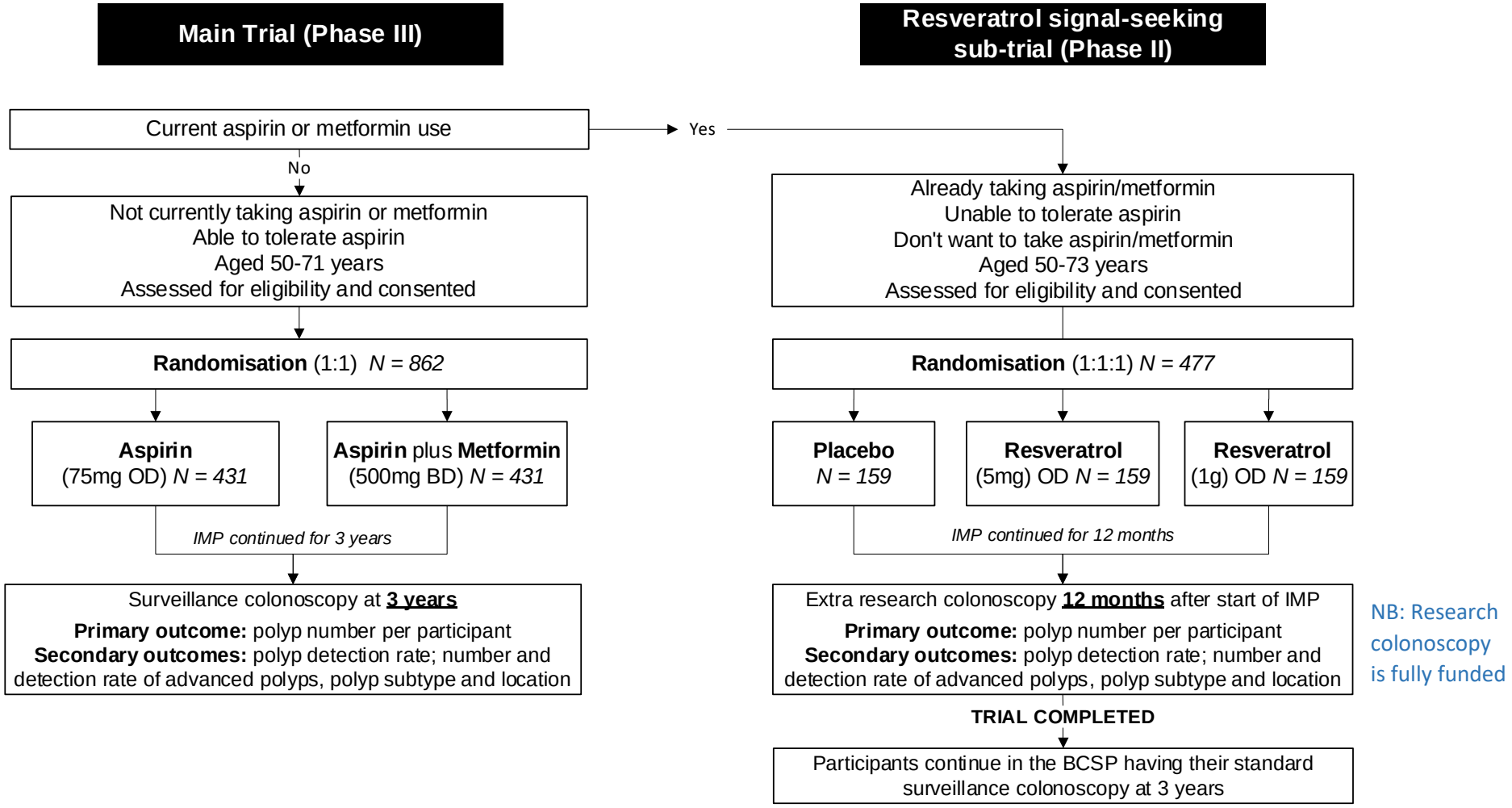
COLO-PREVENT Trial Flow Diagram

PATIENT POPULATION:
Patients identified from the national BCSP across ~60 centres

Patients with the following after a completed screening episode:
1) High risk findings according to BCSP criteria
2) LNPCP with histological R0 *en bloc* excision
3) LNPCP requiring piecemeal excision only where the 2nd site check is a full clearance colonoscopy



NB: Research colonoscopy is fully funded

COLO-PREVENT TRIAL SUMMARY (Protocol version 3.0, 31/08/2023)

