CLINICAL STUDY PROTOCOL

Full Study Title: Effect of Aspirin on Reducing Cancer & Improving Outcomes in Primary Sclerosing Cholangitis

Short Study title / Acronym: Asp-PSC
Products: Aspirin and Placebo
Development Phase: Phase III
Sponsor: Imperial College London
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This protocol describes the Asp-PSC trial and provides information about procedures for enrolling participants to the trial. The protocol should not be used as a guide for the treatment of other participants; every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study, but centres enrolling participants for the first time are advised to contact ICTU to confirm they have the most recent version. Problems relating to this trial should be referred, in the first instance, to ICTU. This trial will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and the International Conference on Harmonisation Good Clinical Practice (ICH GCP) guidelines. It will be conducted in compliance with the protocol, the Data Protection Act 2018 and other regulatory requirements as appropriate.

ABBREVIATIONS

AE	Adverse Event
AFP	Alpha-fetoprotein
AMMF	Alan Morement Memorial Fund
ASP	Aspirin
AST	Aspartate Aminotransferase
BASO	The British Association of Surgical Oncology
BMI	Body Mass Index
BTC	Biliary Tract Cancer
CA	Cancer Antigen
CCA	Cholangiocarcinoma
CI	Chief Investigator
CLDQ	Chronic Liver Disease Questionnaire
COX-2	Cyclooxygenase-2
CRC	Colorectal Cancer
CRF	Case Report Form
CRUK	Cancer Research United Kingdom
CRP	C-Reactive Protein
CT	Computerised Tomography
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of an Investigational Medicinal Product
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
DSUR	Development Safety Update Report
eCCA	Extrahepatic Cholangiocarcinoma
eCRF	Electronic Case Report Form
ERCP	Endoscopic Retrograde Cholangiography
ELF	Enhanced Liver Fibrosis
FBC	Full Blood Count
GCP	Good Clinical Practice
GI	Gastrointestinal
GGT	Gamma-glutamyl Transferase

GMP	Good Manufacturing Practice
HR	Hazard Ratio
HCC	Hepatocellular Carcinoma
HPB	Hepato-Pancreato-Biliary
HRA	Health Research Authority
IBD	Inflammatory Bowel disease
ICMJE	International Committee of Medical Journal Editors
iCCA	Intrahepatic Cholangiocarcinoma
ICHNT	Imperial College Healthcare NHS Trust
ICMJE	International Committee of Medical Journal Editors
ICTU	Imperial Clinical Trials Unit
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product
IND	Investigational New Drug
INR	International Normalised Ratio
IRAS	Integrated Research Application System
ISRCTN	International Traditional Medicine Clinical Trial Registry
ITT	Intention to Treat
MDT	Multidisciplinary Team
MHRA	Medicines and Healthcare Products Regulatory Agency
MIA	Manufacturing Import Authorisation
MRCP	Magnetic Resonance Cholangiography
MRI	Magnetic Resonance Imaging
NASH	Non-alcoholic Steatohepatitis
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NSAID	Non-Steroidal Anti-Inflammatory drugs
OD	Once daily
PBC	Primary Biliary Cholangitis
PFIC	Progressive familial intrahepatic cholestasis
PPIE	Patient Public Involvement Engagement

PSC	Primary Sclerosing Cholangitis
PSC PRO	Primary Sclerosing Cholangitis Patient Reported Outcome
PTC	Percutaneous Transhepatic Cholangiogram
QA	Quality Assurance
QC	Quality Control
QOL	Quality of Life
REC	Research Ethics Committee
RGIT	Research Governance Integrity Team
RR	Risk ratio
RR	Relative risk
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SAP	Statistical Analysis Plan
SIBDQ	Short Inflammatory bowel disease questionnaire
SmPC	Summary of Product Characteristics
SF-36	Short Form-36
SOP	Standard Operating Procedure
SSAR	Suspected Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
TCPN	Therapeutic Cancer Prevention Network Group
TIA	Transient Ischaemic Attack
TMG	Trial Management Group
TSC	Trial Steering Committee
UDCA	Ursodeoxycholic Acid
UK	United Kingdom
US	Ultrasound
U & E	Urea and Electrolytes

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TRIAL SUMMARY

TITLE: Asp-PSC Trial: Effect of Aspirin on Reducing Cancer & Improving Outcomes in Primary Sclerosing Cholangitis (PSC)

OBJECTIVES:

Primary Objective:

To investigate if in patients with PSC and inflammatory bowel disease (IBD), daily low dose aspirin lowers the risk of PSC related cancer/high grade dysplasia, liver decompensation, the need for liver transplantation and all-cause mortality, compared to placebo, over a minimum 5-year period.

Secondary Objective:

Safety and tolerability of aspirin in patients with PSC-IBD and effect on quality of life using disease specific questionnaires.

Translational research objectives:

To collect, store and analyse clinical and radiological data, genomic deoxyribonucleic acid (DNA), serum, cell free DNA and urine samples.

Sub-study objective:

To assess safety, pregnancy outcome and acceptability of the intervention in pregnant women.

Added Benefit:

To create and develop pan-UK PSC bioresource for translational research to help improve the clinical care of patients with PSC.

PHASE: Asp-PSC is a Phase 3 study.

DESIGN: This study will be a multicentre, double-blind, randomised placebo-controlled trial. The study population will include patients with PSC who have a concurrent diagnosis of IBD and who are at least 12 months post diagnosis of PSC. Patients will be randomised in a ratio of 2:1 Aspirin vs Placebo. Accrual will be over 5 years, with a minimum participant follow up of 5 years. Included in this study is an embedded feasibility study, for one year from start of recruitment, to establish recruitment, acceptability, and compliance rates. Randomisation will be stratified by advanced fibrosis/cirrhosis, time since diagnosis of PSC and concomitant usage of oral 5-aminosalicylates.

SAMPLE SIZE: 774 patients need to be recruited to allow the detection of a hazard ratio (HR) of 0.6 with 80% power (significance 0.05), equivalent to a 6% difference in the proportion of patients diagnosed with cancer, undergoing liver transplantation or death from all-cause mortality. This is based on an estimated event rate in the control group of 15% at 5 years accrual and 5 years of minimum follow up. Of note, the number of individuals who develop hepatic decompensation specifically were not part of the original power calculation but are likely to be captured amongst those undergoing transplantation. The Intervention:

placebo randomisation ratio is 2:1, meaning we need to recruit 516 participants in the intervention group and 258 in placebo group. To allow for 20% loss to follow up, we have determined we will need to recruit 968 patients in total**.**

INCLUSION/EXCLUSION CRITERIA

Inclusion Criteria:

1. Age 18 years or above
2. Able to give written and informed consent.
3. Must have an established clinical diagnosis of large duct PSC-based on a standard disease definition of typical cholangiography findings on endoscopic retrograde cholangiography (ERCP) or magnetic resonance cholangiography (MRCP).
4. An established diagnosis of concomitant colonic IBD either in a pattern of Ulcerative Colitis, Crohn's disease or IBD unclassified.
5. Patients must be at least one-year post PSC diagnosis.
6. If pre-treated with ursodeoxycholic acid (UDCA) – UDCA therapy should remain at a stable dose for 12 weeks prior to screening, and not exceeding 20mg/kg/day.
7. Must have had a colonoscopy within the last year of randomisation date as part of routine clinical care. If not this must be done within the screening interval.
8. If a patient has cirrhosis, they must have undertaken a hepatobiliary ultrasound (US), MRCP scan, magnetic resonance imaging (MRI) liver or regional computerised tomography (CT) scan within 6 months of screening date as part of routine clinical care. If not, this must be done within the screening interval.
9. If non-cirrhotic, then the patient must have had an US, MRCP, dynamic MRI or regional CT within the last 12 months as part of routine clinical care. If not, this must be done within the screening interval.

Exclusion Criteria

1. Evidence of concomitant disease(s) that causes secondary sclerosing cholangitis.
2. Evidence of any of the following diseases: IgG4 related disease, PBC, acute or chronic viral hepatitis, alcohol-related liver disease, Wilson disease, Budd-Chiari syndrome, portal vein thrombosis, alpha-1-antitrypsin disease, hepatic sarcoidosis, cystic fibrosis, Progressive familial intrahepatic cholestasis (PFIC), hereditary haemochromatosis, non-alcoholic steatohepatitis (NASH) – those with simple hepatic steatosis without evidence of NASH or liver fibrosis secondary to fatty liver disease are allowed to participate, other metabolic liver disease, active malignancy in the last five years (except treated/excised non-melanomatous skin cancer).
3. Have a previous diagnosis of colorectal cancer, cholangiocarcinoma, gallbladder cancer at any time point.
4. Has received a liver transplant, has been referred for liver transplant assessment, or is listed for a liver transplant.
5. Had any of the following procedures: colonic resection of any nature, including those with a defunctioning ostomy.
6. Consume more than the recommended allowance of 14 units of alcohol per week (as set out by the Department of Health).

7. Current or recent participation in any other clinical trial of an investigational medicinal product (CTIMP) within the last 6 weeks prior to first dose of aspirin/placebo
8. Already taking aspirin.
9. History of non-variceal upper gastrointestinal (GI) bleeding within one year.
10. A history of congestive cardiac failure.
11. A known diagnosis of glucose-6 -phosphate dehydrogenase.
12. Childs Pugh B or C cirrhosis
13. Untreated thyrotoxicosis or hypothyroidism
14. Familial history of a hereditary cancer syndrome, or confirmed genetic predisposition that heightens cancer risk.
15. Vaccination for varicella zoster in the six weeks prior to screening period
16. Known allergy to aspirin
17. A history of NSAID/ aspirin induced asthma and nasal polyps
18. Concurrently taking non-steroidal anti-inflammatory drugs (NSAIDs) in the four weeks prior to screening
19. History of haemophilia and/or other bleeding disorders where aspirin is contraindicated
20. Taking other anti-platelet or anti-coagulant medication (e.g., clopidogrel, prasugrel, warfarin, apixaban, rivaroxaban, dabigatran or therapeutic heparin preparations)
21. Active, or history of recurrent peptic ulcer
22. Patients who are suffering from gout
23. Severe renal impairment
24. Taking methotrexate at a dose of >15mg/week
25. Taking selective serotonin-reuptake inhibitors

TREATMENT/MAIN STUDY PROCEDURES

Patients will be randomised to either aspirin or placebo. Patients will be called at one month after the collection visit. The first month's call will be to ensure drug tolerability and check no immediate adverse events.

During the month one visit, the patients will be asked to for:

1. Medical History
2. Review of Haematology including FBR and INR test if locally available
3. Review of Biochemistry including UE, LFT, GGT, AST, CRP, Vitamin D, B12, ferritin, TSH and T4 and if locally available
4. Adverse Events
5. Concomitant Medications
6. QOL Assessments (PSC-PRO, SF-36, 5D-Itch Scale, SIBDQ, PRO-2 and CLDQ-PSC) to be completed at home.

During the one-month phone call patients may be required to attend an in person visit if clinically required to assess further adverse event reporting, this will be decided by a delegated member of staff responsible for patient care. The following assessments will be undertaken:

1. Vital Signs (Body temperature, pulse rate, respiration rate, blood pressure-if clinically indicated)

2. Targeted Physical Exam (if clinically indicated)

Patients will be seen for study visits at 6 monthly intervals (5 months after the month 1 phone call, then 6 monthly thereafter), ideally in alignment with routine clinical care, for five years.

During each 6-month visit, the patients will be asked to:

1. Documentation of medical history
2. Documentation of vital signs (Body temperature, pulse rate, respiration rate, blood pressure)
3. Weight measurement
4. Targeted Physical Exam (if clinically indicated)
5. Undertake standard of care National Health Service (NHS) blood tests (Full Blood Count (FBC), Urea and Electrolytes (U&E), liver biochemistry, gamma-glutamyl transferase (GGT), aspartate aminotransferase (AST), C-Reactive Protein (CRP), International Normalised Ratio (INR), Vitamin D, Cancer Antigen 19.9 (CA19.9), Alpha-fetoprotein (AFP), B12, ferritin and a TSH and T4). Standard of care faecal calprotectin measurement will be taken yearly. Stool tests will be taken to the local GP for processing. Results should be sent to referring hospital.
6. Adverse event documentation
7. Compete questionnaires: Primary Sclerosing Cholangitis -Patient reported outcome (PSC PRO), Short Form-36 (SF-36), 5D-Itch Scale, and Short Inflammatory bowel disease questionnaire (SIBDQ), PRO-2 (Patient Reported Outcome-2) and Chronic Liver Disease Questionnaire (CLDQ)-PSC, questionnaires can be taken home to do. If Questionnaires are not brought to clinic, site will need to ask patient to complete questionnaires on the day of visit.
8. Documentation of Concomitant Medications
9. Urine and blood samples taken (if patient consented to this).
10. Body mass index (BMI) measurement recorded.
11. Patients will also be asked about their alcohol and smoking habits.
12. A fibroscan will also be undertaken if locally available.
13. Documentation of UKELD Score
14. Note will be made of any intervening cancer diagnosis, decompensating liver events or referral for liver transplantation.
15. Note will also be made of any colonoscopy undertaken and also the histological findings from that examination. Note will also be made of any endoscopic intervention/ cholecystectomy or new cancer diagnosis made.
16. Note will also be made of any recent imaging studies the patients have undergone, the results available from these studies and multidisciplinary team (MDT) outcomes.
17. Collection of aspirin/placebo tablets

Patients will attend an end of treatment visit, 28 days after last study dose.

