Patient Information Sheet

MAIN TRIAL: Aspirin vs Aspirin + Metformin

COLO-PREVENT: A platform for developing COLOrectal cancer PREVENTion therapies

Chief Investigator: Dr Ajay Verma

We are inviting you to take part in a clinical trial. Before you decide whether to take part we would like you to understand why this research is being done and what it would involve. A member of our team will go through the information with you and answer any questions you may have. Please let us know if there is anything which is not clear, or is difficult to understand. Take your time to decide whether or not you wish to take part.

Summary of what will happen if you take part:

- You will be given either aspirin OR aspirin plus metformin tablets to be taken daily up until your surveillance colonoscopy in approximately 36 months' time. Which of these therapies you receive is chosen randomly, meaning there is an equal (50:50) chance of receiving either of these therapy combinations.
- After your first baseline visit, we will ask you to attend research visits every six months. We have designed this trial to fit into your normal Bowel Cancer Screening care as much as possible. We will also contact you by telephone 3 times to check how you are.
- We will ask you to provide samples for safety and research purposes; please see further details about this in the table and information below.

Background

The standard way to identify bowel polyps (small growths on the bowel lining) is by a colonoscopy, which uses a camera to check the large bowel. If polyps are seen with the camera, they are removed at the same time. Removing bowel polyps reduces the risk of bowel cancer in the future, but it does not prevent all cases of bowel cancer. That is why researchers are looking into other possible treatments.

Why are we doing this clinical trial?

We are doing this research to determine if drugs or food supplements could reduce the occurrence of bowel polyps, which in turn will reduce bowel cancer risk. This type of treatment is called 'therapeutic prevention'. In the main trial of the COLO-PREVENT research study we are looking at whether taking **aspirin**, or **aspirin combined with metformin** is better at preventing bowel polyps from re-growing.

Aspirin has been used widely as a painkiller and for symptoms of fever for over a century. There is good evidence that regular use of aspirin can reduce the risk of developing bowel cancer. Clinical trials have also shown that aspirin can prevent bowel polyps in patients. We think that taking daily aspirin after a colonoscopy may help to prevent these bowel polyps from growing and so also reduce bowel cancer risk.

Metformin is used regularly in patients with diabetes to help control their blood sugar. There are studies showing that metformin can reduce the number of bowel polyps. We want to know if more bowel polyps can be prevented if metformin is used together with aspirin, rather than using aspirin alone.

So that we can better understand the biological mechanisms involved in reducing the occurrence of bowel polyps, we would like to collect and analyse blood, tissue and faecal (stool) samples. We are particularly interested in how these simple drugs affect the gut microbiome (bacteria in the gut) and whether they could contribute to the prevention of bowel polyp development.

Why have I been invited?
You are being invited to take part in this research because you have had a colonoscopy in the NHS Bowel Cancer Screening Programme (BCSP) to remove bowel polyps and you will need another colonoscopy in approximately 36 months' time.

Do I have to take part?
No, your participation is voluntary and deciding not to take part will not affect any care that you receive. Please ask if you need more time to make up your mind, or if you need to know more or want to ask any questions. If you do decide to take part in the trial, you can still stop taking part at any time by contacting a member of the trial team using the details at the end of this information sheet. However, data and samples already collected will still be used.

What will happen to me if I take part?
We will ask you to return to hospital following your screening colonoscopy to discuss the trial with you. If you decide to take part, we will ask you to sign a consent form and you will be given a copy to keep. As part of your consent, we seek permission for trial personnel to view relevant sections of your medical records held by the hospital or your GP. This is to confirm whether or not you are eligible to participate and to collect information about your health. Your medical records will be used for the duration of the trial.

During this first visit, we will ask you to complete the assessments that are listed for Visit 1 in the table below. Which therapy you receive is selected at random. You will have a 50:50 chance of receiving one of the following two trial therapies. The trial therapy will need to be taken every day until the day of your surveillance colonoscopy in 36 months' time.

Therapy1 – aspirin tablet
Therapy 2 – aspirin tablet and metformin tablets

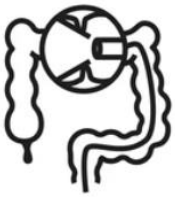
The trial has been designed to fit into your normal Bowel Cancer Screening care. After visit 1, we will ask you to attend extra clinic visits every six months so we can find out how you are getting on with the trial treatment and give you a further six months' supply. A member of your trial team will also contact you by telephone on another two or three occasions during your treatment to ask how

you are getting on. There are **6 research visits and 3 telephone calls** occurring over 3 years in addition to your routine Bowel Cancer Screening appointments.

