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# COLO-PREVENT – do simple drugs (aspirin or aspirin plus metformin) or food supplements (resveratrol) reduce the occurrence of bowel polyps (small growths on the bowel lining), which in turn reduce bowel cancer risk?

**Submission date**
04/05/2022

**Recruitment status**
Recruiting

**Registration date**
01/09/2022

**Overall study status**
Ongoing

**Last Edited**
28/07/2025

**Condition category**
Digestive System

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

## Plain English summary of protocol

Background and study aims
One way of preventing bowel cancer is to take drugs or dietary supplements (this is called therapeutic prevention). Most bowel cancers develop over many years from a polyp (a growth on the bowel wall). Several clinical studies have shown that aspirin use reduces the risk of developing polyps and the drug metformin, which is used in patients to treat diabetes, can also reduce the number of polyps. We want to test whether combining aspirin with metformin is able to prevent more bowel polyps forming than aspirin alone. We will test this in 'high risk' patients taking part in the national Bowel Cancer Screening Programme (BCSP), who have already had several polyps removed at the bowel camera test (colonoscopy). We are also keen to understand whether the dietary agent resveratrol which is found in red grapes, reduces the number of polyps formed. For this part of the study we will test two doses against a 'dummy' tablet in a way that both patients and medical staff do not know what treatment is being given. Patients already taking aspirin or metformin will be able to take part in the resveratrol sub-trial.

Who can participate?
Patients aged 50-71 years (50-73 years in the resveratrol trial) with colorectal polyps.

What does the study involve?
Trial drugs will be given for 3 years in the aspirin and metformin main trial and 12 months in the resveratrol sub-trial, until patients have another planned BCSP colonoscopy, at which time the number and size of polyps will be measured. We will collect blood, faeces, urine and tiny samples of rectal tissue (biopsies) so that we can learn more about how the therapies work, as well as develop 'biomarker' tests to predict who will or won't respond to each therapy. We are particularly interested in examining the effects of the therapies on gut bacteria, which will be analysed using faecal samples. The expected benefit is that the therapies will reduce the number of polyps returning and therefore potentially the risk of developing a bowel cancer. A

major advantage of metformin, aspirin and resveratrol is that they are safe, have few side-effects and are already widely used.

What are the possible benefits and risks of participating?
Benefits:
There is no guarantee that individuals 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.
Risks:
Participation in a randomised controlled trial means that the participant and clinician are not able to choose all aspects of treatment and a careful explanation of the different treatments and toxicities by arm will be given to participants. The protocol has been designed to reflect the standard care pathway for patients on the Bowel Cancer Screening Programme (BCSP) with the minimal number of additional hospital visits and tests (over and above routine care) possible.

Use of low dose aspirin (75mg) will minimise the risk of adverse events; this is the lowest clinically used dose of aspirin in adults and is well tolerated.

To minimise the chances of Gastro Intestinal (GI) toxicity, patients randomised to metformin will start at a low dose of 500mg once daily and this will be increased after four weeks to the full dose of 500mg twice daily. Patients will be advised to take their tablets with or after food to help with treatment tolerance. If GI toxicities do occur this will be managed by dose reduction of metformin or a switch to a modified release (MR) preparation according to local policy.

For those who experience any rare side effects related to the study drugs and/or those who are unable to adhere to the protocol treatment schedule, active participation in the trial will end at this time. However, they will be asked if they wish to continue in the trial for collection of important outcome and safety data.

Blood sampling is required to answer trial objectives, and as per routine care some of these tests are required to be fasted. Usual clinical guidance will be followed and sites will be advised to book visits as early in the morning as possible. Potential patients will be given the opportunity to come back for a further visit if they are not happy to undergo the consent process in a fasted state. Although rectal biopsies are taken as part of routine care during colonoscopies, this type of sampling poses a theoretical risk of perforation or serious bleeding, though this is rare. Only a very small amount of tissue is required for the research rectal biopsies and will be obtained by trained physicians. Participants will be asked to consent to this separately and can still participate in the trial if they do not give their consent to this aspect of the trial.

