising in the UK and worldwide. Treatment has changed a lot in the last 20 years and we now have several powerful injectable medications called 'biologics' and a new powerful tablet medication (for colitis) called tofacitinib (JAK inhibitor, JAKi). These treatments can be very effective, but some people respond better than others and we don't understand why. When a medication doesn't work, a new medication may be tried but sometimes several medication changes are needed to find the right drug for an individual patient. This takes valuable time when patients are not feeling well. Some patients will experience a worsening of their condition or side effects whilst trying to find the best treatment.

We want to understand why patients respond differently to these medications so that, in the future, we can better predict which medication is most likely to work at the time when it is needed most. This is called 'precision medicine'.

Trillions of microbes (bacteria, viruses and fungi) live inside the gut, called the 'gut microbiome'. We think that these microbes affect how well IBD patients respond to treatment. Other things that might affect how an individual responds to treatment include the person's immune system, their genes and even the foods they eat. We plan to study all these different factors in detail as we believe this will give us the best understanding of what causes patients to respond differently to treatment.

Small research studies in people with Crohn's and colitis have shown that certain gut bacteria in stool (faeces) may help predict who will respond or fail to respond to treatment. Therefore, it's important that we carry out bigger studies with more patients to confirm these findings. We will recruit 1,325 patients across the UK who are starting a new advanced therapy treatment for Crohn's or colitis.

IBD BioResource

IBD-RESPONSE will work with another study already underway in the UK. The IBD BioResource is a large study of over 35,000 patients, currently recruiting people with Crohn's and colitis from hospitals across the UK. The main aim of the IBD BioResource is to understand how human genes may cause or protect from Crohn's and colitis, and to link patients to research in order to help understand what drives these conditions and develop new and better treatments. IBD-RESPONSE will work closely with the IBD BioResource and if you are not already part of the IBD BioResource, you will be asked if you would like to take part in the IBD BioResource within 12 months of consenting to this study, and you will be contacted by a member of your local research team or the IBD BioResource team and be provided with further information. By being part of the IBD BioResource the information collected in IBD-RESPONSE can help both studies and be used to support more research in the future.

WHAT WOULD TAKING PART INVOLVE?

Taking part in this study involves completing questionnaires and collecting samples at three different timepoints over 54 weeks. Assessment timepoints have been selected to coincide where possible with when you would receive doses of your prescribed treatment. You will be prompted to complete questionnaires and provide stool samples at the appropriate time e.g., by text message, email or telephone call.

If you decide you would like to take part in the study, you will be asked to provide or confirm your email address so that a link to our online database can be sent to you. The database that we are using is called REDCap. This is managed by the Newcastle upon Tyne Hospitals NHS Foundation Trust and will give you access to provide your consent to be part of the study, access to all the study questionnaires and send you reminders to complete the questionnaires when required. These can be completed on a mobile phone, tablet, computer or laptop.

If you are completing the consent process remotely (for many people this will be in your home), a member of the local study team will be in contact with you by telephone to talk through the consent process.

Questionnaires: we will ask you to complete a series of questionnaires over 4 days at each of the 3 study assessment periods.

These include questionnaires that will ask you about your symptoms including stool frequency, bleeding, pain and tiredness, as well as the impact that your condition is having on your quality of life, including your physical activity levels and mental health.

You will also be asked to provide details about your diet over the previous 2-3 months which will take approximately 30 minutes to complete.

You will receive reminders by email and text message with your consent to complete the questionnaires at each of the time points.

We will also collect some additional information from your medical notes including relevant medical history, current and previous medications and lifestyle details such as smoking habits and vocation. We will collect the first part of your current postcode and the first part of your postcode at the time of your diagnosis. These details will be collected by the team at your local hospital using your medical notes, however you may be asked to confirm answers to questions the research team are unsure about.

The study also involves collecting samples, including stool at home, blood when you come to hospital for visits as part of your routine care, and biopsies only if you come for an endoscopy as part of your routine care during the time you take part in the study.