The table below summarises what will happen to you from the first screening colonoscopy to the end of the trial.

COLO-PREVENT: Main Trial patient care pathway

(Pre-trial) BCSP screening colonoscopy appointment • We give you this Patient Information Sheet. • A member of your routine care team will provide you with the results of your screening colonoscopy following your procedure • If you are in agreement, we will contact you by telephone after this appointment to discuss the trial.	
Visit 1 (Week 0) – Research visit • You can discuss the trial and ask any questions • If you decide to take part, you will be asked to sign a consent form • We will ask you to give a fasted blood sample • We will review your eligibility to enter the trial, record demographic data, complete a medical history, record your blood pressure, and review your current medication(s) • We will ask you to complete a food questionnaire • We will give you a Faecal Immunochemistry Test (FIT) kit to collect a stool sample at home and post to us • You will be randomised to receive aspirin or aspirin with metformin tablets • We will give you six months' supply of your trial therapy	  
Telephone Visit 2 (Week 4) - follow-up call • We will contact you to enquire about your progress and provide advice about the trial drug dosing if you are in the metformin group	
You may be asked to attend routine BCSP appointments as part of your ongoing care, including another procedure to look at your bowel using a camera. It is important that you continue to attend these appointments. They are not part of the research trial.	
Telephone Visit 3 (Week 12) - follow up call • We will contact you to enquire about your progress	

Visit 4 (Week 25) – Research visit • We will ask about how you are and review your usual medication(s) • We will ask you to give a fasted blood sample • We will ask you to return any remaining tablets from visit 1, or the empty containers • We will give you another six months' supply of your trial therapy	
Visit 5 (Week 52) – Research visit • We will ask about how you are and review your usual medication(s) • We will ask you to complete a food questionnaire • We will ask you to give a fasted blood sample • We will give you a Faecal Immunochemistry Test (FIT) kit to collect a stool sample at home and post to us • We will ask you to return any remaining tablets from visit 4, or the empty containers • We will give you another six months' supply of your trial therapy	
Visits 6, 7 and 8 (every 6 months) – Research visits • We will ask about how you are and review your usual medication(s) • We will ask you to complete a food questionnaire at visit 7 only • We will ask you to give a fasted blood sample (visits 6 and 7 only) • We will ask you to return any remaining tablets from previous visits, or the empty containers • We will give you another six months' supply of your trial therapy	
Visit 9 (Week 154 / 36 months) - <u>Surveillance BCSP colonoscopy</u> • We will need you to collect a stool sample on a Faecal Immunochemistry Test (FIT) kit at home <u>before</u> your colonoscopy and post this to us • You will have your planned colonoscopy in the BCSP. This will be the same as the routine procedure in the BCSP, except that we will ask your permission to collect 6 research biopsies from the lining of the bowel. **We ask you not to mention which drug(s) you were taking for the trial to the person(s) doing your procedure so they may remain impartial.** • We will collect a fasted blood sample before or after the colonoscopy • We will ask about how you are and review your usual medication(s) • We will ask you to complete a food questionnaire • We will ask you to return any remaining tablets, or the empty containers • You will stop taking your trial therapy on the day of your colonoscopy	 

Visit 10 (Week 156) – Post surveillance colonoscopy telephone consultation

- You will receive the results from your latest colonoscopy from your BCSP usual care team, who will discuss any follow-up arrangements within the BCSP. This telephone call will be approximately 2 weeks after your colonoscopy
- A member of your research team will also call you to ask about how you have been since you stopped taking your trial therapy and review your usual medication(s)

This is the end of your participation in the COLO-PREVENT Trial

Please expect and allow for your research visits to be approximately 4 hours in duration, as you will need to wait for the results of your blood test for safety reasons before we can dispense your supply of trial therapy to take home with you. At visit 1 some safety blood tests will be prioritised following your consent, so that the results can be issued during your visit in order to determine whether you are eligible to participate in the trial. If the blood results indicate you do not meet the requirements for the trial, you will not progress any further and your consent will be void (invalidated). This would not affect your continuing usual care.