Patients will then be followed up yearly for a minimum of 5 years for data collection only.

OUTCOME MEASURES

PRIMARY ENDPOINTS

The composite primary endpoints are defined as occurrence of any of the following:

1. Hepatobiliary cancer (including gallbladder cancer/high grade dysplasia, pancreas, cholangiocarcinoma [CCA] or hepatocellular [HCC]) or colorectal cancer/high grade dysplasia
2. Listing for Liver transplantation
3. All-cause mortality

SECONDARY ENDPOINTS

1. To investigate gastrointestinal bleeding risk ((Common Terminology Criteria for Adverse Events (CTCAE) grade 3 or 4)) between daily low dose aspirin and placebo in patients with PSC-IBD
2. Progressive liver disease, as evidenced by either ascites, variceal bleeding (any site), hepatic encephalopathy (investigator discretion) or development of cirrhosis with Child Pugh B or C stage
3. To investigate the rates of referral for liver transplantation between daily low dose aspirin and placebo in patients with PSC-IBD
4. To investigate the rates of acute cholangitis between daily low dose aspirin and placebo in patients with PSC-IBD
5. To investigate IBD flare frequency between daily low dose aspirin and placebo in patients with PSC-IBD
6. To investigate the rates colonic surgery/resection for severe IBD between daily low dose aspirin and placebo in patients with PSC-IBD
7. Safety and tolerability of aspirin in patients with PSC-IBD and effect on quality of life using disease specific questionnaires.

TRANSLATIONAL RESEARCH OUTCOMES

To develop a prospective clinical, imaging and specimen biobank of samples from patients with PSC-IBD to allow future studies to be undertaken in which the performance of novel diagnostic biomarkers for the early detection and prognostication of PSC related cancer will be determined.

IMP: 75mg Aspirin or matched placebo taken orally daily once daily (OD) for five years.

1 BACKGROUND

1.1 CLINICAL SETTING

1.1.1 Primary Sclerosing Cholangitis and Cancer Risk

PSC is an immune-mediated liver disease which is associated with a unique type of IBD of the colon. Chronic inflammation at biliary and colonic mucosal sites results in the potential for epithelial cells to undergo a dysplasia/adenocarcinoma transition sequence (1, 2). No medical therapy has been proven to slow disease progression. Consequently, over 50% of

patients develop hepatopancreatobiliary (HPB) cancer or chronic liver failure in need of transplantation. Moreover, for the majority of patients (around 70%) that develop IBD there is a 30% (20) lifetime risk of colorectal cancer (CRC) – tenfold greater than that of IBD alone. The estimated prevalence of PSC in the UK is around 6/100,000 and PSC represents over 10% of all UK indications for liver organ transplantation. Moreover, PSC is now leading indication for liver transplantation in several European countries (3, 4).

The standardised incidence ratio of HPB cancer and CRC in PSC is estimated at around 400-fold (5); and a recent systematic review and meta-analysis reported summary relative risks (RR) of 584.4 (CI 269.4 – 1267.5) for CCA, 155.5 (125.3 – 193.0) for HPB cancer overall, 30.2 (12.0 – 76.2) for liver cancer including HCC, 6.1 (4.2 – 8.9) for colorectal cancer (CRC) and 4.1 (3.0 – 5.7) for all cancers (6). Furthermore, for those that develop a bile duct cancer, the overall survival is normally less than one-year from diagnosis.

PSC is also the commonest predisposing cause of CCA, itself the second commonest primary liver cancer in the Western World (7). The risk for developing CCA in PSC is highest within the first year of diagnosis (8). After that, the yearly incidence of CCA is 0.5-1.5%, with a lifetime risk of 15-18%, and a risk ratio (RR) of 150 times that of the general population.

At present due to a lack of evidence, there is no agreed guidance on how surveillance for CCA should be undertaken for patients with PSC, nor consistency in published national or international guidelines. In addition, a recent large-scale audit of clinical care showed a complete lack of a co-ordinated approach in the UK for cancer surveillance in PSC with some not offering it at all (9). This is despite a wealth of evidence indicating improved post-cancer survivorship for patients undergoing annual cancer surveillance with combination HPB imaging (10). However, the optimal imaging modality and interval for surveillance is unknown.

Patients with PSC and HPB cancer frequently present at a late and incurable stage of disease with an average life expectancy being less than 12 months from diagnosis. Moreover, whilst patients with PSC-induced decompensated liver disease may be eligible for liver transplantation, the development of cancer is currently a contraindication in the UK. In the few countries where liver transplantation for CCA is carried out, only a very few per cent of PSC patients qualify (7). ***There is, therefore, an urgent and unmet need to find new therapies that could prolong cancer free survival in PSC.***

1.2 INVESTIGATIONAL AGENT AND RATIONALE FOR STUDY

1.2.1 Evidence That Aspirin Imparts Protective Effects against CCA, CRC and HCC

Based on pre-clinical, epidemiological and randomised data aspirin may have anti-cancer effects, with the strongest evidence currently pertaining to CRC.

Cohort studies found that aspirin significantly reduces the risk of CRC in the general population. In a 2017 nested case-control study set in UK primary care (11), users of low-dose aspirin had a significantly reduced risk of CRC (RR 0.66, 95% CI 0.60-0.74). The reduction in risk was apparent across all age strata and with all aspirin groups. After five years of therapy, the RR for Dukes Stage A CRC was 0.53 (0.24-1.19). In a separate retrospective cohort study of over 612,000 patients, 5,118 (2.5%) out of 204,170 aspirin

users were diagnosed with CRC; and 2073 (1.0%) died of malignancy. Aspirin usage significantly reduced CRC mortality (HR = 0.59; 95% CI 0.56 to 0.62) (12).

In the double-blind, randomised CAPP2 trial, 861 patients with Lynch syndrome, which carries a high risk of CRC, patients were randomly assigned to receive aspirin daily or placebo. The long-term results of the CAPP2 trial found, on a per-protocol analysis, significantly reduced overall risk for the aspirin group: HR 0·63 (CI 0·43-0·92; p=0·018) (13). The recommendation that these patients be considered for daily aspirin has recently been incorporated into National Institute for Health and Care Excellence (NICE) guidelines (14).

Epidemiological evidence has also been accumulating in recent years that aspirin use is associated with a reduced risk of developing hepatobiliary cancer, including in PSC. A recent meta-analysis of all observational studies on aspirin for the prevention of digestive tract cancers estimated the pooled relative risk (RR) of cancer for regular aspirin use versus non-use using random effects models (15). In this study, regular aspirin use was associated with a reduced risk of crc (RR 0.73, 95% CI 0.69-0.78, 45 studies), squamous-cell oesophageal cancer (RR 0.67, 95% CI 0.57-0.79, 13 studies), adenocarcinoma of the oesophagus and gastric cardia (RR 0.61, 95% CI 0.49 – 0.77, 10 studies), stomach cancer (RR 0.64, 95% CI 0.51-0.82, 14 studies), hepato-biliary tract cancer (RR 0.62, 95% CI 0.440-0.86, five studies), and pancreatic cancer (RR 0.78, 95% CI 0.68-0.89, 15 studies).

Focussing on CCA, a hospital-based case-control study found that aspirin use was significantly associated with a 2.7 to 3.6-fold decreased risk for both main anatomical sub-types of CCA: intrahepatic (iCCA) and extrahepatic (eCCA), with adjusted odds ratios (OR) of 0.29 – 0.35 (16). Furthermore, there was up to a 50% reduction specifically in PSC-associated CCA. Further support for aspirin's potentially protective effect against CCA in the wider population comes from two meta-analyses. Lapummuaypol et al.'s systematic review examined five observational studies with a total of over 9.2 million enrolled patients (17). The pooled OR of CCA in aspirin users was 0.56. No significant association between NSAID use and CCA was found.

Additionally, a systematic review and meta-analysis by Xiong et al. examined nine studies, consisting of 12,535 people who developed CCA and 92,750 healthy controls (18). There was a significantly decreased risk of CCA in those using aspirin. Moreover, this relationship was detected only in case-control studies (OR=0.65; 95% CI=0.38–0.93), and the reduction was across all anatomical sites of CCA (iCCA, OR=0.33 (95% CI=0.26–0.39) & eCCA, OR=0.56, 95% CI=0.41–0.73).

There is also emerging epidemiological evidence that aspirin may have benefit as adjuvant therapy (19), including improving survival after a diagnosis of biliary tract cancer (BTC). Jackson et al. investigated the association between post-diagnosis aspirin use and BTC survival (20). Even use of post-diagnosis aspirin, at low dose, was associated with decreased risk of death in patients with Gall Bladder Cancer (HR, 0.63; 95% CI, 0.48-0.83), CCA (HR, 0.71; 95% CI, 0.60-0.85), Ampulla of Vater Cancer (HR, 0.44; 95% CI, 0.26-0.76), and overlapping BTC (HR, 0.68; 95% CI, 0.50-0.92). The authors noted that the survival benefit of aspirin observed in their study is on par with the current standard of care for these cancers.

This work is further supported by Liao et al.'s recent study of newly diagnosed BTC patients included 2,519 (16%) taking aspirin post BTC diagnosis (21). After a mean follow-up of 1.59 years, the 5-year survival rate was 27.4%. The multivariate-adjusted HR for postdiagnosis aspirin users, as compared with nonusers, was 0.55 (95% CI: 0.51 to 0.58) for BTC-specific death. Cancer-specific mortality was lower with post-diagnosis aspirin use in patients with all major BTC subtypes. The authors concluded randomised trials are required to investigate aspirin's efficacy in BTC.

A recent nationwide Swedish registry study examined long term effects of low dose aspirin on incident HCC, liver related mortality and gastrointestinal bleeding in persons with chronic viral hepatitis B or C infection, which are established risk factors for cirrhosis, HCC and CCA (22). Over 50,000 non-aspirin users were compared to over 14,000 patients taking low dose aspirin. Use of aspirin was associated with a significantly lower risk of HCC than no use of aspirin. Adjusted HRs were 0.90 (95% CI, 0.76 to 1.06) for 1 to less than 3 years of aspirin use, 0.66 (95% CI, 0.56 to 0.78) for 3 to less than 5 years of use, and 0.57 (95% CI, 0.42 to 0.70) for 5 or more years of use. The 10-year risk of gastrointestinal bleeding did not differ significantly between users and nonusers of aspirin.

A summary of the statistically significant findings of the protective effects of aspirin use against HPB cancers and CRC is provided in Table 1.

Table 1: Summary of studies reporting statistically significant protective effects of Aspirin against cancers PSC-IBD patients are at high risk of

Evidence of Aspirin Users' Potential Protection against HPB and CRC Cancers
1. Choi et al. 2016: **OR 0.29 – 0.35** for all CCA subtypes (50% reduction in PSC associated CCA) (16)
2. Simon et al. 2020: **HR 0.57** for HCC (22)
3. Lapumnuaypol et al. 2019: **OR 0.56** for CCA (Meta-analysis) (17)
4, Xiong et al. 2018: iCCA **OR 0.33** for iCCA; **OR=0.56** for eCCA (Meta-analysis) (18)
5. Bosetti et al. 2020: **RR 0.62** for HPB cancers (15)
6. Garcia Rodriguez et al. 2017**: RR 0.53** for Dukes Stage A CRC (11)
7. Burn et al 2020: CAPP-2 Randomised Controlled Trial: **HR 0·63** for CRC in Lynch syndrome (13)
Post-diagnosis aspirin use associated with decreased biliary tract cancer-specific mortality
7. Liao et al. 2021: **HR 0.55** (21)
8. Jackson et al. 2019: **HR 0.44 to 0.71** across all BTC sites (20)

1.3 POSTULATED ANTI-CANCER BIOLOGICAL MECHANISMS OF ASPIRIN

The biological plausibility of aspirin reducing the risk of CCA and CRC, in parallel to the published epidemiological data, has been extensively reviewed and includes its ability to: inhibit Cyclooxygenase-2 (COX-2) in dysplastic tissue (which promotes inflammation and cell proliferation), inhibit activation of nuclear factor Kb, prevent platelet aggregation (which may slow metastatic spread), modulate Wnt signalling via both COX-dependent and COX-independent pathways, upregulate tumour suppressor genes and stabilise DNA mismatch-repair proteins (23). Furthermore, established and recognised cell lines of CCA have been shown to be inhibited by aspirin (24). Therefore, given the unmet need for patients with PSC and also the clear epidemiological evidence that aspirin reduces cancers that reduce survival in PSC we have proposed the following hypothesis that this protocol will test.

1.4 HYPOTHESIS

Aspirin reduces the risk of PSC-related cancer occurrence, prolongs overall survival and liver transplant free survival in patients with both PSC-IBD.

1.5 WHAT THE STUDY WILL ADD

We anticipate this study will show that low dose daily aspirin safely results in improvements in cancer free survival, overall survival and liver transplant free survival in

patients with PSC-IBD. If so, this would lead to a change in clinical practice nationally and internationally; and will positively address a major area of unmet need in this cohort of patients, for whom no therapy currently has been shown to alter the natural history of disease progression and cancer free survival. A positive result in favour of aspirin would trigger a rapid review and update of the British Society of Gastroenterology's UK-PSC Clinical Practice Guidelines (1) and we anticipate that a new recommendation to repurpose daily low-dose aspirin (a readily available, low-cost medication) to people with PSC would mean our findings could be put into practice almost immediately after the end of the trial.