Stool samples: You will be provided with a 'home collection' kit from the study team to collect your stool samples. These sample kits may be given to you when you are at the hospital attending your appointment or may be sent to you by post. The kits will contain all you need to collect a stool sample at home, including instructions. It will also have freepost, pre-addressed, Royal Mail return packaging that you can use to send your stool sample to the Newcastle University research laboratory. You will be asked to collect one stool to transfer to two tubes for the study.

Blood samples: If you are attending the hospital for a clinical appointment prior to starting treatment (assessment 1) or within 10-20 weeks after commencing treatment (assessment 2), you will be asked to provide a blood sample at each visit. We will collect approximately 20mL of blood (approximately 4 teaspoons), which will be sent to members of the IBD-RESPONSE team at the Wellcome Sanger Institute in Cambridge by the study team at your hospital site. Researchers at the Wellcome Sanger Institute will look at the genetic information in your blood sample. Remaining blood (including plasma, the liquid part of blood that carries cells), will be sent to Newcastle University for analysis and biobanking (storing for future research use). If you do not attend a routine appointment within either of the assessment time points, blood samples will not be taken.

Biopsy samples: If you are scheduled to have a colonoscopy or flexible sigmoidoscopy while you are participating in the study, we will ask to collect additional research biopsy samples from the part of your intestine affected by Crohn's or colitis; your colon (large intestine) and/or terminal ileum (small intestine). We will also collect some details about your disease severity at the time of the colonoscopy or flexible sigmoidoscopy. Samples of tissue are already routinely taken during these procedures as part of standard Crohn's and colitis NHS care, but we will ask to collect up to 12 additional biopsy samples in total (6 from the colon in all patients and a further 6 from the terminal ileum in Crohn's participants). Biopsy samples will be sent to the Wellcome Sanger Institute and Newcastle University for analysis. Any remaining biopsy tissue will be stored at Newcastle University for use in future research (biobanked).

If you are booked in for an endoscopy at the same time as your study assessment, we will ask you to collect your stool samples and complete questionnaires before, or 2 weeks after, your endoscopy. This is because the bowel preparation/cleansing that you need to take for the procedure may have an impact on your gut microbes for up to 2 weeks.

As part of this study we will also ask permission to access samples stored by the NHS from previous endoscopies or operations you may have had to undertake research. We would also like to be able to access endoscopy images or videos from previous procedures you have had or have during this study.

HOW WILL MY SAMPLES BE USED?

We want to know how your gut microbiome can influence how well you respond to a new IBD treatment. As your genes, immune system and even the foods you eat may affect this, it is important to look at the whole picture.

Genes are made up of DNA codes which we can find in your body's cells and RNA, a molecule similar to DNA, then converts this code to control how cells behave. When you give us a blood, stool or biopsy sample, we separate out the DNA and RNA from the samples, analyse it, and store this information safely. This allows us to identify genes in human and microbe cells, by 'sequencing' or 'genotyping', that may be important determinants of treatment response. This is similar to reading a book of the human body, where the chapters are human or microbial cells, genes are the sentences and DNA (or RNA) are the words.

We may also look for other things in your blood, stool and biopsy sample now or in future using stored samples. Examples of other research includes looking at:

- Different types of cells such as those involved in the immune system and stem cells
- Proteins such as antibodies
- Metabolites (molecules that form from chemical reactions in your body)

We may also grow some cells from your biopsies, called organoids, which will be used to study how different cells of the intestine behave and interact with one another and/or other microbes, metabolites, medications or food. Organoids are 3D models of cells that grow from the cells that are present in biopsies collected at the time of endoscopy. They imitate the environment inside of the gut. Future research with organoids could help us to better understand the causes of Crohn's and colitis and how to develop or test new treatments. Studying organoid models also helps avoid the use of animals for medical research.

We may also contact your local site team and local NHS archives to get access to biopsy or surgical samples that have previously been taken or are taken during this study as part of your standard of care. We will follow all the required processes set up by the NHS archive and ensure your samples are treated with care.

WHO HAS ACCESS TO MY SAMPLES AND DATA?

Data about you e.g. personal details and information about your health, will be stored in secure electronic databases. You will be given a unique study ID code, which will be used to identify your samples and questionnaires without using any personal details. Any information from analysis (genetic and other tests) will be stored separately from your personal details using the unique study ID. Access to your personal details will be available to authorised members of the local study team (for example, your treating clinician and research nurses at site).