Blood collection: We will ask you to provide fasting blood samples to assess your health and to understand how these drugs work to prevent bowel polyps. Fasting means you will not be able to eat or drink (other than water), apart from taking your regular medication, in the 8 to 10 hours before your appointment. We will book your appointment as early in the morning as possible. You are advised to bring refreshments with you to have after the blood test. Fasting blood samples are required 6 times during the 3-year period you will be on the trial.

The amount of blood we take at each visit for the trial is 50ml (about 3 tablespoons). The blood test may cause some mild discomfort and occasionally some bruising, but this is usually short lived.

Faecal Immunochemistry Test (FIT): This is the same test that you did as part of the Bowel Cancer Screening Programme before being invited for your screening colonoscopy. We will give you the FIT kit to take a stool sample at home and post this to us. The final stool sample for the trial will need to be taken before your colonoscopy.

Polyp tissue samples: We would like your permission to look at polyp tissue taken from your bowel during your routine screening and surveillance colonoscopies.

Rectal biopsies: The taking of biopsies (small pieces of tissue) during your colonoscopy is a routine procedure and is very safe. At your surveillance colonoscopy, we would like to ask your permission to take 6 additional biopsies for research purposes from the lining of the bowel. This is to try to understand why bowel polyps come back and how treatment can affect this. Although there is a theoretical risk of perforation or serious bleeding this is very rare as the biopsies taken are very

small. You usually cannot feel the actual biopsy though you may be aware of a tugging sensation as it is taken. Consent for the rectal biopsies is optional.

As these tests are solely for research and safety purposes, and not for diagnosis, we will not be able to send the results to you or your GP.

Your participation in the trial will end at your routine consultation following your surveillance colonoscopy. You will no longer receive the trial therapy, either from your GP or the research team after your surveillance colonoscopy. You will continue in the Bowel Cancer Screening Programme as normal.

What are the possible benefits of taking part?
There is no guarantee that you will personally benefit from taking part. All participants taking part in this trial will be helping to make a significant contribution to medical knowledge about preventing the formation of bowel polyps. This may help other patients in the future.

What are the possible disadvantages and risks of taking part?
The effects and discomforts of tests and procedures are outlined earlier in this information sheet. Disadvantages for participants include the small number of extra visits and tests that will need to be made. If you have private medical insurance, you should check with your insurance company before agreeing to take part to ensure that your medical insurance is not affected.

What are the potential side-effects of trial medication?
Both metformin and aspirin have an excellent safety record and are well tolerated, although there are some recognised side-effects which have been detailed below.

Metformin has been used in patients without diabetes in a number of studies. Although it is used to reduce blood sugar levels in patients with diabetes, it does not do this in patients with normal sugar levels. Metformin can cause some gastrointestinal side effects (nausea, vomiting, diarrhoea, abdominal pain and loss of appetite) and so, as per normal guidelines for the use of metformin, we will start at a very low dose and build this up to a dose that we know the majority of patients manage without problems. Other common side effects are taste disturbance and vitamin B12 deficiency. If you are randomised to receive metformin in addition to aspirin, we will test your vitamin B12 levels annually at visits 5, 7 and 9. Patients taking metformin are also advised to avoid acute alcohol intoxication because this is associated with an increased risk of lactic acidosis (a condition in which there is too much acid in the body). Finally, we know that metformin can cause problems with the kidneys if they are not monitored properly, and will therefore measure your kidney function while you are on trial and advise if you need to alter the dose of metformin.

Aspirin has an excellent safety record and has been used for many years. A low dose of aspirin is being used in this trial in order to reduce the risk of any stomach upset or other stomach problems (e.g. dyspepsia). Increased bleeding tendency is a common side effect. Serious bleeding from the stomach and upper bowel can occur but this is rare. It is thought to occur once or twice every time

one thousand patients take treatment for one year. For example, in the Add Aspirin trial which has recruited thousands of patients, including people with bowel cancer, the risk of bleeding from the gut was very low in patients taking aspirin. Current results show that some minor bleeding was seen in <1% of patients with no patients out of a total of 1253 having more serious bleeding. There is an even smaller risk of stroke in people using aspirin. Participants that experience any rare severe aspirin-related side effects would be advised to permanently discontinue aspirin immediately.

Combining metformin with aspirin has not been tested before in a trial like this. Therefore, although we do not think there will be a problem, we will provide you with very clear advice as to when you should stop the trial therapy before any CT scan, surgical procedure or repeat colonoscopy that you are due to undergo.