Where is the study run from?
University of Leicester (UK)

When is the study starting and how long is it expected to run for?
April 2022 to May 2031

Who is funding the study?
Cancer Research UK

Who is the main contact?
Nafisa Boota, coloprevent@leicester.ac.uk

https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-looking-at-aspirin-metformin-and-resveratrol-to-prevent-bowel-polyps-colo-prevent

# Contact information

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# Additional identifiers

### EudraCT/CTIS number
2022-000531-23

### IRAS number
1005142

### ClinicalTrials.gov number
Nil known

### Secondary identifying numbers
0834, IRAS 1005142, CPMS 53642

# Study information

## Scientific Title
COLO-PREVENT – A phase 2/3 randomised platform trial assessing the efficacy of aspirin, aspirin plus metformin, or resveratrol, for colorectal polyp prevention in patients undergoing surveillance in the Bowel Cancer Screening Programme

## Acronym
COLO-PREVENT

## Study objectives
1. To assess the benefits and harms of combining metformin and aspirin compared to aspirin alone for the prevention of colorectal polyps in patients with high risk finding identified through the BCSP.
2. To assess whether Resveratrol prevents colorectal polyps in high risk individuals and identify the most active dose in a Signal-Seeking sub-trial.
3. To assess the safety and tolerability of aspirin and metformin in combination compared to aspirin alone in the main trial.
4. To assess the safety and tolerability of each dose of resveratrol compared to placebo in the sub-trial.

## Ethics approval required
Old ethics approval format

## Ethics approval(s)
Approved 14/06/2022 East Midlands - Nottingham 2 Research Ethics Committee (Equinox House, City Link, Nottingham, NG2 4LA, UK; +44 207 104 8169; nottingham2.rec@hra.nhs.uk), ref: 22/EM/0109

## Study design
Interventional open label randomized parallel group controlled trial including a double blind sub trial

## Primary study design
Interventional

## Secondary study design
Randomised parallel trial

## Study setting(s)
Hospital

## Study type(s)
Treatment

## Participant information sheet

## Health condition(s) or problem(s) studied
Patients with high risk findings undergoing surveillance in the national Bowel Cancer Screening Programme

## Interventions
For the Main trial, participants are randomised in a 1:1 ratio and have an equal chance of receiving one of the following therapies:
Therapy1 – aspirin tablet
Therapy 2 – aspirin tablet and metformin tablets

Aspirin 75mg tablets once daily OR Aspirin 75mg tablets once daily AND Metformin hydrochloride 500mg tablets twice daily will be taken orally for the duration of the surveillance period within the BCSP, up until the exit colonoscopy at 3 years. For participants randomised to Therapy 2 in the main trial, metformin 500mg will be started once daily for 4 weeks. This 4 week run-in period is for the purposes of maximising gastrointestinal tolerability. If the participant is tolerating the 500mg dose of metformin, they will be advised to increase their dose to twice daily, with one tablet to be taken with breakfast and one tablet to be taken with their evening meal. If tolerated, the maximum daily dose of metformin will be 1g for the remainder of the trial. The main trial is not blinded (open-label) and participants and the research team will be aware of the treatment assignment.

For the resveratrol sub-trial, participants will be randomised in a 1:1:1 ratio and have an equal chance of receiving one of the following three treatment arms:
Therapy 1 - 5mg resveratrol capsules
Therapy 2 - 1g resveratrol capsules
Therapy 3 - placebo (dummy) capsules

Resveratrol 5mg or resveratrol 250mg (X4 to give a total daily dose of 1g) or placebo capsules will be taken orally once daily for a period of 1 year, until the day of the participant's research colonoscopy. The sub-trial will be double-blinded, so the research team and participants will not be aware of treatment assignment.

A web-based system from a third party (Sealed Envelope Ltd.) for the purposes of randomisation will be used for both arms of the trial.