Data collected as part of the study will be stored in a secure electronic database called REDCap, using your unique study ID. The staff responsible for managing the REDCap database at The Newcastle upon Tyne NHS Foundation Trust and Newcastle Clinical Trails Unit will also have access to some parts of your personal details. Paper copies of questionnaires (if used) will only include your unique study ID and never any personal details. One of the health questionnaires used in this study asks you to record your current level of anxiety/depression. Should you record being severely or extremely anxious/depressed, staff within the Newcastle Clinical Trails Unit will notify the Principal Investigator at your hospital site, using your unique study ID. These investigators have access to the data collected, however this notification is to ensure this is brought to their attention swiftly.

Samples will be mainly analysed by the IBD-RESPONSE team led from Newcastle University, but other centres around the UK including the Wellcome Sanger Institute, University of Oxford, University of Cambridge, Imperial College London, Kings College London, University of Exeter, Queen Mary University of London and University of Edinburgh may analyse some study data. All samples will be stored in an ethically approved biobank for future research and will be overseen by a study management group (responsible for day-to-day management of the study) and a study oversight committee (which has overall responsibility for the study and includes independent clinicians, scientists and patient representatives).

With consent, your semi-anonymised data will be shared with the IBD BioResource and researchers who are part of the IBD-RESPONSE team across the UK, to allow for a more robust data analysis and comparison of outcomes. These may include:

- Access to data only e.g. genetic information, questionnaires, age, sex, information associated with your postcode such as socio-economic status.
- Access to data and samples e.g. medication history, stored samples (including DNA and organoids) and questionnaires.

The samples and data collected during the study may be requested by external researchers during or after the study. Before any of your anonymised data is given to external researchers, they will need to satisfy the following checks:

- Researchers requesting access to samples/data are required to submit their research questions and get approval for their study from an independent research ethics committee.
- The applications are then considered by the study management group (who has overall responsibility of approving the use of the samples) and, if needed, by the study oversight committee.
- Once approved, researchers will be given access to your anonymised data, which may mean that they get to keep your anonymised data. However, they will need to keep the data safe as defined by law. Under no circumstances will information that identifies you personally, be disclosed.

Requests could come from researchers who are working in the public and charitable sector such as universities, research institutes, or from commercial companies such as pharmaceutical companies developing new treatments, either in the UK or overseas. Your samples will not be used for animal testing or animal research.

At the end of the study, anonymised study data, including sequencing data, will be uploaded to a public online archiving domain as is considered best practice by funding bodies and research journals. This will allow researchers to access anonymised data for any future research.

WHAT HAPPENS TO MY SAMPLE AFTER THE STUDY?

On completion of the study, any remaining donated samples will be transferred to the care of the Newcastle Biobank. The samples are stored in a secure room in Newcastle University as part of the Newcastle Biobank. The samples will be anonymised and any information regarding your identity will be removed. Only trained staff will have access to the samples. Organoid samples will also be kept and used for future research at the Wellcome Sanger Institute following completion of the study.

Samples within the Newcastle Biobank or the Wellcome Sanger Institute will mostly be used by research teams in the UK. In some cases, researchers located overseas, for example in Europe and the USA, may wish to use these samples. As described above, researchers from other countries will need to have ethical approval in their own countries which are comparable to those in the UK. They will also need to sign a legal agreement which says that they must follow the rules on how the samples are used and disposed of and how they will handle the information. This is to ensure all samples are treated appropriately and to ensure the standards are equal to that in the UK.

The samples may be used by commercial partners. Any benefits from these will be used to directly improve patient care or enable us to conduct further research. Under UK law, sample donors are not entitled to a share of any profits which may result from this activity. Samples collected from this study will not be used for any animal testing or animal research.

DO I HAVE TO TAKE PART?

No, it is up to you to decide whether you want to take part in this study. If you agree to take part, you will be asked to complete a consent form. You will be given a copy of your signed consent form, which is yours to keep. If you choose not to take part, your care will not be affected. You will receive the usual care you would expect to receive from your IBD team.