A full list of side effects, including rare events, are detailed in the Patient Information Leaflet (PIL) provided with the trial therapy.

Pregnancy and participation in the trial

Due to the nature of this trial, women who are pregnant, breastfeeding or who intend to become pregnant are not eligible to participate. To be eligible to participate, women of childbearing potential must also have a negative blood pregnancy test as part of screening at visit 1. Women of childbearing potential or male participants with partners of childbearing potential must agree to use an acceptable method of birth control (e.g. condoms) for the duration of the trial. This is for safety reasons to prevent any possible harm to an unborn baby. Women of childbearing potential will also need to have a blood pregnancy test at the end of their participation at visit 9.

If you or your partner become pregnant during the trial, you must inform the research team immediately. We will advise you/your partner about your/their medical care and collect information about your/your partner's pregnancy and the health of the baby.

During your time on the trial

You will need to take your trial therapy as directed by your trial team (e.g. Research Nurse). If you experience any problems or are told that you need surgery while taking the trial therapy, you should contact a member of your trial team on the number provided at the end of this information sheet.

While you are taking the trial therapy, we will ask you about the other medication you take and advise about any precautions. We ask that you avoid taking any other medication that contains aspirin. Examples of medication you can buy in a chemist, pharmacy or shop that contain aspirin are: Askit Powders, Beechams Powders, Disprin and Anadin. If you need pain relief, you can take medication that doesn't contain aspirin, such as paracetamol. If you need to take a prescription non-steroidal anti-inflammatory drug (NSAID) such as ibuprofen naproxen, diclofenac etc.) more than three times a week you will not be able to join the trial. If you are taking a NSAID tablet or capsule less frequently, we ask you to try an alternative medication such as paracetamol. Please note that ibuprofen is also available 'over-the-counter' from Pharmacies or shops (an example is Nurofen). If you are unsure whether a preparation contains ibuprofen please check with the Pharmacist or the

Shop Assistant. If you are admitted to hospital with an infection that requires treatment with antibiotics, we will need to monitor your kidney function. There are no dietary restrictions.

Permission to contact your GP

Your GP will be informed of your participation in this trial. We may also need to inform them of any abnormal blood results or relevant information that needs to be followed up. By signing the consent form you are agreeing that your GP can be notified.

What if new information becomes available?

During the course of a trial, new information about the trial treatment sometimes becomes available, for example a previously unknown potential side effect. If this happens, we will tell you and ask you if you wish to stay in the trial. If you decide to leave the trial, your standard care will continue. If you stay in the trial you may be asked to sign a new consent form.

What will happen to any samples I give?

Any samples we take will be coded (pseudonymised), which means that the laboratory researchers who are carrying out any tests cannot identify you. Samples will initially be stored at your local hospital and then transported for analysis to the Cancer Prevention Group laboratories at the University of Leicester. All information that is collected will be kept strictly confidential.

Coded samples may also be shared with other researchers (i.e., other academic and industry collaborators) for specialist analysis now and in the future. These may be universities, NHS organisations or companies involved in health and care research inside and outside of the UK and Europe.

With your permission, we will check your health status via your healthcare records, including the results of any future colonoscopy tests you may have to see if any polyps have returned. We will do this for up to 10 years after your participation in the trial. You will also be asked if we can link this data to that from your research samples during this time.

Finally, with your permission, we will store your name and contact details for up to 10 years after the end of this trial; for the purposes of contacting you about future research opportunities. Your contact details will be stored securely on the Research Filestore at the University of Leicester. Access to this data will be limited to those who need access to it only.

Access to your data for these purposes is optional and you do not need to agree to this to be able to participate in the trial. We will specifically ask your permission for this on the consent form.

Are there expenses payments?

Unfortunately we are unable to reimburse you for any travel expenses or the time you are contributing from the trial funding.

What if there is a problem?

It is very unlikely that you will be harmed by taking part in this type of research trial. However, if you wish to complain or have any concerns about the way you have been approached or treated in connection with the trial, you should ask to speak to the local trial team on >>Insert local site contact details<< who will do their best to answer your questions. If you remain unhappy and wish to address your concerns or complaints on a formal basis you should contact the Patient Information & Liaison Service (PALS) as below.

If something does go wrong and you are harmed during the research and this is due to someone's negligence then you may have grounds for legal action for compensation against the University of Leicester but you may have to pay your legal costs. The normal NHS complaints service will still be available to you (if appropriate).