1.6 RISK: BENEFIT RATIO

The overall risks of low dose aspirin are deemed to be low, based on several published trials of aspirin use in cancer prevention, often at much higher doses than we will be using. The safety of aspirin is key to several of our secondary endpoints. The potential benefits from the literature include lower cancer risk and improved survival.

2 OBJECTIVES AND ENDPOINTS

2.1 PRIMARY OBJECTIVE

To investigate if in patients with PSC and inflammatory bowel disease (IBD), daily low dose aspirin lowers the risk of PSC related cancer/high grade dysplasia, liver decompensation, the need for liver transplantation and all-cause mortality, compared to placebo, over a minimum 5-year period.

2.2 PRIMARY ENDPOINTS

The composite primary endpoints are defined as occurrence of any of the following:

- Hepatobiliary cancer (including gallbladder cancer/high grade dysplasia, pancreas, cholangiocarcinoma [CCA] or hepatocellular [HCC]) or colorectal cancer/high grade dysplasia
- Listing for Liver transplantation
- All-cause mortality

2.3 SECONDARY OBJECTIVE:

Safety and tolerability of aspirin in patients with PSC-IBD and effect on quality of life using disease specific questionnaires.

2.4 SECONDARY ENDPOINTS

1. To investigate gastrointestinal bleeding risk ((Common Terminology Criteria for Adverse Events (CTCAE) grade 3 or 4)) between daily low dose aspirin and placebo in patients with PSC-IBD
2. Progressive liver disease, as evidenced by either ascites, variceal bleeding (any site), hepatic encephalopathy (investigator discretion) or development of cirrhosis with Child Pugh B or C stage
3. To investigate the rates of referral for liver transplantation between daily low dose aspirin and placebo in patients with PSC-IBD
4. To investigate the rates of acute cholangitis between daily low dose aspirin and placebo in patients with PSC-IBD
5. To investigate IBD flare frequency between daily low dose aspirin and placebo in patients with PSC-IBD
6. To investigate the rates colonic surgery/resection for severe IBD between daily low dose aspirin and placebo in patients with PSC-IBD
7. To investigate the quality of life between daily low dose aspirin and placebo in patients with PSC-IBD using disease specific questionnaires.

2.5 TRANSLATIONAL RESEARCH OBJECTIVES:

To collect, store and analyse clinical and radiological data, genomic deoxyribonucleic acid (DNA), serum, cell free DNA and urine samples.

2.6 TRANSLATIONAL RESEARCH OUTCOMES

To develop a prospective clinical, imaging and specimen biobank of samples from patients with PSC-IBD to allow future studies to be undertaken in which the performance of novel diagnostic biomarkers for the early detection and prognostication of PSC related cancer will be determined.

2.7 SUB-STUDY OBJECTIVE:

To assess safety, pregnancy outcome and acceptability of the intervention in pregnant women.

2.8 ADDED BENEFIT:

To create and develop pan-UK PSC bioresource for translational research to help improve the clinical care of patients with PSC.

The timepoint of evaluation of all endpoints are over a minimum period of 5 years of follow up. Please see table in section 5.6.

3 STUDY DESIGN

This study will be performed at approximately 60 investigational sites in the United Kingdom. This is a randomised, double-blind, multicentre, placebo-controlled study performed with a 2:1 randomisation ratio of Aspirin vs placebo. Participants will be randomised to one of 2 treatments, as shown in Table 3.2. Aspirin or placebo will be administered in single oral dose of 75 mg once per day for 5 years.

3.1 DESIGN

The Asp-PSC study will be a prospective, multicentre, Phase III double-blind, randomised controlled trial across the UK. **The intervention will be 75mg OD of aspirin** versus placebo. The study will be coordinated by the ICTU. Patients that have a diagnosis of large duct PSC of at least greater than one year in duration and IBD will be invited to take part. For the purpose of this study the time of diagnosis will be from when they had a confirmatory diagnostic investigation i.e., MRCP, ERCP, percutaneous transhepatic cholangiogram (PTC) or liver biopsy.

The study will randomise participants in a 2:1 ratio of aspirin vs placebo. The choice of randomisation ratio design was guided by our Patient and Public Involvement and Engagement (PPIE) group. The PPIE group advocated that such design will increase interest in participation in the study, as the probability of getting the active intervention (low dose aspirin) is higher than getting the placebo.

Recruitment will be completed within 5 years, with a minimum required participant follow up of 5 years. An embedded feasibility phase will be included to establish recruitment and acceptability and determine continuation of funding.

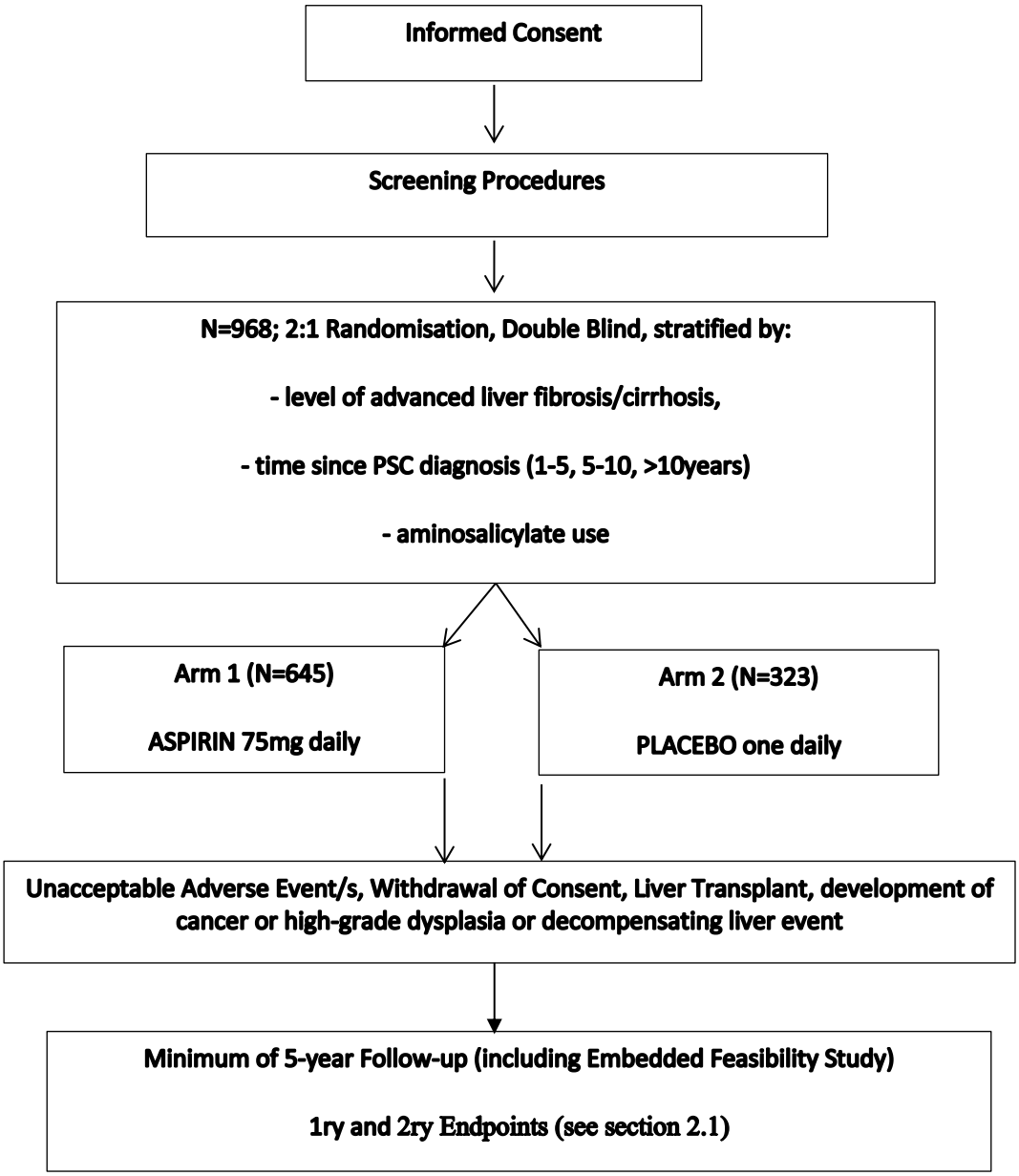
Randomisation will be stratified by fibrosis stage (as determined by Enhanced Liver Fibrosis (ELF) markers and/or fibroscan; if ELF and Fibroscan scores are concordant, the

ELF test will be utilised), time since PSC diagnosis (as determined by 1-5 years, 5-10 years or >10 years), and concomitant aminosalicylate use.

3.2 TREATMENT REGIMENS

Treatments	Estimated number of *participants* needed to detect the predefined effect size	Number of participants to be recruited including a 20% drop out
Aspirin	516	645
Placebo	258	323
Total number of *participants*	774	968

3.3 STUDY FLOW CHART SUMMARY



4 PARTICIPATION ENTRY

4.1 STUDY SETTING AND POPULATION

The patients proposed in this study will be enrolled from NHS hospitals trusts in the UK who form part of the established NIHR Liver Clinical Research Network BASL-SIG for Immune-Mediated Liver Disease. The Asp-PSC study will be done in conjunction/parallel with the prospective observational UK-PSC registry study to maximise patient recruitment.

UK-PSC was initially a large NIHR study set up by Dr Rushbrook in 2008 to look at the genetics of PSC. In this study, UK-PSC established a pan-UK patient cohort that led to several large genetic studies being undertaken in PSC along with high level clinical phenotyping data. Over 2,900 PSC patients have so far consented and been recruited to this project. This covers over 190 NHS trusts. We intend to directly approach PSC leads where these patients are seen. We anticipate at least 30% of these Trusts will recruit patients to this trial and therefore plan to have 60 active sites. To support recruitment, PSC Support (the UK patient organisation for people affected by PSC) will share information about the study to the PSC community through their dedicated research news bulletins and online patient support group of 3,300 members.

In the set-up phase of this trial the investigator team will continue the already begun series of preliminary meetings with recognised UK PSC investigators from various NHS sites from around the UK. Following on from this, the Asp–PSC study managerial team will set up the study with the local Research and Development team. Given the nature of this trial we will aim to do this across 60 NHS trusts, around 40% of the sites that have recruited to the UK-PSC network. Table 4.2 summarises the anticipated numbers of centres, and expected enrolment, and Figure 2 graphs the projected recruitment over 5 years. Patients recruited in the first year’s feasibility stage (see section 4.2) will be included in the final analysis.

4.2 ANTICIPATED NUMBERS OF CENTRES AND EXPECTED ENROLMENT

Year	Number of Centres (cumulative)	Type and number of Centres opened	No. patients enrolled (cumulative)
1	10	Transplant Centres (N=5) Tier 2 Liver Centres (N=5)	80
2	30	Transplant Centres (N=5) Tier 2 Liver Centres (N=10) Other Centres (N=15)	300
3	40	Transplant Centres (N=5) Tier 2 Liver Centres (N=15) Other Centres (N=20)	500
4	60	Transplant Centres (N=5) Tier 2 Liver Centres (N=20) Other Centres (N=35)	750
5	60	Transplant Centres (N=5) Tier 2 Liver Centres (N=20) Other Centres (N=35)	968

There will be **no exceptions** (waivers) to eligibility requirements at the time of enrolment. Questions about eligibility criteria should be addressed **prior** to attempting to enrol the participant.

The eligibility criteria for this trial have been carefully considered and are the standards used to ensure that only medically appropriate participants are entered. Participants not meeting the criteria should not be entered into the trial for their safety and to ensure that the trial results can be appropriately used to make future treatment decisions for other people with similar diseases or conditions. It is therefore vital that exceptions are not made to these eligibility criteria.

Participants will be considered eligible for enrolment in this trial if they fulfil all the inclusion criteria and none of the exclusion criteria as defined below.

4.3 INCLUSION/EXCLUSION CRITERIA

4.3.1 The Inclusion Criteria:

1. Age 18 years or above
2. Able to give written and informed consent.
3. Must have an established clinical diagnosis of large duct PSC-based on a standard disease definition of typical cholangiography findings on endoscopic retrograde cholangiography (ERCP) or magnetic resonance cholangiography (MRCP).
4. An established diagnosis of concomitant colonic IBD either in a pattern of Ulcerative Colitis, Crohn’s disease or IBD unclassified.
5. Patients must be at least one-year post PSC diagnosis.
6. If pre-treated with ursodeoxycholic acid (UDCA) – UDCA therapy should remain at a stable dose for 12 weeks prior to screening, and not exceeding 20mg/kg/day.

7. Must have had a colonoscopy within the last year of randomisation date as part of routine clinical care. If not this must be done within the screening interval.
8. If a patient has cirrhosis, they must have undertaken a hepatobiliary ultrasound (US), MRCP scan, magnetic resonance imaging (MRI) liver or regional computerised tomography (CT) scan within 6 months of screening date as part of routine clinical care. If not, this must be done within the screening interval.
9. If non-cirrhotic, then the patient must have had an US, MRCP, dynamic MRI or regional CT within the last 12 months as part of routine clinical care. If not, this must be done within the screening interval.