## Intervention Type
Drug

## Phase
Phase III

## Drug/device/biological/vaccine name(s)
Aspirin, metformin hydrochloride, resveratrol

## Primary outcome measure
Polyp number measured by MPP (Mean number of Polyps per Participant) at exit surveillance colonoscopy
154 weeks for main trial
52 weeks for sub-trial

## Secondary outcome measures
Measured at exit surveillance Colonoscopy (154 weeks for main trial; 52 weeks for sub-trial).
1. Polyp Detection Rate (PDR, proportion of individuals with one or more qualifying* pre-malignant polyp(s) at surveillance)
2. Advanced polyps (measured as MPP and PDR); these are defined as serrated polyp ≥10mm,

serrated polyp with any dysplasia, adenoma ≥10mm, adenoma with high-grade dysplasia
3. Polyp subtype based on histopathology (adenoma/serrated); also reported as MPP and PDR
4. Location of polyps (right colon - any part of the colon proximal to the splenic flexure; left colon – the rectum and the colon distal to and including the splenic flexure)
5. Polyp size (maximum dimension in mm as described in the histopathology report or endoscopic size if no histopathological size available)

Safety measured from first administration of IMP until the final visit at 156 weeks for the main trial and 54 weeks for the sub-trial:
6. Adverse events, including clinically significant bleeding episodes and GI tolerability.

Compliance measured in the main trial at: weeks 25, 52, 78, 104, 130 and 154; resveratrol sub-trial at: weeks 25 and 52
7. Assessment of compliance by counting residual numbers of tablets/capsules returned by each patient.

Exploratory endpoints
8. Measurement of molecular (glucose, insulin (HOMA), HbA1c, triglycerides, cholesterol, IGFBP-3, free IGF-1) and physical (BMI, waist circumference) markers of metabolic status.
9. Assessment of dietary patterns and fat intake using the EPIC FFQ.
10. Plasma drug concentrations and metabolite profile for resveratrol and metformin.
11. Urinary resveratrol/metabolite levels in 20% of participants in the sub-trial from randomly selected sites that are willing and able to collect urine samples.
12. In the main trial: Measurement of pharmacodynamic biomarkers common to both aspirin and metformin, including p65, pS6/S6 and cleaved PARP in tissue samples.
13. In the resveratrol sub-trial: Analysis of tissue and plasma pharmacodynamic biomarkers, including NQO1, protein carbonyls, Ki67 proliferation index, MLX and CIDEB.
14. Characterisation of the gut microbiome.

### Overall study start date
29/04/2022

### Completion date
31/05/2031

## Eligibility

### Key inclusion criteria
Current inclusion criteria as of 28/07/2025:

General inclusion criteria for both trials:
1. Patients with high risk findings (≥2 premalignant polyps including ≥1 advanced colorectal polyp; or ≥5 premalignant polyps) at a completed screening episode according to BCSP criteria
2. Patients with a large (≥20mm) non-pedunculated colorectal polyp that is resected with histological R0 en bloc excision at a completed screening episode
3. Patients with a large (≥20mm) non-pedunculated colorectal polyp after piecemeal excision. These will only be eligible if the 2nd site check is a full clearance colonoscopy
4. Adequate renal function, defined as GFR ≥45ml/min/1.73m2, at any time in the preceding 4 weeks
5. Willing and able to consent to participate in trial

Inclusion criteria for the main trial but not the resveratrol Signal-Seeking trial:
6. Aged 50-71 years

Additional inclusion criteria for the resveratrol Signal-Seeking trial only:
7. Aged 50-74 years
8. Use of aspirin, including as an anti-platelet therapy, is permitted in the signal-seeking trial

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Previous inclusion criteria:

General inclusion criteria for both trials:
1. Patients with high risk findings (≥2 premalignant polyps including ≥1 advanced colorectal polyp; or ≥5 premalignant polyps) at a completed screening episode according to BCSP criteria
2. Patients with a large (≥20mm) non-pedunculated colorectal polyp that is resected with histological R0 en bloc excision at a completed screening episode
3. Patients with a large (≥20mm) non-pedunculated colorectal polyp after piecemeal excision. These will only be eligible if the 2nd site check is a full clearance colonoscopy
4. Adequate renal function, defined as GFR ≥45ml/min/1.73m2, at any time in the preceding 4 weeks
5. Willing and able to consent to participate in trial