PALS Contact Details:
Tel: <<insert Freephone number>> between the hours of 10.00am and 4.00pm
Email: <<insert local PALS email address>>
Write to: Patient Advice and Liaison Service, <<insert Name of Hospital and PALS address>>

How will we use information about you?
The University of Leicester [and its clinical trials unit, the Leicester Clinical Trials Unit] and your local participating hospital will need to use information from your medical records for this research project. This information will include:

- your name / initials / biological sex / date of birth / NHS number / ethnicity / contact details

People will use this information to do 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 instead. We will keep all information about you safe and secure on hospital or University secure systems.

With your permission, we will share some of your coded information with researchers running other research studies in this and other organisations. These may be universities, NHS organisations or companies involved in health and care research inside and outside of the UK and Europe. They must follow our rules about keeping your coded information safe.

Once we have finished the trial, we will keep some of the data so we can check the results. The University of Leicester (trial Sponsor) is the data controller for this trial and is responsible for looking after your information and using it properly. Your hospital will keep identifiable information about you in archive for 25 years after the trial has finished. We will write our reports in a way that no-one can work out that you took part in the trial.

If you are deemed not eligible for the trial your de-identified information (initials and year of birth) will be added to a screening log along with the details of your ineligibility.

What are your choices about how your information is used?
You can stop being part of the trial at any time, without giving a reason, but we will keep information about you that we already have. The investigator may also withdraw you from the trial for medical reasons, or if you lose the ability to consent to take part. If you choose to stop taking the trial medication, we would like you to remain in the trial in order to continue collecting research samples and information about your health. If you no longer wish to attend the outpatient hospital visits, we would like to collect data from you remotely over the telephone and from your medical records. If you are in agreement, we would like you to return for final collection of samples at your surveillance colonoscopy visit.

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.

If you agree to take part in this trial, you will have the option to take part in future research using your data and samples saved from this trial.

If you fail to attend trial visits and do not formally withdraw, we will continue to collect important data from your medical records.

Where can you find out more about how your information is used?
Further information on how data is used in research is available on the NHS Health Research Authority website, if you would like a printed copy please ask a trial team member:
https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/data-protection-and-information-governance/gdpr-guidance/templates/template-wording-for-generic-information-document/

You can find out more about how the University of Leicester use your information:
Web: https://www2.le.ac.uk/offices/ias and www.coloprevent.co.uk
Telephone: 0116 229 7945
Email: dpo@le.ac.uk

What will happen to the results of the research trial?
The results will be analysed by scientists and doctors who specialise in developing cancer prevention treatments. Any positive results from this trial will provide a basis for helping to develop future treatment schedules for people with bowel polyps. The results of the trial will be presented to medical researchers at scientific meetings and published in scientific or medical journals. Participants will of course remain anonymous. Once the study has finished, you may visit the COLO-PREVENT website www.coloprevent.co.uk for a results summary detailing what we have learned; we will also direct you towards the full scientific results of the study.

Who is organising and funding the research?

This research is being carried out by a network of doctors across the UK, sponsored by the University of Leicester, and funded by Cancer Research UK. The Leicester Clinical Trials Unit are overseeing the organisation and management of the trial. None of the trial doctors will be paid for including you in the trial.

Who has reviewed and checked the trial?

All research in the NHS is reviewed by an independent group of people called a Research Ethics Committee, who work to protect your safety, rights, wellbeing and dignity. This trial has been reviewed and approved by the independent Research Ethics Committee East Midlands – Nottingham 2 (reference: 22/EM/0109). In addition, the Research Ethics Committee will observe the progress and results of this trial. Review has also been undertaken by independent experts during this trial's development.

Patient advocates have also been involved in developing the trial, and writing the patient information documents. This is to ensure the voice of the patients, their views and any concerns about the trial, have been taken into account.

What happens next?

If you would like to take part in this trial, or want to discuss it further, please let someone in your care team know, or use the contact details below.

Local site team: <<Insert Principal Investigator name>>; <<Insert local site contact details>>

In you have any concerns and are feeling unwell, please seek medical attention (for out of hours contact the NHS 111 service). In the event of an emergency, please contact emergency services on 999.

COLO-PREVENT central co-ordinating team: coloprevent@leicester.ac.uk

Thank you for considering participation in the trial and for taking time to read this information sheet.

Please keep a copy of this and your signed consent form.