4.3.2 The Exclusion Criteria:

1. Evidence of concomitant disease(s) that causes secondary sclerosing cholangitis.
2. Evidence of any of the following diseases: IgG4 related disease, PBC, acute or chronic viral hepatitis, alcohol-related liver disease, Wilson disease, Budd-Chiari syndrome, portal vein thrombosis, alpha-1-antitrypsin disease, hepatic sarcoidosis, cystic fibrosis, Progressive familial intrahepatic cholestasis (PFIC), hereditary haemochromatosis, non-alcoholic steatohepatitis (NASH) – those with simple hepatic steatosis without evidence of NASH or liver fibrosis secondary to fatty liver disease are allowed to participate, other metabolic liver disease, active malignancy in the last five years (except treated/excised non-melanomatous skin cancer).
3. Have a previous diagnosis of colorectal cancer, cholangiocarcinoma, gallbladder cancer at any time point.
4. Has received a liver transplant, has been referred for liver transplant assessment, or is listed for a liver transplant.
5. Had any of the following procedures: colonic resection of any nature, including those with a defunctioning ostomy.
6. Consume more than the recommended allowance of 14 units of alcohol per week (as set out by the Department of Health).
7. Current or recent participation in any other clinical trial of an investigational medicinal product (CTIMP) within the last 6 weeks prior to first dose of aspirin/placebo
8. Already taking aspirin.
9. History of non-variceal upper gastrointestinal (GI) bleeding within one year.
10. A history of congestive cardiac failure.
11. A known diagnosis of glucose-6 -phosphate dehydrogenase.
12. Childs Pugh B or C cirrhosis
13. Untreated thyrotoxicosis or hypothyroidism
14. Familial history of a hereditary cancer syndrome, or confirmed genetic predisposition that heightens cancer risk.
15. Vaccination for varicella zoster in the six weeks prior to screening period
16. Known allergy to aspirin
17. A history of NSAID/ aspirin induced asthma and nasal polyps
18. Concurrently taking non-steroidal anti-inflammatory drugs (NSAIDs) in the four weeks prior to screening
19. History of haemophilia and/or other bleeding disorders where aspirin is contraindicated
20. Taking other anti-platelet or anti-coagulant medication (e.g., clopidogrel, prasugrel, warfarin, apixaban, rivaroxaban, dabigatran or therapeutic heparin preparations)
21. Active, or history of recurrent peptic ulcer

22. Patients who are suffering from gout
23. Severe renal impairment
24. Taking methotrexate at a dose of >15mg/week
25. Taking selective serotonin-reuptake inhibitors

5 PROCEDURES AND MEASUREMENTS

5.1 IDENTIFICATION OF RECRUITMENT AND PARTICIPANTS

Patients will be identified by the local PI who will be responsible for the study conduct at each site and by their associated investigator team as determined by the local study delegation log.

Patients will be identified by means of the following ways:

1) From local clinic lists

2) From lists of patients identified by the British Association of the Study of the liver/BSG PSC UK Audit

3) From lists of patients held by UK-PSC for the local site.

4) From clinics in a prospective manner

Local PIs and the central team will have ethical permission to write to patients to invite them to take part in the study locally. Once randomised patients (following signed consent and undertaking a defined 60-day screening period) will be called at one month following collection visit. This study visit will be to ensure drug tolerability and check no immediate adverse events. After this time point, patients will be seen at 6 monthly intervals (5 months after month 1 visit, then 6 monthly thereafter) in alignment with routine clinical care during which a research visit will be undertaken.

5.2 SCREENING AND PRE-RANDOMISATION EVALUATIONS

Written informed consent to enter and be randomised into the trial must be obtained from participants after explanation of the aims, methods, benefits and potential hazards of the trial and **before** any trial-specific procedures are undertaken. The only procedures that may be performed in advance of written informed consent being obtained are those that would be performed on all patients as a usual standard of care e.g., annual colonoscopy for IBD, fibroscan, liver imaging and routine biochemical or haematological analysis.

5.2.1 Screening assessments

1. Confirmation the patient has consented.
2. Confirmation that the patient meets both the inclusion and exclusion criteria.
3. Confirmation that the patient has had a colonoscopy within the last 12 months with either random biopsies or dye surveillance.
4. Confirmation that if the patient is cirrhotic (defined by either liver histology, imaging features, or vibration controlled transient elastography (VCTE) (KPa >14.4)), the patient has a liver USS or CT/dynamic MRI/MRCP within the last 6 months.
5. Confirmation that if the patient is non-cirrhotic, they have undergone a form of liver imaging (either US, MRI liver with contrast, MRCP or regional CT) with in the last year of randomisation date.
6. Determine of liver fibrosis by, Fibroscan or ELF testing.
7. Documentation of past medical history
8. Documentation of prescribed medication

9. Documentation of demographics
10. Documentation of vital signs
11. Documentation of height and weight
12. Documentation of adverse events
13. Questionnaires: PSC-PRO, SF-36, 5D-Itch Scale, and SIBDQ, PRO-2 and PSC CLDQ-PSC
14. Routine NHS blood tests (FBC, UE, LFT, GGT, AST, CRP, INR, Vitamin D, CA19.9, AFP, B12, ferritin and a TSH and T4
15. Physical examination
16. Research blood and urine samples.
17. ERCP/ Spyglass Cholangioscopy result collection.

5.3 RANDOMISATION AND BLINDING

In this study patients will be randomised to aspirin or placebo in a 2:1 ratio, in a double blinded manner. Within this study a small number of factors have been preidentified that will need to be controlled for in the randomisation process. We therefore utilise randomisation stratified by degree of fibrosis (binary, as determined by ELF score >9.8, OR Fibroscan score of >9.6 Kpa), disease duration (as determined by 1-5 years, 5-10 years or >10 years) and concurrent use of aminosalicylates (yes or no). Once the patient has been randomised they will be asked to attend a collection visit for collection of aspirin/placebo.

5.4 CODE BREAKING/UNBLINDING

The investigator has the primary right to break blind to treat participant in emergency situations, and have access for rapid unblinding. The opinion to break the blind is with the investigator, and that the investigator does not need to discuss with the sponsor .

If a local investigator is required to unblind the patient, this can be done within the electronic case report form (eCRF) in case of an emergency with additional help provided by the ICTU Study Manager. Unblinding should generally only be considered in the event of medical or safety needs (for example, an operation is required, or an overdose has been taken) where knowledge of the participant's treatment allocation could change clinical management. Following unblinding, the reason for the decision to unblind and the relevant parties must be documented in the participant's medical record and on the Unblinding CRF. Treatment identification information should be kept confidential and should be disseminated only to those individuals that must be informed for medical management of the participant. If a participant requires unblinding, for example due to an upper GI bleed, they will have reached an end point and come off the trial. Their data will be used in the final analysis. An unblinding manual will be provided to sites to instruct on the unblinding process.

5.5 UNBLINDING

In most acute clinical situations, it should be possible to clinically manage a participant by assuming they have been taking 75mg of aspirin daily and/or by subsequently withholding the trial medication if appropriate. Nonetheless, there may be occasional clinical circumstances where knowledge of treatment allocation is essential to help guide urgent clinical management. If unblinding is considered, this should first be discussed with the Trials Unit and/or the local trial Principal Investigator wherever possible.

5.5.1 Gastrointestinal bleeding

Participants suspected of having a gastrointestinal bleed should have their trial medication stopped and should be managed according to standard local pathways. Standard treatment for gastrointestinal bleed should be initiated without delay and the patient should be managed by assuming they have been taking aspirin 75mg daily. It is not expected that emergency unblinding should be necessary in such events. Nonetheless, if a situation arises where knowledge of the trial treatment allocation would alter the immediate clinical management of a participant, this should be confirmed by the relevant specialist locally and unblinding can be performed.

5.5.2 Haemorrhagic Stroke / Intracranial Haemorrhage

Participants suspected of having an intracranial haemorrhage should have their trial medication withheld and should undergo appropriate neuroimaging and clinical management without delay. If the diagnosis is confirmed, then the trial medication should be stopped. It is not expected that emergency unblinding will be necessary in the event of an intracranial haemorrhage, however if a situation arises where knowledge of the trial treatment allocation would alter the immediate clinical management of a participant, this should be confirmed by the relevant specialist locally and unblinding can be performed. It should be noted that trial medication can be withheld for up to 3 months while decisions about subsequent management are confirmed. To discuss individual cases please contact the Asp-PSC team at the CCTS during working hours.

5.5.3 Ischaemic Stroke / Transient Ischaemic Attack (TIA)

The treatment of an ischaemic stroke or TIA frequently involves the use of aspirin and/or other anti-platelet medication. Standard treatment for an ischaemic stroke or TIA should be initiated without delay, and this may include administration of standard doses of anti-platelet therapy, including aspirin, where indicated. It is possible that a trial participant may have taken up to a maximum of 75mg of aspirin earlier that day but, under most circumstances, we expect the risks of not treating an ischaemic stroke or TIA to outweigh the potential risks of a higher cumulative dose of aspirin over one day, however local clinical judgement should be exercised. It is not expected that emergency unblinding will be necessary in the event of an ischaemic stroke or TIA, however if a clinical situation arises where knowledge of the trial treatment allocation would alter the immediate clinical management of a participant, this should be confirmed by the relevant specialist locally and unblinding can be performed. It should be noted that trial medication can be withheld for up to 3 months while decisions about subsequent management are confirmed. To discuss individual cases with the trial's vascular advisors please contact the Asp-PSC team at the Trials Unit during working hours.

5.5.4 Surgery

When a surgical intervention is planned, anti-platelet therapy is often withheld temporarily. Trial treatment can be withheld for up to 3 months but please ensure that the Trials Unit is informed. For participants who require emergency surgery, where knowledge of treatment allocation would alter immediate surgical management, this should be confirmed by the surgical team involved locally and unblinding can be performed.

5.6 VISIT SCHEDULE

The table below shows an outline of the proposed study visit schedule.

Study Period Screening →

Time-point → Assessments ↓	Day-0-60	Collection	Week 4 (month 1)	Every 24 Weeks(+ 14 days)	Every 52 weeks (+/-8 weeks)	End of Treatment: 28 days	Yearly follow up for 5 years post EOT
Randomisation	X						
Informed Consent	X						
Medical History	X		X	X		X	
Demographics	X						
Vital Signs (Body temperature, pulse rate, respiration rate, blood pressure)	X		X[6]	X		X	
Height	X						
Weight	X			X		X	
Targeted Physical Exam (if clinically indicated)	X		X[6]	X		X	
Haematology including coagulation[1]	X		X	X			
Biochemistry[1]	X		X	X			
LFTs including AST if locally available[1]	X		X	X			
Tumour markers Ca 19-9, AFP[1]	X			X			
Adverse Events	X		X	X			
Concomitant Medications	X		X	X		X	
QOL Assessments (PSC-PRO, SF-36, 5D-Itch Scale, SIBDQ, CLDQ-PSC and PRO-2)	X		X	X		X	
Research Urine Sample Collection	X			X			
Research Blood Collection	X			X			
US/Dynamic MRI Liver/Dynamic CT within 6 months of randomisation date	X[2]						

US liver, MRCP or dynamic MRI/CT within 12 months of randomisation date	X[3]						
US/MRI/MRCP/CT at follow up				X[2]	X[3]		
ERCP/Spyglass Cholangioscopy result collection[4]	X			X		X	
Colonoscopy	X[5]				X		
Record of treatment endpoints and survival				X		X	X
Non-invasive assessment of liver fibrosis (serum ELF test)	X						
UKELD Score	X			X			
Stool sample for faecal calprotectin					X		
Fibroscan result collection if available [5]	X			X			
Collection of aspirin/placebo		X[7]		X			

1. *Only collect bloods if this is standard of care, if not please use last set of bloods for the eCRF*
2. *Cirrhosis only Patient*
3. *Patient without Cirrhosis*
4. *As per standard of care*
5. *If locally available, use last scan available from 12 months of randomisation date.*
6. *Patient may have assessment if clinically needed after month one phone call.*
7. *Participant's Contact Card and Questionnaires for one month visit should also be given.*

5.7 FOLLOW-UP

After successful randomisation, patients will attend a collection visit for collection of aspirin/placebo, please ensure the participant contact's card is given and the questionnaires to be completed at month one phone call.

Patients will be called at month one, 4 weeks after the collection visit. The first month's phone call will be to ensure drug tolerability and check no immediate adverse events.

During the month one phone call, the patients will be asked to for:

1. Medical History
2. Review of Haematology including FBR and INR test if locally available
3. Review of Biochemistry including UE, LFT, GGT, AST, CRP, Vitamin D, B12, ferritin, TSH and T4 and if locally available
4. Adverse Events
5. Concomitant Medications

6. QOL Assessments (PSC-PRO, SF-36, 5D-Itch Scale, SIBDQ, PRO-2 and CLDQ-PSC)

During the one-month phone call patients may be required to attend an in person visit if clinically required to assess further adverse event reporting, this will be decided by a delegated member of staff responsible for patient care. The following assessments will be conducted:

1. Vital Signs (Body temperature, pulse rate, respiration rate, blood pressure-if clinically indicated))
2. Targeted Physical Exam (if clinically indicated)

After this time point, patients will be seen at 6 monthly intervals (5 months after month 1 phone call, then 6 monthly thereafter) ideally in alignment with routine clinical care during which a research visit will be undertaken.

