

<b>Project Title:</b>	A randomised controlled trial of eicosapentaenoic acid (EPA) and/or aspirin for colorectal adenoma (or polyp) prevention during colonoscopic surveillance in the NHS Bowel Cancer Screening Programme: The seAFood polyp prevention trial
<b>Project Ref:</b>	09-100-25
<b>Cost:</b>	£912,924
<b>Lead Applicant &amp; Institution:</b>	Professor Mark Hull Molecular Gastroenterology University of Leeds
<b>Start Date:</b>	Anticipated 1 November 2010
<b>Plain English Summary:</b>	<p>One way of preventing bowel (or colon) cancer is giving drugs or dietary supplements (called chemoprevention). Most bowel cancers develop from a polyp (a growth on the bowel wall; also known as an adenoma) over many years. Therefore, clinical trials of promising chemoprevention agents usually monitor polyps detected at a bowel camera test (called colonoscopy) over short periods of time (up to 3 years).</p> <p>Eicosapentaenoic acid (EPA) is an omega (w)-3 polyunsaturated fatty acid (PUFA) naturally present in oily fish such as mackerel. A recent clinical trial showed that taking pure EPA for 6 months reduced bowel polyp number and size by around 20% compared to 'dummy' capsules. We also know from previous trials that aspirin use reduces polyp risk by around 15%, although the best and safest dose of aspirin for bowel cancer prevention is unclear. A major advantage of w-3 PUFA and aspirin as chemoprevention agents is that they are safe, have few side-effects and are already used widely by people with heart and/or stroke disease.</p> <p>We want to test whether EPA, alone or in combination with aspirin, prevents bowel polyps in 'high risk' patients taking part in the National Bowel Cancer Screening Programme (BCSP), who have already had several polyps removed at colonoscopy. We will give the four possible combinations of active or 'dummy' (placebo) drugs in a way that both patients and medical staff do not know what treatment is being given.</p> <p>Trial drugs will be given for 12 months until patients have another scheduled BCSP colonoscopy, at which time the number and size of polyps will be measured. We will collect blood, urine and colon samples during the trial so that we can learn more about how EPA and aspirin work, as well as develop 'biomarker' tests to predict who will or will not respond to chemoprevention.</p> <p>We need to give trial drugs to 678 patients in order to confidently demonstrate a minimum 20% decrease in polyp recurrence. Taking into</p>

	<p>account patients who are ineligible for the trial (such as existing aspirin users), do not want to take part, or stop taking trial medication, we need to contact approximately 1400 'high risk' patients with polyps. Due to the large scale of the BCSP, we can identify this number of patients in 2 years using only 15 of more than 40 existing BCSP Centres in England.</p> <p>The trial will last for 4 years including set-up and analysis of results. Because the trial will take place in the BCSP, only one extra out-patient clinic visit and some blood/urine sampling will be needed, which means that the overall cost of the trial (particularly the costs to the NHS) is comparatively low for such a big trial.</p> <p>The research team consists of Doctors, Scientists, a BCSP Nurse and a Patient Representative, who together have experience of polyp trials, direct involvement in the BCSP and expertise in biomarker measurement.</p>
<p><b>Abstract:</b></p>	<p><u>Research design:</u> A randomised, double-blind, placebo-controlled 2 x 2 factorial trial integrated into the screening and surveillance phases of the National Bowel Cancer Screening Programme (BCSP).</p> <p><u>Study population:</u> BCSP patients stratified as 'high risk' (<math>\geq 5</math> small adenomas or <math>&gt;3</math> adenomas with at least one <math>&gt;10</math> mm in diameter) after adenoma clearance at screening colonoscopy. Exclusion criteria to include regular aspirin use, aspirin/fish hypersensitivity, peptic ulcer disease and colorectal resection.</p> <p><u>Planned interventions:</u> Enteric-coated eicosapentaenoic acid (EPA) free fatty acid 2 g daily po or placebo (medium-chain triglyceride Migyol 810™) AND enteric-coated aspirin 300 mg daily po or placebo, for 12 months until scheduled BCSP 'high risk' surveillance colonoscopy.</p> <p><u>Proposed outcome measures:</u> Primary efficacy end-point; the number of patients with at least one adenoma detected at BCSP surveillance colonoscopy at 12 months. Secondary end-points; the number of patients with at least one 'advanced' (<math>&gt;10</math> mm diameter, high-grade dysplasia or villous component) adenoma; the total number of adenomas per patient; the number of patients re-classified as 'intermediate risk' (for subsequent three year BCSP surveillance colonoscopy); adverse events (AE) including clinically significant bleeding episodes; erythrocyte and mucosal PUFA incorporation; production of EPA- and aspirin-dependent eicosanoids including prostaglandin E3, 18R-HEPE and resolvin (Rv) E1; analysis of resected adenoma tissue.</p> <p><u>Assessment and follow up:</u> Compliance and AE monitoring, as well as blood/tissue sampling, all integrated into the BCSP with only one extra visit at 6 months. Colonoscopy and polypectomy complications monitored by the BCSP. Colonoscopic outcomes post-intervention available via the BCSP database.</p> <p><u>Proposed sample size:</u> 678 individuals randomised equally to the four treatment arms for 80% power, with 5% two-sided significance, to detect a minimum 18% relative reduction in adenoma recurrence (from 60% to 49%) in each two-arm comparison. This is less than the EPA effect observed in a familial adenomatous polyposis (FAP) RCT and below the reduction in polyp number at one year (38%) in previous aspirin polyp prevention trials. Assuming 40% ineligibility (including 20% aspirin use) and a 15% drop-out rate, 1400 'high risk' individuals need to be identified at screening colonoscopy.</p>

	<p><u>Statistical analysis:</u> ITT analysis using an 'at the margins' approach and direct estimation of relative risk by Poisson regression (with robust standard errors), including treatment arm as an explanatory variable. Predictive value of EPA and eicosanoid biomarkers for adenoma outcomes determined by multiple logistic regression with known clinical factors (eg. adenoma characteristics) as independent variables.</p> <p><u>Project timetable:</u> 50 'high risk' patients will be identified in each of 15 BCSP Centres per year. Accrual to be completed in 2 years with full primary outcome data available 3 years from the start of randomisation. Six months set-up and six months for clinical and biomarker data analysis are integrated into the four year project.</p>
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