Trial 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 national Bowel Cancer Screening Programme
Short title	COLO-PREVENT: A platform for developing COLOrectal cancer PREVENTion therapies
Trial acronym	COLO-PREVENT
Chief Investigator	Dr Ajay Verma
Lead Applicant	Professor Karen Brown
Joint Lead Applicant	Professor Mark Hull
Clinical Phase	Main trial: Phase III Signal-Seeking sub-trial: Phase II
Trial Design	Main trial: Interventional, preventative, multi-centre, open-label, parallel, randomised control trial. Signal seeking sub-trial: Interventional, preventative multi-centre, double-blinded, pharmacodynamic, pharmacokinetic, mechanistic, placebo, parallel, randomised controlled trial.
Trial Participants	Patients identified as high risk for colorectal cancer according to Bowel Cancer Screening Programme (BCSP) criteria. This includes: - patients with **'high risk'** findings after completion of a BCSP screening episode - patients with a **large non-pedunculated colorectal polyp**
Planned Sample Size	Main trial: 862 Sub-trial: 477 Total sample size for the two arms: 1339
Treatment duration	Main Trial: 3 years Sub-Trial: 1 year
Follow up duration	Participants are followed up until approximately 2 weeks after their exit surveillance colonoscopy
Planned Trial Period	97 months (from FPFV to LPLV)
Investigational Medicinal Product(s)	Aspirin Metformin Resveratrol
Formulation, Dose, Route of Administration	Aspirin - 75mg tablets (enteric coated) to be taken orally once daily Metformin – 500 mg tablets to be taken orally twice a day with breakfast and evening meal Resveratrol – participants in the sub-trial will be randomised to receive one of the following blinded treatments to be taken once daily: 5mg resveratrol (1X 5mg resveratrol and 3X placebo tablets) 1g resveratrol (4X 250mg resveratrol) Placebo (4X placebo tablets)

Eligibility criteria	**Inclusion criteria** *General inclusion criteria for both trials:* • Adequate renal function, defined as GFR ≥35ml/min/1.73m^2, at any time in the preceding 4 weeks • Willing and able to consent to participate in trial Participants must meet ONE of the following criteria: • 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 **OR** • Patients with a **large** (≥20mm) **non-pedunculated colorectal polyp** that is resected with **histological R0 *en bloc excision*** at a completed screening episode **OR** • Patients with a **large** (≥20mm) **non-pedunculated colorectal polyp** after **piecemeal excision.** These will only be eligible if the subsequent **2nd site check** is a **full clearance colonoscopy** *Inclusion criteria for the main trial but not the resveratrol Signal-Seeking trial:* • Aged 50-71 years *Additional inclusion criteria for the resveratrol Signal-Seeking trial only:* • Aged 50-73 years • Use of aspirin, including as an anti-platelet therapy, is permitted in the signal-seeking trial **Exclusion criteria** ***General exclusion criteria for both trials:*** • Malignant change in a polyp • Known clinical diagnosis or gene carrier of a hereditary CRC predisposition (FAP, hereditary nonpolyposis CRC) • Previous or newly diagnosed inflammatory bowel disease • Previous or planned colorectal resection • Known bleeding diathesis or concomitant non-aspirin anti-coagulant or anti-platelet agent • Abnormal liver function consisting of any of the following, at any time in the preceding 4 weeks: o 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) o Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥2.5 x ULN • Inability to comply with trial procedures and use of therapies. • Pregnant or lactating women • Women of child-bearing potential unwilling to use appropriate methods of birth control (see protocol section 8.10)

	• Males with partners who are WOCBP and are unwilling to use effective methods of contraception • Serious medical illness interfering with trial participation including inability to have future colonoscopic surveillance. • 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:*** • 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 • Allergic or intolerant to ibuprofen or naproxen, metformin, aspirin or salicylate • Diabetic patients on drug treatment • Current or previous treatment with metformin • Known history of peptic ulcer disease • Known history of lactic acidosis or predisposing conditions • 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 • Use of long-term systemic corticosteroids ***Additional exclusion criteria for the resveratrol Signal-Seeking trial only*** • Unable to abstain from ingestion of OTC supplements containing resveratrol for the trial duration • Known yeast allergy • Sensitivity or allergy to any of the capsule excipients	
	Objectives	**Outcome Measures**
Primary	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 findings, 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.	**Primary** Polyp number measured as MPP (Mean number of Polyps per Participant). **Secondary** • Polyp Detection Rate (PDR, proportion of individuals with one or more qualifying* pre-malignant polyp(s) at surveillance) • 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. • Polyp subtype based on histopathology (adenoma/serrated); also reported as MPP and PDR.

		• 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). • Polyp size (maximum dimension in mm as described in the histopathology report [or endoscopic size if no histopathological size available) ** Please refer to definition in figure 2*
Secondary	1) To assess the safety and tolerability of aspirin and metformin compared to aspirin alone. 2) To assess the safety and tolerability of each resveratrol dose compared to placebo.	**Safety** Adverse events, including clinically significant bleeding episodes and GI tolerability. **Compliance** Assessment of compliance by counting residual numbers of tablets/capsules See protocol section 3.6 for list of exploratory outcomes.