During each 6-month visit, the patients will be asked to:

1. Documentation of medical history
2. Documentation of vital signs (Body temperature, pulse rate, respiration rate, blood pressure)
3. Weight measurement
4. Targeted Physical Exam (if clinically indicated)
5. Undertake standard of care National Health Service (NHS) blood tests (Full Blood Count (FBC), Urea and Electrolytes (U&E), liver biochemistry, gamma-glutamyl transferase (GGT), aspartate aminotransferase (AST), C-Reactive Protein (CRP), International Normalised Ratio (INR), Vitamin D, Cancer Antigen 19.9 (CA19.9), Alpha-fetoprotein (AFP), B12, ferritin and a TSH and T4). Standard of care faecal calprotectin measurement will be taken yearly. Stool tests will be taken to the local GP for processing. Results should be sent to referring hospital.
6. Adverse event documentation
7. Compete questionnaires: Primary Sclerosing Cholangitis -Patient reported outcome (PSC PRO), Short Form-36 (SF-36), 5D-Itch Scale, and Short Inflammatory bowel disease questionnaire (SIBDQ), PRO-2 (Patient Reported Outcome-2) and Chronic Liver Disease Questionnaire (CLDQ)-PSC. Questionnaires can be taken home to do. If Questionnaires are not brought to clinic, site will need to ask patient to complete questionnaires on the day of visit.
8. Documentation of Concomitant Medications
9. Urine and blood samples taken (if patient consented to this).
10. Body mass index (BMI) measurement recorded.
11. Patients will also be asked about their alcohol and smoking habits.
12. A fibroscan will also be undertaken if locally available.
13. Documentation of UKELD Score
14. Note will be made of any intervening cancer diagnosis, decompensating liver events or referral for liver transplantation.

15. Note will also be made of any colonoscopy undertaken and also the histological findings from that examination. Note will also be made of any endoscopic intervention/ cholecystectomy or new cancer diagnosis made.
16. Note will also be made of any recent imaging studies the patients have undergone, the results available from these studies and multidisciplinary team (MDT) outcomes.
17. Collection of aspirin/placebo tablets

Certain assessments will be required every 12 months following standard of care practice:

1. US/MRI/MRCP/CT at follow up if the patient does not have Cirrhosis
2. Data from colonoscopy
3. Stool sample for faecal calprotectin test

An end of treatment visit will be performed 28 days after last study dose:

4. Documentation of medical history
5. Documentation of vital signs (Body temperature, pulse rate, respiration rate, blood pressure)
6. Weight measurement
7. Targeted Physical Exam (if clinically indicated)
8. Documentation of Concomitant medication
9. QOL Assessments (PSC-PRO, SF-36, 5D-Itch Scale, SIBDQ, CLDQ-PSC and PRO-2)
10. ERCP/Spyglass Cholangioscopy result collection as standard of care.
11. Record of treatment endpoints and survival

5.7.1 Laboratory Evaluations

The blood tests (FBC, UE, LFT, GGT, AST, CRP, INR, Vitamin D, CA19.9, AFP, B12, ferritin and TSH and T4) will be performed locally and the results will be recorded on the eCRF.

The conduct of these analyses will be in accordance to the local NHS laboratory and accredited pathology service. These will be performed if these bloods are standard of care, ELF testing will be conducted at screening and sent to a central laboratory for testing at iQur and results will be sent back to the local site. This will also be used centrally for the randomisation process. Full instructions will be provided in a laboratory manual.

11ml of blood will be taken at screening visit and 43ml of blood will be taken every 6 month follow up for 5 years. 10ml of Urine samples will be taken at screening visit and every 6 months for 5 years. These will be collected in accordance to the separate laboratory manual. These will be stored at participating sites at -80 degrees Celsius and shipped annually on dry ice to the Norwich Biorepository. Biosamples will be made accessible to other research groups via an application process. Patients may choose not to donate research samples but still remain on the trial. A serum sample will be sent to iQur for ELF testing. This is not an optional sample.

i) **Haematology**: This will include local labs for FBC and INR at standard of care visits.

ii) **Biochemistry:** This will include U&E, Liver function tests, GGT, aspartate transaminase, CRP, vitamin D, CA19.9, AFP, B12 a ferritin and TSH and T4 at standard of care visits.

iii) **Research Urine sample**: A urine sample is to be performed in all participants at screening and each study visit in accordance with the laboratory manual. Samples will be collected and stored at -80 degrees in accordance with the laboratory manual. Samples will be shipped annually to the Norwich Biorepository.
iv) **Faecal calprotectin samples** will be taken every 12 months. Measurements of faecal calprotectin will be performed using local/site-specific hospital laboratory assays.

In all cases, patients will be consented for the **collection and use of their biological samples** and a full chain of custody will be maintained for all samples throughout their lifecycle. The Investigator at each site is responsible for maintaining a record of full traceability of biological samples collected from patients while these are in storage at the site, either until shipment or disposal. Any person(s) responsible for temporarily holding samples, e.g. sub-contracted service provider must keep full traceability of samples from initial receipt of sample to further shipment or disposal (as appropriate).

Norwich Research Park Biorepository will keep overall oversight of research Biosamples the entire lifecycle through internal procedures and monitoring of study sites. iQur will keep oversight of the ELF testing sample.

5.8 INCIDENTAL FINDINGS

Any incidental findings will be identified and reviewed and acted upon by the local PI who will determine if they should be handled and investigated by the local clinical team, a different secondary NHS team or passed to the primary care team.

6 TREATMENTS

6.1 TREATMENT ARMS

Within this study an oral formulation of enteric coated aspirin will be compared to placebo (manufactured so that it looks identical) by the designated provider. IMP will be dispensed in bottles. The medication will be distributed to participating sites via processes managed by ICTU during the screening period with the patient being randomised ahead of collection visit. The IMP will be manufactured under Good Manufacturing Practice by The Royal Free Hospital Pharmacy. Currently the legal status of aspirin is licensed for approval in the UK. For the purposes of this trial the Summary of product characteristics (SmPC) will be used for regulatory approval.

A list of side effects can be found in appendix 9 in SmPC.

6.2 LABELLING AND PACKAGING

The IMP will be packaged and labelled in bottles ahead of distribution of participating sites. The label will contain:

- Manufacturing Import Authorisation (MIA) (IMP)
- For Clinical Trials Use Only
- Aspirin EC 75mg/Placebo Tablets
- Store at Room Temperature, under 25°C
- 92 Tablets
- Asp-PSC Trial
- IRAS Number:
- Sponsor:
- Principal Investigator:
- Site Name/Number:
- Subject ID/Randomisation ID:
- Batch Number:
- Expiry:
- Kit Number:
- For Oral Use only
- Internal Label code:
- Date dispensed:
- Keep out of reach and sight of children

6.3 STORAGE AND DISPENSING

Information regarding storage and dispensing will be found in the IMP manual provided to sites.

6.4 DOSAGE, DURATION AND COMPLIANCE

The IMP will be taken once a day in the morning or evening with a glass of water. The IMP will be taken orally. All IMP compliance will be recorded daily in a patient diary. The

compliance of the drug will be checked at each 6-monthly visit, where the number of tablets left in the boxes will be manually counted and recorded in the eCRF. Post study (5 years) the IMP will be withdrawn.

6.5 ACCOUNTABILITY

The IMP is only to be prescribed by the PI or delegated investigator and dispensed by delegated members of the research team at the participating site for participants within the trial as specified in this protocol. ICTU will facilitate IMP shipment to participating sites via the distributor. A full accountability trail of the trial medication will be maintained from receipt at the participating site until destruction.

6.6 DRUG INTERACTIONS

See appendix 9 for drug interactions.

6.6.1 Contraindicated Medications

Patients should not take any of the following contraindicated medications whilst taking aspirin/placebo:

- Concurrent use of other antiplatelet or anticoagulant agents
- Methotrexate at doses of more than 15mg/week
- Uricosuric agents such as probenicid and sulfinpyrazone
- Selective serotonin reuptake inhibitors
- NSAIDs

6.6.2 Need to prescribe concurrent oral corticosteroids

If patient who has been enrolled into this study needs corticosteroids prescribing, they should be assumed to be taking aspirin as their IMP. All patients therefore prescribed oral corticosteroids should be co-prescribed a proton pump inhibitor (or Histamine 2 Receptor blocker if intolerant) as prophylaxis against Gastrointestinal bleeding for the duration that corticosteroid is prescribed.

6.7 DOSE MODIFICATIONS FOR ADVERSE EVENTS

This is not applicable in this study.

6.8 OVERDOSE OF IMP

Although considerable inter-individual variations are involved, it can be considered that the toxic dose of aspirin is about 200 mg/kg in adults. The lethal dose of acetylsalicylic acid is 25-30 grams. Salicylate poisoning is usually associated with plasma concentrations >350 mg/L (2.5 mmol/L). Plasma concentrations above 500 mg/l in adults generally cause severe toxicity. Most adult deaths occur in patients whose concentrations exceed 700 mg/L (5.1 mmol/L). Single doses less than 100 mg/kg are unlikely to cause serious poisoning.

Plasma salicylate concentrations should be measured urgently for patients who are thought to have ingested more than 125 mg/kg of aspirin. The sample should be taken at least 2 hours (symptomatic patients) or 4 hours (asymptomatic patients) after ingestion, since it may take several hours for peak plasma concentrations to occur **and up to 12 hours for enteric-coated preparations.** A repeat sample should be taken in ALL symptomatic patients and those with concentrations greater than 500 mg/L after a further 2 hours because of the possibility of continuing absorption. Under these circumstances, measurements should be repeated every 3 hours until concentrations are falling.

6.8.1 Symptoms

Common features include vomiting, dehydration, tinnitus, vertigo, deafness, sweating, warm extremities with bounding pulses, increased respiratory rate and hyperventilation. Some degree of acid-base disturbance is present in most cases.

A mixed respiratory alkalosis and metabolic acidosis with normal or high arterial pH (normal or reduced hydrogen ion concentration) is usual in adults. Acidosis may increase salicylate transfer across the blood brain barrier.

Uncommon features include haematemesis, hyperpyrexia, hypoglycaemia, hypokalaemia, thrombocytopaenia, increased INR/PTR, intravascular coagulation, renal failure and non-cardiac pulmonary oedema.

Other symptoms may include: headache, nausea, or abdominal pain.

Central nervous system features including confusion, restlessness, hallucinations, disorientation, coma, cardiovascular collapse, respiratory arrest and convulsions are less common in adults than in children.

If a toxic dose has been ingested, hospital admission is required.

Activated charcoal should be given if a patient presents within one hour of ingestion of more than 250 mg/kg. The plasma salicylate concentration should be measured, although the severity of poisoning cannot be determined from this alone and the clinical and biochemical features must be considered. Elimination is increased by urinary alkalinisation, which is achieved by the administration of 1.26% sodium bicarbonate. The urine pH should be monitored. Correct metabolic acidosis with intravenous 8.4% sodium bicarbonate (first check serum potassium). Forced diuresis should not be used since it does not enhance salicylate excretion and may cause pulmonary oedema.

Haemodialysis is the treatment of choice for severe poisoning and should be considered in patients with plasma salicylate concentrations >700 mg/L (5.1 mmol/L), or lower concentrations associated with severe clinical or metabolic features. Patients over 70 have increased risk of salicylate toxicity and may require dialysis at an earlier stage.

Other symptoms should be treated symptomatically.

6.9 PERMANENT DISCONTINUATION OF STUDY TREATMENT

Participants may discontinue study treatment for the following reasons:

- At the request of the participant

- Adverse Event/ Serious Adverse Event
- Allergic reaction to IMP
- If the investigator considers that a participant's health will be compromised due to adverse events or concomitant illness that develop after entering the study.
- In the event they are prescribed another anti-platelet agent or anti-coagulant

The primary reason for discontinuation must be recorded in the eCRF and the patient's medical records. If a participant chooses to discontinue their trial treatment, they should continue to be followed up as according to the schedule defined in the protocol. Every effort should be made to encourage participants not to withdraw from the study.

6.9.1 Withdrawal from Study

Withdrawal from the study refers to discontinuation of study treatment and study procedures and can occur for the following reasons:

- Participant decision
- Investigator Decision
- Loss to follow-up
- Death

Data will still be collected for participants for follow up unless they withdraw from further data collection.

If a participant dies whilst participating in the study, a 'Statement of Death' eCRF must be completed. The following information will be collected: date of death, cause of death and if the death is related to disease.

6.9.2 Procedures for Withdrawal from Study

In the event of a patient withdrawing from the study, no further visits or follow up will be conducted. The primary reason must be recorded in the eCRF and the patient's medical records. Any data and samples already collected will be retained and analysed.

Where a patient has been lost to follow-up, this should be recorded on the eCRF with their last known contact date and survival status at the time. If appropriate, patients who withdraw will be replaced.

6.9.3 Temporary Discontinuation of IMP in the study

Patients will be allowed to discontinue their IMP for up to a 3-month period if required for clinical reasons, for example the need for surgery or if they become pregnant and wish to discontinue the IMP for the first trimester, and then continue for a total of five years follow-up.

7 PHARMACOVIGILANCE

7.1 ADVERSE EVENT (AE)

An AE is any untoward medical occurrence in a patient or clinical trial participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the trial medication, whether or not considered related to the IMP.