By signing a consent form, this means that you fully understand what taking part in the study means for you. That's why it is really important that you take as much time as you want to read this information sheet and ask lots of questions.

WHAT ELSE DO I NEED TO KNOW ABOUT TAKING PART?

Pregnancy: If you are pregnant or become pregnant while in the study, you can still take part. You will be asked to complete a page in the REDCap database to let the study team know that you are pregnant, and to let us know about any changes that may be made to your medications during or after pregnancy.

Surgery: If you undergo surgery to remove a section of bowel during this study, we will ask your local study team for information about this operation.

WHAT ARE THE POSSIBLE BENEFITS AND RISKS OF TAKING PART?

Benefits: In the short term this study will not help you directly as the results will not change the treatment you receive. However, the information we get from this study will help to improve our understanding of the links between gut microbes, genes, diet and IBD. Our goal is to better understand the complicated relationship between these different factors and IBD. Our aim is to use this information to create a tool that can predict response to treatment in IBD. In the future, we hope it will benefit lots of IBD patients, potentially including you, by helping to select the best drug at the right time for individual patients.

Risks: By joining the study, we will ask you to donate some blood samples and biopsies (only if you have an endoscopy during the study period). These samples will be collected by qualified and trained staff. Blood sampling can cause discomfort and may cause a small bruise. Biopsies are taken as part of routine clinical care. When a biopsy is taken, there is a small risk of bleeding and there is a very small risk, that the procedure could create a hole in the bowel (perforation). The specific risks of undergoing a colonoscopy or flexible sigmoidoscopy will be discussed with you in line with the NHS consent process for each endoscopic procedure you undergo; this is part of standard NHS practice.

WHAT IF I CHANGE MY MIND?

Even if you agree to take part, you can change your mind at any time. Your care will not be affected, and you will continue to receive the usual care you would expect from your IBD team. You do not need to explain the reasons, but it is helpful to the study if you do. If you do withdraw from the study, we will keep the information and samples collected from you up to the point of withdrawal and may collect data recorded in your NHS medical records during the study period. This is because this information is still very useful to us.

WILL I BE PAID TO DO THIS STUDY?

You will not receive any payments for taking part in the study. As this study will be completed at home or during routine clinical appointments, travel and parking expenses are not covered and will not be reimbursed.

WHAT WILL HAPPEN TO ME WHEN THE STUDY ENDS?

You will continue to receive standard care like any other patient with your condition under the care of your doctors and specialist nurses.

WHAT IF SOMETHING GOES WRONG?

If you have a concern about any aspect of this study, you can speak to a member of your hospital's IBD-RESPONSE team who will do their best to answer your questions. Further contact details are included at the end of this information sheet. If you are still unhappy and wish to raise your concerns with someone who is not directly involved in your care and you are based in England or Wales, you can contact your local Patient Advice and Liaison Service (PALS). You can find your nearest PALS office on the NHS website, or ask your GP surgery, hospital or phone NHS 111 for details of your nearest PALS. If you live in Scotland, you can contact the Patient Advice Support Service (PASS), website www.cas.org.uk or phone 0800 917 2127. If you live in Northern Ireland, you can contact the Patient and Client Council, website www.patientclientcouncil.hscni.net or phone 0800 917 0222.

In the unlikely event that you are harmed during the study and this is due to someone's negligence (they were careless) you may have grounds for legal action and compensation, but you may need to meet your own legal costs.

The Newcastle Clinical Trials Unit, part of Newcastle University, are managing the study on behalf of The Newcastle upon Tyne Hospitals NHS Foundation Trust. Newcastle University also has insurance arrangements in place to cover Newcastle University staff involved in designing and managing the study.

WHO IS ORGANISING AND FUNDING THE STUDY?

Chief Investigator: The doctor in charge of the study is Dr Chris Lamb, a Consultant Gastroenterologist and Clinician Scientist. He works for Newcastle University and at the Newcastle upon Tyne Hospitals NHS Foundation Trust.

Study Sponsor: The Newcastle upon Tyne Hospitals NHS Foundation Trust is the study Sponsor and has responsibility for the study. The study is managed by the Newcastle Clinical Trials Unit, Newcastle University, on behalf of the Sponsor.