Inclusion criteria for the main trial but not the resveratrol Signal-Seeking trial:
6. Aged 50-71 years

Additional inclusion criteria for the resveratrol Signal-Seeking trial only:
7. Aged 50-73 years
8. Use of aspirin, including as an anti-platelet therapy, is permitted in the signal-seeking trial

## Participant type(s)
Patient

## Age group
Adult

## Lower age limit
50 Years

## Upper age limit
74 Years

## Sex
Both

## Target number of participants
862 for main trial, 477 for sub trial

## Key exclusion criteria
General exclusion criteria for both trials:
1. Malignant change in a polyp.
2. Known clinical diagnosis or gene carrier of a hereditary CRC predisposition (FAP, hereditary

nonpolyposis CRC).
3. Previous or newly diagnosed inflammatory bowel disease.
4. Previous or planned colorectal resection.
5. Known bleeding diathesis or concomitant non-aspirin anti-coagulant or anti-platelet agent.
6. Abnormal liver functions consisting of any of the following, at any time in the preceding 4 weeks:
6.1. Serum bilirubin ≥1.5 x ULN (except for participants with Gilbert's disease, for whom the upper limit of serum bilirubin is 51.3µmol/l or 3mg/dl)
6.2. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥2.5 x ULN
7. Inability to comply with trial procedures and use of therapies.
8. Pregnant or lactating women. Women of child-bearing potential must agree to use appropriate methods of birth control (see protocol section 8.6)
9. Males with partners who are WOCBP and are unwilling to use effective methods of contraception
10. Serious medical illness interfering with trial participation including inability to have future colonoscopic surveillance.
11. Participants who have been administered an investigational medicinal product for another research trial in the last 30 days or ≤5 elimination half-lives.

Exclusion criteria for the main trial but not the resveratrol Signal-Seeking trial:
12. Regular (>3 doses per week) prescribed or 'over the counter' (OTC) aspirin or regular (>3 doses per week) prescribed or OTC non-aspirin NSAID use.
13. Allergic or intolerant to ibuprofen or naproxen, metformin, aspirin or salicylate.
14. Diabetic patients on drug treatment.
15. Current or previous treatment with metformin
16. Known history of peptic ulcer disease.
17. Known history of lactic acidosis or predisposing conditions.
18. Prior use of NSAIDs is not an exclusion if they are self-prescribed and the patient is willing to stop use for the duration of the trial.
19. Use of long-term systemic corticosteroids

Additional exclusion criteria for the resveratrol Signal-Seeking trial only
20. Unable to abstain from ingestion of OTC supplements containing resveratrol for the trial duration.
21. Known yeast allergy
22. Sensitivity or allergy to any of the capsule excipients

### Date of first enrolment
30/09/2022

### Date of final enrolment
31/01/2028

## Locations

### Countries of recruitment
United Kingdom

### Study participating centre

-
United Kingdom
-

# Sponsor information

### Organisation
University of Leicester

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### Sponsor type
University/education

### Website
http://www.le.ac.uk/

### ROR
https://ror.org/04h699437

# Funder(s)

### Funder type
Charity

### Funder Name
Cancer Research UK

### Alternative Name(s)
CR_UK, Cancer Research UK - London, CRUK

### Funding Body Type
Private sector organisation

### Funding Body Subtype
Other non-profit organizations

### Location
United Kingdom

# Results and Publications

### Publication and dissemination plan
Peer reviewed scientific journals
Internal report
Conference presentation
Other publication
Submission to regulatory authorities
Other
We are requesting specific consent to share pseudonymised trial data with our research collaborators in other academic institutions and industry partners for future research.

### Intention to publish date
31/05/2032

### Individual participant data (IPD) sharing plan
The current data sharing plans for this study are unknown and will be available at a later date

### IPD sharing plan summary
Data sharing statement to be made available at a later date

### Study outputs

| Output type | Details | Date created | Date added | Peer reviewed? | Patient-facing? |
|---|---|---|---|---|---|
| HRA research summary | | | 28/06/2023 | No | No |
| Protocol file | version 4 | 11/12/2024 | 28/07/2025 | No | No |