7.2 ADVERSE REACTION (AR)

All untoward and unintended responses to an IMP related to any dose administered. All AEs judged by either the reporting investigator or the sponsor as having reasonable causal relationship to a medicinal product qualify as adverse reactions (ARs). The expression of reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

7.3 UNEXPECTED ADVERSE REACTION

An AR, the nature or severity of which is not consistent with the applicable product information as set out in the Reference Safety Information (RSI) i.e. summary of product characteristics (SmPC).

When the outcome of the adverse reaction is not consistent with the applicable product information this adverse reaction should be considered as unexpected. **Side effects documented in the RSI section of the SmPC which occur in a more severe form than anticipated are also considered to be unexpected.**

Expectedness assessment will be performed by the Sponsor or person delegated by the Sponsor to assess expectedness.

For this study this will be the local PI who makes a determination of this.

7.4 CAUSALITY

The assignment of causality for adverse events should be made by the investigator responsible for the care of the participant using the definitions in the table below.

If any doubt about the causality exists, the local investigator should inform ICTU who will notify the Chief Investigator. The pharmaceutical companies and/or other clinicians may be asked to advise in some cases.

In the case of discrepant views on causality between the investigator and others, all parties will discuss the case. In the event that no agreement is made, the Medicines and

Healthcare Products Regulatory Agency (MHRA) will be informed of both points of view. For the purpose of causality, the following definitions will be used.

Unrelated: No evidence of any causal relationship
Unlikely: There is little evidence to suggest there is a causal relationship (e.g., the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment).
Possible: There is some evidence to suggest a causal relationship (e.g., because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g., the patient's clinical condition, other concomitant treatments).
Probable: There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Definite: There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

7.5 SEVERITY OF ADVERSE EVENTS

Severity of AEs will be assessed using the grading scales found in the National Cancer Institute CTCAE version 5.0 (27th November 2017), by attributing the most relevant CTCAE term, Grade 1 = Mild, Grade 2 = Moderate, Grade 3 = Severe, Grade 4 = Life Threatening and Grade 5 = Death. Where it is not possible to attribute a specific CTCAE term, a term may be attributed by the investigator and assessed according to the introduction under Grades in CTAE version 5.0 i.e., grade 1=mild; grade 2=moderate; grade 3=severe; grade 4=life-threatening; grade 5= fatal.

CTCAE version 5.0 is accessible online here:
https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm

7.6 ADVERSE EVENT RECORDING

All AEs should be recorded in the patient's medical notes and entered into the eCRF within 10 days.

Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical trial participant administered a medicinal product and which does not necessarily have a causal relationship with this product.
Adverse Reaction (AR)	Any untoward and unintended response to an investigational medicinal product related to any dose administered/trial treatment

Unexpected Adverse Reaction (UAR)	An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator's Brochure for an unauthorised product or summary of product characteristics (SPC) for an authorised product or treatment
Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)	Any AE or AR that at any dose: • results in death • is life threatening* • requires hospitalisation or prolongs existing hospitalisation** • results in persistent or significant disability or incapacity • is a congenital anomaly or birth defect • or is another important medical condition***
* The term life threatening here refers to an event in which the patient is at risk of death at the time of the event; it does not refer to an event that might hypothetically cause death if it was more severe (e.g., a silent myocardial infarction) ** Hospitalisation is defined as an in-patient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisation for pre-existing conditions (including elective procedures that have not worsened) do not constitute an SAE *** Medical judgement should be exercised in deciding whether an AE or AR is serious in other situations. Important AEs or ARs that may not be immediately life threatening or result in death or hospitalisation, but may seriously jeopardise the participant by requiring intervention to prevent one of the other outcomes listed in the table (e.g., a secondary malignancy, an allergic bronchospasm requiring intensive emergency treatment, seizures or blood dyscrasias that do not require hospitalisation, or development of drug dependency).	

If the event is classified as 'serious' then an SAE form must be completed within the eCRF within 24 hours of the site becoming aware.

Severity or grading of Adverse Events
The severity of all AEs in this trial should be graded using the adverse event gradings in v5.0 CTCAE criteria.

For the purposes of the study, AEs will be followed up according to local practice until the event has stabilised or resolved, or the Follow-up Visit, whichever is sooner. SAEs will be recorded up to 28 days after the last study dose.

7.7 ABNORMAL LABORATORY TEST RESULTS

All clinically important abnormal laboratory test results occurring during the study will be recorded as adverse events. The clinically important abnormal laboratory tests will be repeated at appropriate intervals until they return either to b or to a level deemed

acceptable by the investigator and the clinical monitor, or until a diagnosis that explains them is made.

7.8 SERIOUS ADVERSE EVENTS (SAE)

7.8.1 Definition of SAE

An SAE is defined as any event that

- Results in death;
- Is life-threatening*;
- Requires hospitalisation or prolongation of existing inpatient's hospitalisation**;
- Results in persistent or significant disability or incapacity;
- Is a congenital abnormality or birth defect;

* "Life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
** "Hospitalisation" means any unexpected admission to a hospital department. It does not usually apply to scheduled admissions that were planned before study inclusion or visits to casualty (without admission).
Medical judgement should be exercised in deciding whether an adverse event/reaction is serious in other situations. Important adverse events/reactions that are not immediately life-threatening, or do not result in death or hospitalisation but may jeopardise a subject, or may require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious.

7.9 REPORTING OF SAES

Rapid reporting of all SAEs i.e., within 24 hours of the site becoming aware, occurring during the study must be performed as detailed in the study-specific pharmacovigilance manual.

SAE will be reported from time of randomisation until 28 days after last study dose.

Active monitoring of participants after the end of the trial is not required but if the investigator becomes aware of safety information that appears to be drug related, involving a participant who participated in the study, even after an individual participant has completed the study, this should be reported to the Sponsor.

All SAEs will be reviewed by the Chief Investigator or a designated medically qualified representative to confirm expectedness and causality.

Reporting of SAEs and review by the CI will be via the trial data collection system (eCRF).

Please note that for the purposes of the trial that the development of a PSC related cancer, hepatic decompensation, flare of IBD activity and cholangitis are expected events during the natural history of the disease. These are not considered AEs but will be recorded on the checklist and eCRF.

7.10 DEFINITION OF A SERIOUS ADVERSE REACTION (SAR)

A SAR is defined as a SAE that is judged to be related to any dose of study drug administered to the participant.

7.10.1 Definition of Suspected Unexpected Serious Adverse Reaction (SUSAR)

Any SAR that is NOT consistent with the applicable product information as set out in the Reference Safety Information (RSI) section of the Investigator Brochure (IB) or Summary of Product Characteristics (SPC).

7.10.2 Reporting of SUSARs

SUSARs should be notified to the appropriate **regulatory authority, the relevant REC and the Sponsor in accordance with regulatory requirements**. SUSARs which are fatal or life-threatening will be reported not later than seven days after alerting the sponsor to the reaction. Any additional relevant information will be sent within eight days of the report.

A SUSAR which is not fatal or life-threatening will be reported within 15 days of first knowledge by the sponsor. The sponsor will inform all investigators about SUSARs occurring on the study. This will be by means of email to all study investigators.
Follow up of participants who have experienced a SUSAR should continue until recovery is complete or the condition has stabilised. SUSAR reports should be unblinded prior to submission.

7.11 DEVELOPMENTAL SAFETY UPDATE REPORTS / ANNUAL SAFETY REPORTS

Developmental Safety Update Reports (DSUR) / Annual Safety reports will be submitted to the Sponsor, the Ethics Committee and Regulatory Authority in accordance with local / national regulatory requirements.

7.12 PREGNANCY

At the IMP dose used there is no need to avoid or use additional contraception for this study. There are convincing data to show that low-dose aspirin (150 or 75mg daily) protects against severe pre-eclampsia and foetal growth restriction if commenced before 16 weeks' gestation (27)(28). Furthermore, a meta-analysis of eight RCTs that gave low-dose aspirin before 14 weeks to 7564 participants compared to 7670 participants that served as controls reported no significant difference in the rate of congenital malformations (29). Thus participants planning pregnancy, or those who become pregnant will not be asked to stop treatment, although they may stop taking the study drug before 11 weeks if they elect to do this. Pregnancy outcome data relating to maternal disease severity and maternal and fetal outcomes will be collected from trial participants. Participants can also continue to breastfeed if they wish to do so.

If a patient on trial becomes pregnant, they should be referred to the Obstetric Team for enhanced antenatal care in line with UK clinical practice for women with chronic liver disease.

7.13 REPORTING URGENT SAFETY MEASURES

If any urgent safety measures are taken the CI/Sponsor shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the MHRA and the relevant REC of the measures taken and the circumstances giving rise to those measures.

8 STATISTICAL ANALYSES

8.1 DESIGN

This study will be a multicentre, double-blind, randomised placebo-controlled trial. The study population will include patients with PSC who have a concurrent diagnosis of IBD and are at least 12 months post diagnosis of PSC. Patients will be randomised in a ratio of 2:1 Aspirin vs Placebo. Accrual will be over 5 years, with a minimum participant follow up of 5 years. Included in this study is an embedded feasibility study for 12 months from the start of recruitment to establish recruitment, acceptability and compliance rates. Randomisation will be stratified by the following factors: 1) degree of fibrosis (binary, as determined by ELF score >9.8, OR Fibroscan score of 9.6 kPA), disease duration (as determined by 1-5 years, 5-10 years or >10 years) and concurrent use of aminosalicylates (yes or no).

8.2 SAMPLE SIZE AND POWER CONSIDERATIONS

774 patients need to be recruited to the trial (2:1 randomisation) to allow us to detect, with 80% power (alpha 0.05), a HR of 0.6, equivalent to a difference between groups of 6% in the proportion of patients experiencing any of the components of the primary outcome, namely a new cancer diagnosis, or requiring liver transplant or any cause mortality. The intervention:placebo ratio is 2:1, meaning we will need to recruit 516 participants in the intervention group and 258 in the placebo group. This is based on an estimated event rate in the control group of 15% at 5 years (2), 5 years of accrual and 5 years of minimum follow up. To allow for 20% loss to follow up, we have determined we will need to recruit 968 patients.

8.3 PLANNED RECRUITMENT RATE

See section 4.2 for recruitment table.

8.4 STATISTICAL ANALYSIS

A Statistical Analysis Plan (SAP) will be written and approved before data lock. This document will outline all analyses for all the outcomes listed in the Protocol.

8.5 ANALYSIS OF PRIMARY AND SECONDARY OUTCOMES

Summaries of continuous variables will be presented as mean and standard deviations if normally distributed, and as medians and inter-quartile ranges for skewed data. Categorical variables will be presented as frequencies and percentages in the form of summary tables. Time to event endpoints will be graphically displayed using Kaplan-Meier curves comparing treatment groups. Median time to event and 2-sided 95% confidence intervals will be reported. All statistical tests will be two-tailed with a 5% significance level. A Cox proportional hazard model will be used to estimate the HR between the two groups. The model will be adjusted by the randomisation stratification factors and centre. If the assumption for the Cox model are not met we will use an alternative model.

8.6 PRIMARY EFFICACY OUTCOME ANALYSIS

The composite primary endpoint is defined as occurrence of any of the following components:

1. Hepatobiliary cancer (including gallbladder cancer/high grade dysplasia, pancreatic cancer, cholangiocarcinoma [CCA] or HCC) or colorectal cancer/high grade dysplasia
2. Liver transplantation
3. All-cause mortality

Using the Kaplan-Meier method, curves for the combined event free survival (where events are cancer/high grade dysplasia need of liver transplant and overall mortality will be presented for each treatment arm, with time from randomisation until the first failure event. The primary inferential comparison between treatment groups will estimate the HR with 95% CI. The HR will be estimated using a Cox proportional hazards model adjusted by the stratification factors, if the proportional hazard assumptions are met. If the proportional hazard assumptions are not met alternative methods will be used to estimate the difference between groups.

8.7 SECONDARY OUTCOMES' ANALYSIS

Secondary endpoints include GI bleeding, progressive liver disease, IBD flares including the need for colectomy, referral for liver transplantation, acute cholangitis and quality of life.

This will be done by using the chi-squared test and logistic regression adjusted by stratification factors and other pre-defined factors. Quality of life data will be analysed using a mixed regression model, adjusted by stratification factors and other predefined factors, to take into account the repeated measures in time.

A Statistical Analysis Plan (SAP) will be written ahead of looking at the data, and will be signed off by the research team and shared with the DMEC and TSC.

8.8 MISSING DATA

Appropriate methods of imputation will be used to deal with missing data, if the missing data are more than 20%. Details of the type of analysis will be included in the SAP.

9 REGULATORY, ETHICAL AND LEGAL ISSUE

9.1 DECLARATION OF HELSINKI

The investigator will ensure that this study is conducted in full conformity with the 1964 Declaration of Helsinki and all subsequent revisions.

9.2 GOOD CLINICAL PRACTICE

The study will be conducted in accordance with the guidelines laid down by the International Conference on Harmonisation for Good Clinical Practice (ICH GCP E6 guidelines).