Study Funders: The Medical Research Council (MRC), the Leona M. and Harry B. Helmsley Charitable Trust and the Wellcome Sanger Institute are the funders of this study.

WHO HAS REVIEWED THIS STUDY?

This study was reviewed and approved by the Research Ethics Committee (Ref: 21/WA/0228) and the Health Research Authority (HRA). The Newcastle Upon Tyne Hospitals NHS Foundation Trust has reviewed all the study documentation and assessed the risks of this study as part of their responsibility as study Sponsor. This is to ensure that we are not doing anything harmful to you during the study and that your data is collected safely and stored securely.

WHAT IF RELEVANT NEW INFORMATION BECOMES AVAILABLE?

If during the course of the study new information becomes available that is relevant to you, we will tell you about it. We will discuss whether you should or would like to withdraw from the study.

WHAT WILL HAPPEN TO THE RESULTS OF THE RESEARCH STUDY?

- The results will be written in medical journals and presented in meetings to other doctors, nurses, researchers and patients.
- A report will be written for the study funders.
- All study data that is published will be anonymous. Your identity will always be protected.
- Fully anonymised data and samples collected during the study, will be made available to other researchers to help inform other research studies.
- Individual results will not be fed back to you.

WILL MY TAKING PART IN THIS STUDY BE KEPT CONFIDENTIAL?

Yes. You will not be named in any results, reports or on websites.

All the information that you provide during the course of this study will be securely stored. Paper copies of your study information will be stored in locked files or rooms at your local hospital. Electronic copies of your study information will be stored on a secure, password-protected computer database provided by REDCap. Only authorised members of the study team at the hospital and Newcastle Clinical Trials Unit will be granted access to the database.

Some parts of your medical records and the data collected for the study will be looked at by authorised persons from the Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle University and/or the Newcastle Clinical Trials Unit to check that the study is being conducted to the correct standards. All will have a duty of confidentiality to you as a research participant.

The study team at your hospital will have access to your information during the study to organise planned visits as well as for ongoing safety.

Very occasionally, information might be given during the study that we would have a legal obligation to pass on to others, for instance information which suggested you or others were at risk of harm. In this case, confidentiality would be broken so that we could pass this information to the relevant people. You would be informed of this.

At the end of the study, all study information will be kept in a secure storage area (this is called archiving) for at least 5 years. This makes sure any queries about the running of the study have been answered. All information will be held securely to make sure we protect your confidentiality, after which it will be safely destroyed. Anonymised data and samples from this study may be stored indefinitely to answer additional research questions and to benefit future research studies.

HOW WILL WE USE INFORMATION ABOUT YOU?

We will need to use information from you and from your medical records for this research project. This information will include your name, initials, date of birth, postcode and contact details. People will use this information to carry out the research or to check your records to make sure that the research is being done properly. People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number (study ID) instead. We will keep all information about you safe and secure.

Once we have finished the study, we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study.

WHAT ARE YOUR CHOICES ABOUT HOW YOUR INFORMATION IS USED?

- You can stop being part of the study at any time, without giving a reason, but we will keep information about you that we already have.
- If you choose to stop taking part in the study, we would like to collect information about your health from the IBD BioResource and/or your medical records. If you do not want this to happen, tell us and we will stop.
- We need to manage your records in specific ways for the research to be reliable. This means that we won't be able to let you see or change the data we hold about you.

WHERE CAN YOU FIND OUT MORE ABOUT HOW YOUR INFORMATION IS USED?

You can find out more about how we use your information:

- at www.hra.nhs.uk/information-about-patients/
- our leaflet available from www.hra.nhs.uk/patientdataandresearch
- by asking one of the research team
- by sending an email to the Sponsor Data Protection Officer at nuth.dpo@nhs.net

FURTHER INFORMATION AND CONTACT DETAILS

If you have any further questions or would like any further information about the study or the rights of participants, please feel free to contact the people below.

They are also who you or your doctor should contact in the event of an emergency, if your study participation is in any way involved.

[LOCAL CONTACT DETAILS]

Thank you for reading this information sheet.