Table 1: Trial Assessments for Main Trial (Aspirin or Aspirin + Metformin; 3 year intervention; open-label)

Procedure (Time (T) in weeks)	Pre-trial BCSP colonoscopy Visit 0	Research visit Visit 1 T= 0 weeks	Telephone call Visit 2 T= 4 weeks	Telephone call Visit 3 T= 12 weeks	Research visit Visit 4 T= 25 weeks	Research visit Visit 5 T= 52 weeks	Every 6 months Research visits Visits 6, 7 & 8 6 monthly	Exit surveillance colonoscopy Visit 9 T= 154 weeks	Post-surveillance colonoscopy telephone visit Visit 10 T= 156 weeks
Colonoscopy (routine clinical procedure)	●							●	
Provide trial information (PIS)	●								
Colonoscopy results (routine care)	●								●
Eligibility assessment		●							
Informed consent		●							
Medical History and Demographics		●							
Fasting blood samples & processing -safety & research[b]		●			●	●	● (visits 6 & 7 only)	●	
Blood serum pregnancy test if applicable		●						●	
Food Frequency Questionnaire (FFQ)		●				●	● (visit 7 only)	●	
BP measurement		●							
Concomitant medication recording		●	●	●	●	●	●	●	●
Eligibility confirmation & Randomisation		●							
Trial drug dispensing		●[a]	**Increase metformin dose from 500mg OD to BD**		●	●	●		
Research faecal sample		●				●		● (prior to colonoscopy)	
Adverse Events		●[c]	●	●	●	●	●	●	●
Compliance (pill counting)					●	●	●	●	
Rectal biopsies								●	
Diagnostic FFPE blocks		●						●	
Last dose of trial drug								●	
End of trial participation									●

[a] Trial medication to start the day after participant has collected a baseline research faecal sample (obtained on a FIT kit). [b] Locally processed: fasting lipid profile, FBC, LFT, U&E, eGFR, HbA1c, glucose; annual vit B12 testing for metformin arm participants. Research samples: IGFBP-3, IGF-I, insulin, PK/PD, exploratory research biomarkers. [c] AEs recorded from first dose.

Visits 2 & 3 have a **±1 week** window, except for metformin arm participants where visit 2 has a window of **+1 week**. Visits 4-9 have a **±2 week** window. Visit 10 has a **+1 week** window.

Table 2: Trial Assessments for Signal-Seeking Sub-Trial (Blinded allocation: resveratrol 5mg or 1g, or placebo; 1 year intervention)

Procedure (Time (T) in weeks)	Pre-trial BCSP colonoscopy	Research visit Visit 1 T= 0 weeks	Telephone call Visit 2 T= 2 weeks	Telephone call Visit 3 T= 12 weeks	Research visit Visit 4 T= 25 weeks	Surveillance (research) colonoscopy Visit 5 T= 52 weeks	Post-surveillance colonoscopy telephone call Visit 6 T= 54 weeks
Colonoscopy[a]	●					●	
Provide trial information (PIS)	●						
Colonoscopy results	●[f]						●
Eligibility assessment		●					
Informed consent		●					
Medical History and Demographics		●					
Fasting blood samples & processing -safety & research[c]		●			●	●	
Blood serum pregnancy test if applicable		●				●	
Food Frequency Questionnaire (FFQ)		●				●	
Concomitant medication recording		●	●	●	●	●	●
Eligibility confirmation & Randomisation		●					
Trial drug dispensing		●[b]			●		
Provision of urine sample[d]		●			●	●	
Research faecal sample		●				● (prior to colonoscopy)	
Adverse Events		●[e]	●	●	●	●	●
Compliance (pill counting)					●	●	
Rectal biopsies						●	
Diagnostic FFPE blocks		●				●	
Last dose of trial drug						●	
End of trial participation							●

[a] First colonoscopy is a routine clinical procedure, second colonoscopy is a research procedure. [b] Patient to commence their trial medication the day after they have collected a baselineresearch faecal sample (obtained on a FIT kit). [c] Locally processed: FBC, LFT, U&E, eGFR, HbA1c, fasting lipid profile, glucose. Research samples: insulin, IGFBP-3, IGF-I, PK/PD, exploratory research biomarkers. [d] Urine will be collected from 20% of patients from randomly selected sites that are willing and able to collect urine. [e] Adverse events collected from first dose. [f] Where routine consultations are undertaken remotely following a screening colonoscopy, potential participants will need to be brought into hospital for visit 1.

Visits 2 & 3 have a **±1 week** window. Visits 4 and 5 have a **±2 week** window. Visit 6 has a **+1 week** window.