9.3 RESEARCH ETHICS COMMITTEE (REC) APPROVAL

9.3.1 Initial Approval

Prior to the shipment of IMP and the enrolment of participants, the REC must provide written approval of the conduct of the study at named sites, the protocol and any amendments, the Participant Information Sheet and Consent Form, any other written information that will be provided to the participants, any advertisements that will be used and details of any participant compensation.

9.3.2 Approval of Amendments

Proposed amendments to the protocol and aforementioned documents must be submitted to the REC for approval. Amendments requiring REC approval may be implemented only after a copy of the REC's approval letter has been obtained.

Amendments that are intended to eliminate an apparent immediate hazard to participants may be implemented prior to receiving Sponsor or REC approval. However, in this case, approval must be obtained as soon as possible after implementation.

Amendments to the Protocol and other documents (e.g., changes to eligibility criteria, outcomes, sample size calculations, analyses) will be agreed by the TMG. Such amendments will be forwarded to the Sponsor for confirmation as to whether it is either substantial or non-substantial and will then be submitted to the Health Research Authority or Ethics Committee for categorisation and approval.

Once the amendment has been categorised it will be sent to relevant sites for consideration in accordance with standard HRA processes and timescales. Amendments must not be implemented until HRA approval is received and sites have either confirmed

acceptance or, no objection has been received within the defined timescale. Notification will be sent by CTS to trial personnel to confirm when an amendment can be implemented.

9.3.3 Annual Progress Reports

Annual Progress Reports will be submitted to the Research Ethics Committee (REC) and the Sponsor in accordance with local / national requirements. The Annual Progress Report will also detail all SAEs recorded.

9.3.4 End of Trial Notification

The REC will be informed about the end of the trial, within the required timelines.

The end of trial notification will be submitted within 90 days of the end of trial definition being met. In the event of a premature halt of the trial, the timeframe is 15 days, and the reasons should be clearly explained in the notification.

9.4 REGULATORY AUTHORITY APPROVAL

The study will be performed in compliance with United Kingdom regulatory requirements. Clinical Trial Authorisation from the appropriate Regulatory authorities must be sought prior to the start of the study. In addition, the Regulatory Authority must approve amendments prior to their implementation (as instructed by the Sponsor), receive SUSAR reports and annual safety updates and be notified of the end of the trial. This study has Clinical Trials Authorisation from the UK Competent Authority; MHRA. **Reference: tbc**

9.5 HRA APPROVAL

HRA approval will be obtained prior to starting the study. Each participating site will confirm capacity and capability prior to commencing. The HRA and all participating sites also need to be notified of all protocol amendments to assess whether the amendment affects the institutional approval for each site.

9.6 NON-COMPLIANCE AND SERIOUS BREACHES

All protocol deviations and protocol violations will be reported via the eCRF and reviewed by the Chief Investigator and reported to the ICTU Quality Assurance (QA) Manager on a monthly basis. Protocol violations will be reported to the Sponsor. An assessment of whether the protocol deviation/violation constitutes a serious breach will be made.

A serious breach is defined as:

- A breach of the conditions and principles of GCP in connection with a trial or the trial protocol, which is likely to affect to a significant degree:
- The safety or physical or mental integrity of the UK trial participants; or
- The overall scientific value of the trial

The Sponsor will be notified within 24 hours of identifying a likely Serious Breach. If a decision is made that the incident constitutes a Serious Breach, this will be reported to the MHRA and REC within 7 days of becoming aware of the serious breach.

9.7 INSURANCE AND INDEMNITY AND SPONSOR

For the purposes of this trial the sponsor will be:
Imperial College London
Research Governance and Integrity team
Room 221, Medical School Building
St Marys Campus, Norfolk Place
London W2 1PG
United Kingdom

Please note that Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study.

Delegated responsibilities will be assigned to the NHS trusts taking part in the trial.

9.8 TRIAL REGISTRATION

The study will be registered on the following trial databases in accordance with requirements of the International Committee of Medical Journal Editors (ICMJE) regulations:

• Cancer Research UK

• ISRCTN

9.9 INFORMED CONSENT

Patients will be provided with a Patient Information Sheet (PIS) and given time to read it fully. Following a discussion with a medical qualified investigator, any questions will be satisfactorily answered and if the participant is willing to participate, written informed consent will be obtained. During the consent process it will be made completely and unambiguously clear that the participant is free to refuse to participate in all or any aspect of the trial, at any time and for any reason, without incurring any penalty or affecting their treatment.

Consent will be re-sought if significant information becomes available that affects the participant's consent in any way. This will be documented in a revision to the patient information sheet and the participant will be asked to sign an updated consent form. These will be approved by the ethics committee prior to their use.

Informed consent will be obtained either in person by a member of the research team at the affiliated NHS site using a paper consent form.

9.10 CONTACT WITH GENERAL PRACTITIONER

The local PI or delegated member of staff will send a copy of a participation letter to the patients GP. This will inform the GP that the participant is taking part in the study, provided the participant agrees to this, and information to this effect is included in the Participant Information Sheet and Informed Consent. A copy of the letter should be filed in the Investigator Site File.

9.11 PARTICIPANT CONFIDENTIALITY

The investigator must ensure that the participant's confidentiality is maintained. On the eCRF or other documents submitted to the Sponsors, participants will be identified by a participant ID number only. Documents that are not submitted to the Sponsor (e.g., signed informed consent form) should be kept in a strictly confidential file by the investigator.

The investigator shall permit direct access to participants' records and source documents for the purposes of monitoring, auditing, or inspection by the Sponsor, authorised representatives of the Sponsor, NHS, Regulatory Authorities and RECs.

9.12 DATA PROTECTION AND PARTICIPANT CONFIDENTIALITY

The investigators and study site staff will comply with the requirements of the Data Protection Act 2018 concerning the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

9.13 END OF TRIAL

For the purposes of this clinical trial, the end of the trial will be when the last participant has completed 5 years follow up since the date of randomisation and the final end of trial visit.

9.14 STUDY DOCUMENTATION AND DATA STORAGE

The investigator must retain essential documents until notified by the Sponsor, and for at least ten years after study completion. Participant files and other source data (including copies of protocols, original reports of test results, IMP dispensing logs, correspondence, records of informed consent, and other documents pertaining to the conduct of the study) must be retained. Documents should be stored in such a way that they can be accessed/data retrieved at a later date. Consideration should be given to security and environmental risks.

No study document will be destroyed without prior written agreement between the Sponsor and the investigator. Should the investigator wish to assign the study records to another party or move them to another location, written agreement must be obtained from the Sponsor.

10 DATA MANAGEMENT

10.1 SOURCE DATA

The following source data will be recorded in this study:

- Medical records
- Laboratory reports
- Diaries and questionnaires
- IMP documentation
- Radiological imaging and reports
- Colonoscopy reports and histology reports
- Scan reports
- ELF Results
- Questionnaires

Please note that all of these will need to be recorded on the eCRF.

Copies of standard of care scans completed from randomisation to the end of trial will be collected and sent to Norfolk and Norwich NHS Foundation Trust for storage.

10.2 LANGUAGE

eCRFs will be in English. Generic names for concomitant medications should be recorded in the eCRF wherever possible. All written material to be used by participants must use vocabulary that is clearly understood and be in the language appropriate for the study site.

10.3 DATABASE

Data will be captured using the electronic Case Report Form (eCRF). Data will be entered under the study ID onto the eCRF held on servers based at ICTU. Access to the database will be via unique, individually assigned (i.e. not generic) usernames and passwords, and only accessible to members of the Asp-PSC trial team, and external regulators if requested. The servers are protected by firewalls and are patched and maintained according to best practice. The physical location of the servers is protected physically and environmentally in accordance with ICTU SOPs.

The database software provides a number of features to help maintain data quality, including maintaining an audit trail, allowing custom validations on all data, allowing users to raise data query requests, and search facilities to identify validation failure/ missing data.

After completion of the trial the database will be retained on the servers of ICTU for on-going analysis of secondary outcomes.

The identification, screening and enrolment logs, linking participant identifiable data to the study ID, will be held locally by the trial site. This will either be held in written form in a

locked filing cabinet or electronically in password protected form on hospital computers. After completion of the trial the identification, screening and enrolment logs will be stored securely by the sites for 10 years unless otherwise advised by ICTU.

10.4 DATA COLLECTION

Full details of data collection will be documented in a data management plan approved prior to study opening. Details of procedures for eCRF completion will be provided in a study manual.

10.5 ARCHIVING

All trial documentation, including that held at participating sites and ICTU, will be archived for a minimum of 10 years following the end of the study.

11 STUDY MANAGEMENT STRUCTURE

11.1 TRIAL STEERING COMMITTEE

An independent Trial Steering Committee (TSC) will be convened including as a minimum an independent Chair, independent clinician, independent statistician and two lay members. The role of the TSC is to provide overall supervision of trial conduct and progress. Details of membership, responsibilities and frequency of meetings will be defined in a separate Charter.

11.2 TRIAL MANAGEMENT GROUP

A Trial Management Group (TMG) will be convened including the Chief Investigators, co-investigators and key collaborators, trial statistician/s, ICTU Study Manager, ICTU Operations Manager and the PPIE leads. The TMG will be responsible for day-to-day conduct of the trial and operational issues. Details of membership, responsibilities and frequency of meetings will be defined in separate terms of Reference.

11.3 INDEPENDENT DATA MONITORING COMMITTEE

An Independent Data Monitoring Committee (IDMC) will be convened including as a minimum an independent Chair, independent clinician and independent statistician. The role of the IDMC is to monitor the efficacy and safety of study data and report its findings to the TSC. Details of membership, responsibilities and frequency of meetings will be defined in a separate Charter.

11.4 EARLY DISCONTINUATION OF THE STUDY

It is possible that the study will require early discontinuation e.g., on IDMC recommendation to the TSC. Were this to occur then the relevant actions would be completed by ICTU, to include management of patients on active study treatment and informing the Sponsor, REC and MHRA.

11.5 RISK ASSESSMENT

A study-specific risk assessment will be performed prior to the start of the study to assign a risk category of 'low', 'medium' or 'high' to the trial. Risk assessment will be carried out by the ICTU QA Manager in collaboration with the ICTU Study Manager and the result will be used to guide the monitoring plan. The risk assessment will consider all aspects of the study and will be updated as required during the course of the study.

11.6 MONITORING

The study will be monitored periodically by trial monitors to assess the progress of the study, verify adherence to the protocol, ICH GCP E6 guidelines and other national/international requirements and to review the completeness, accuracy and consistency of the data.

11.6.1 Central Monitoring at ICTU

Trial staff will review eCRF data for errors and missing key data points. The trial database will also be programmed to generate reports on errors and error rates. Essential trial issues, events and outputs, including defined key data points, will be detailed in the Asp-PSC trial Data Management Plan.

11.6.2 On-site Monitoring

The frequency, type and intensity of routine and triggered on-site monitoring will be detailed in the Asp-PSC Monitoring Plan. The Monitoring Plan will also detail the procedures for review and sign-off of monitoring reports. In the event of a request for a trial site inspection by any regulatory authority, ICTU must be notified as soon as possible.

11.6.2.1 Direct access to participant records

Participating investigators must agree to allow trial related monitoring, including audits, REC review and regulatory inspections, by providing access to source data and other trial related documentation as required. Participant consent for this must be obtained as part of the informed consent process for the trial.

11.7 QUALITY CONTROL AND QUALITY ASSURANCE

Quality Control will be performed according to ICTU internal procedures. The study may be audited by a Quality Assurance representative of the Sponsor and/or ICTU. All necessary data and documents will be made available for inspection. The study may be participant to inspection and audit by regulatory bodies to ensure adherence to GCP and the NHS Research Governance Framework for Health and Social Care (2nd Edition).

11.8 PEER REVIEW

This protocol was generated from an original grant application which was peer reviewed by CRUK, ahead of the decision to grant funding, by three experts in the field of PSC and CCA. The protocol was also endorsed and reviewed by all members of the TMG.

11.9 PUBLIC INVOLVEMENT

11.9.1 Patient and Public Involvement and Engagement (PPIE)

The PPIE for this study has been by undertaken by Martine Walmsley (PSC patient/ PSC Support); and Helen Morement, Founder and CEO of AMMF – The Cholangiocarcinoma Charity. PSC Support and AMMF are national charities, helping people affected by PSC and CCA through education, support, advocacy and research. Martine and Helen are the PPIE leads for the study. They have been extensively involved in planning this proposal from the conception of the idea. PSC Support highlighted that one of the most difficult aspects of living with PSC for patients is the emotional impact, particularly uncertainty about the future and that reducing cancer risk was very important to people affected by PSC.

The PPIE members have extensive experience: working directly with patients at risk of and living with PSC cancers, running research focus groups for patients and loved ones, working with Healthcare/Research teams including developing and supporting novel research proposals and study protocols, collating feedback from and disseminating research findings to patients, and helping to develop national clinical practice guidelines (including for PSC, CCA and liver transplantation).

They have been extensively involved in developing this proposal from conception so that we could draw on experiences and views of people affected by the risk of PSC-related cancers when planning the trial design. The PPIE leads and affected patients met monthly over two years to understand patient priorities (including the realities of cancer risk and the importance of reducing that risk from a patient perspective), appetite for taking part in longer studies, developing the trial design to ensure it was acceptable to patients, and understanding any concerns.

The PSC Support charity carried out a national survey of almost 200 PSC patients to gauge interest and availability for this trial (https://www.pscsupport.org.uk/surveys/aspirin-to-prevent-cancer-in-psc). The survey found that the majority of patients:

i) believe it is ‘extremely important’ to reduce cancer risk for people with PSC (90%)
ii) would be interested in taking part in a 5-year study (86%), and
iii) are not already taking aspirin (87%)

The PPIE members have been integral to our planning and advised on:

- Randomisation ratio (to give participants a higher chance of receiving active drug than placebo)
- Recruitment strategy (for example, what aspects of the design would be appealing or a barrier to participation; appetite for participation in trials)
- Inclusion and exclusion criteria

- Patient Reported Outcome Measures (which tools were preferred by PSC patients following previous focus group work by PSC Support and their willingness to regularly complete multiple questionnaires)
- Relevant outcomes (including utilising this opportunity to collect longitudinal data from PSC patients for future biomarker discovery as there are currently no convincing surrogate endpoints for clinical trials).

11.9.2 Patient & Public Involvement & Engagement (PPIE) Lead

The ICTU Study Manager will act as PPIE Lead along with Martine Walmsley and Helen Morement. Tailored training and support will be given to the leads by the ICTU PPIE Coordinator. The PPIE Leads will undertake a number of activities including: developing role descriptions with PPIE Advisory Group; supporting PPIE training needs; acting as PPIE liaison; ensuring involvement is aligned to UK Standards for Public Involvement; providing impact feedback on activities; planning meetings and keeping a PPIE impact log**.**

11.9.3 PPIE Collaboration Plan

In addition to our two PPIE Co-Investigators who are embedded as part of the main Investigator Team and Trial Management Group (TMG) for the life of the trial, two people living with PSC will be members of the Trial Steering Committee.

Given the length of the trial and the nature of PSC, membership may change as some members become too sick to participate. Membership will be drawn from PSC Support's ongoing network of patients and loved ones from across the UK who are interested in being involved in research. Lay Trial Steering Committee members will join with different needs and levels of expertise, knowledge and experience, and the PPIE Lead will offer tailored training and support to members to build skills and confidence as and when required. People at risk of developing PSC cancers are a diverse population and the aim is to reflect that so that a wide range of views and perspectives are heard. To that end, focus groups will be used when necessary and collect and review optional demographic data, addressing any under-represented groups.

Allowing meeting attendance via teleconferencing widens participation as it allows people to join from all corners of the UK, including those who are clinically vulnerable to COVID. We will send printed materials to those who need them and liaise by phone call if Zoom is not accessible for some members. One lay member of the public will sit on the Independent Data Monitoring Committee. They will be recruited from the People in Research and Cancer Research UK networks.

PPIE will be engaged to contribute to activities at the following milestones:
Trial Set-Up

- Review of key sections of the protocol to identify preventable barriers to recruitment and retention.
- Assist in the development of patient facing materials, such as the recruitment documents, Patient Information Sheet (PIS) and consent form to ensure ease of understanding and use of appropriate language (online focus group activity).

Ongoing Trial

- Review recruitment rate and provide feedback on the recruitment strategy as part of the Trial Steering Committee.
- Review lay interim reports (if there are any) and changes to any patient-facing documentation or communications (online focus group activity).

Trial End

- Review and assist in the development of key messages and the final lay report for dissemination to participants, the public and PSC patients including producing engaging media such as infographics and videos (online focus group activity).
- Advise on key messages and dissemination avenues (online focus group activity).

With the support of the ICTU Study Manager and Chief Investigator, the PPIE leads will prepare background pre-reading for any focus groups required and the draft the documents for review. Using online focus groups will help us to ensure a diverse range of patients' perspectives are considered throughout trial life cycle. The PPIE leads will also support the team at Investigator Meetings by providing the patient perspective on the study.

11.9.4 PPIE Evaluation and Feedback

A detailed log of PPIE activities and their impact will be kept throughout trial, to enable evaluation of PPIE impact. The log will include PPIE trial aims; PPIE methods used; PPIE results (positive/negative); extent that PPIE influenced the trial and a reflection on progress. Impact feedback to TSC and focus group members will be given throughout trial to keep engagement and motivation levels high and also after trial involvement has concluded. This feedback summary will include suggestions made; how suggestions were taken on board and overall impact on the trial.
The ICTU study manager has considerable experience working as PPIE liaison for clinical trials, supporting patients who wish to act as PPIE collaborators for trial groups and focus groups. Further support will be provided by the PPIE Lead/Chief Investigator where needed.

11.10 PUBLICATION AND DISSEMINATION POLICY

The results will be available as a lay summary (available to download or view), produced in collaboration with our PPIE members as well as links to the Open Access scientific, peer-reviewed publications. Results will also be shared by the patient organisations, PSC Support and AMMF, via their newsletters, social media and Patient Information Days and conferences.

Information concerning the study, patent applications, processes, scientific data or other pertinent information is confidential and remains the property of the Sponsor. The investigator may use this information for the purposes of the study only.

It is understood by the investigator that the Sponsor will use information developed in this clinical study in connection with the development of the IMP and, therefore, may disclose it as required to other clinical investigators and to Regulatory Authorities. In order to allow the use of the information derived from this clinical study, the investigator understands that

he/she has an obligation to provide complete test results and all data developed during this study to the Sponsor.

Verbal or written discussion of results prior to study completion and full reporting should only be undertaken with written consent from the Sponsor.

Therefore, all information obtained because of the study will be regarded as CONFIDENTIAL, at least until appropriate analysis and review by the investigator(s) are completed.

A Clinical Study Report summarising the study results will be prepared and submitted to the REC within a year of the end of study.

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13 REVISION HISTORY

Version	Date	Summary of changes
1.0	23/08/2023	N/A
2.0	20/10/2023	• Exclusion Criteria updated • Contraindicated section updated • Pregnancy section updated • Unblinding section updated

14 SIGNATURE PAGE 1 (CHIEF INVESTIGATORS)

The signature below constitutes approval of this protocol by the signatory, on behalf of the Protocol Development Group, and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol including all statements regarding confidentiality.

Study Title: Asp-PSC Trial: Effect of Aspirin on Reducing Cancer & Improving Outcomes in Primary Sclerosing Cholangitis

Protocol Number: C/45/2022

Signed: _____

Professor Shahid Khan

Date: _____

Signed: _____

Dr Simon Rushbrook

Date: _____

15 SIGNATURE PAGE 2 (SPONSOR)

The signature below constitute approval of this protocol by the signatory.

Study Title: Asp-PSC Trial: Effect of Aspirin on Reducing Cancer & Improving Outcomes in Primary Sclerosing Cholangitis

Protocol Number: C/45/2022

Signed: _____

Keith Boland
Imperial College London
Research Governance and Integrity team
Room 221, Medical School Building
St Marys Campus, Norfolk Place
London W2 1PG
United Kingdom

Date: _____

16 SIGNATURE PAGE 3 (STATISTICIAN)

The signature below constitute approval of this protocol by the signatory.

Study Title: Asp-PSC Trial: Effect of Aspirin on Reducing Cancer & Improving Outcomes in Primary Sclerosing Cholangitis

Protocol Number: C/45/2022

Signed: _____

Dr Francesca Fiorentino
King's College London

Date: _____

17 SIGNATURE PAGE 4 (PRINCIPAL INVESTIGATOR)

The signature of the below constitutes agreement of this protocol by the signatory and provides the necessary assurance that this study will be conducted at his/her investigational site according to all stipulations of the protocol including all statements regarding confidentiality.

Study Title: Asp-PSC Trial: Effect of Aspirin on Reducing Cancer & Improving Outcomes in Primary Sclerosing Cholangitis

Protocol Number: C/45/2022

Address of Institution: _____

_____

_____

Signed: _____

Print Name and Title: _____

Date: _____

18 APPENDICES

Appendix 1: PSC-PRO (26)

The PSC-PRO is a validates disease specific questionnaire frequently employed in clinical trials of patients with PSC to derive quality of life outcomes. It covers 29 items across two main outcomes: 'symptoms' and 'impact of symptoms'.

Module 1 – PSC Symptoms

Scores: 0 = "no symptoms" to 10 = "symptoms as bad as you could imagine"; recall period 24 hours.

1. Are you currently experiencing a flare-up of your PSC symptoms (also known as acute cholangitis or an infection in the bile ducts)? *Y/N*
2. Over the past 24 hours, how bad was the pain in your upper abdomen due to PSC at its worst?
3. Over the past 24 hours, how bad was the discomfort in your upper abdomen due to PSC at its worst?
4. Over the past 24 hours, how bad was your itching at its worst?
5. Over the past 24 hours, how bad was your physical tiredness at its worst?
6. Over the past 24 hours, how bad was the yellowing of your eyes or skin at its worst?
7. Over the past 24 hours, how bad was your difficulty concentrating at its worst?
8. Over the past 24 hours, how bad was your nausea at its worst?
9. Over the past 24 hours, how bad was your mental tiredness at its worst?
10. Over the past 24 hours, how bad was the darkening (brown or tea color) of your urine at its worst?
11. Over the past 24 hours, how bad were your fever (high temperature) symptoms?
12. Over the past 24 hours, how bad were your chills?
13. Over the past 24 hours, how bad were your sweats?

Module 2 - Impacts of Symptoms

Scores: 1 = "Never" to 5 = "Always"; recall period 7 days.

Physical Function

1. Over the past 7 days, how often was it difficult for you to go up or down stairs because of your PSC?
2. Over the past 7 days, how often did you have to rest or take breaks because of your PSC?
3. Over the past 7 days, how often were you limited in what you could do physically because of your PSC?
4. Over the past 7 days, how often was it difficult for you to lift or carry objects because of your PSC?

Activities of Daily Living

5. Over the past 7 days, how often was it difficult for you to complete household chores because of your PSC?
6. Over the past 7 days, how often did you have difficulty falling or staying asleep because of your PSC?
7. Over the past 7 days, how often was it difficult to run errands or get things done outside the home because of your PSC?
8. Over the past 7 days, how often did you avoid certain foods because of your PSC?

Work Productivity

9. Are you currently employed or self-employed? *Y/N (if N then skip the section)*
10. Over the past 7 days, how often did PSC interfere with your productivity at work?
11. Over the past 7 days, how often did you limit your hours at work because of your PSC?
12. Over the past 7 days, how often was it an extra effort to do your work because of your PSC?
13. Over the past 7 days, how often was it difficult to concentrate on your work because of your PSC?

Role Function

14. Over the past 7 days, how often did you need to ask for help around your home because of your PSC?
15. Over the past 7 days, how often did you feel like a burden on your family because of your PSC?
16. Over the past 7 days, how often were you limited in the activities you could do with your family because of your PSC?
17. Over the past 7 days, how often was it difficult to enjoy time with your family because of your PSC?

Emotional Impact

6

18. Over the past 7 days, how often were you worried about your health because of your PSC?
19. Over the past 7 days, how often were you depressed about your health because of your PSC?
20. Over the past 7 days, how often did you feel emotional stress because of your PSC?

21. Over the past 7 days, how often did you feel scared about the future because of your PSC?

Social/Leisure Impact

22. Over the past 7 days, how often did you limit your social activities because of your PSC?
23. Over the past 7 days, how often did you limit the things you did for enjoyment because of your PSC?
24. Over the past 7 days, how often did you isolate yourself from other people because of your PSC?
25. Over the past 7 days, how often did you have limited energy for sexual activity because of your PSC?

Quality of Life

26. Over the past 7 days, how often was it difficult to work towards your goals in life because of your PSC?
27. Over the past 7 days, how often were you unable to enjoy life because of your PSC?
28. Over the past 7 days, how often did you feel like you missed out on meaningful activities because of your PSC?
29. Over the past 7 days, how often did you feel discouraged about your quality of life because of your PSC?

Appendix 2: SF-36

SF-36 QUESTIONNAIRE

Name:_____ **Ref. Dr:**_____ **Date:** _____
ID#: _____ **Age:** _____ **Gender: M / F**

Please answer the 36 questions of the **Health Survey** completely, honestly, and without interruptions.

GENERAL HEALTH:
In general, would you say your health is:
Excellent Very Good Good Fair Poor
Compared to one year ago, how would you rate your health in general now?
Much better now than one year ago
Somewhat better now than one year ago
About the same
Somewhat worse now than one year ago
Much worse than one year ago
LIMITATIONS OF ACTIVITIES:

The following items are about activities you might do during a typical day. Does your health now limit you in these
activities? If so, how much?
Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports.
Yes, Limited a lot Yes, Limited a Little No, Not Limited at all
Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf
Yes, Limited a Lot Yes, Limited a Little No, Not Limited at all
Lifting or carrying groceries
Yes, Limited a Lot Yes, Limited a Little No, Not Limited at all
Climbing several flights of stairs
Yes, Limited a Lot Yes, Limited a Little No, Not Limited at all
Climbing one flight of stairs
Yes, Limited a Lot Yes, Limited a Little No, Not Limited at all
Bending, kneeling, or stooping
Yes, Limited a Lot Yes, Limited a Little No, Not Limited at all
Walking more than a mile
Yes, Limited a Lot Yes, Limited a Little No, Not Limited at all
Walking several blocks
Yes, Limited a Lot Yes, Limited a Little No, Not Limited at all
Walking one block
Yes, Limited a Lot Yes, Limited a Little No, Not Limited at all
Bathing or dressing yourself
Yes, Limited a Lot Yes, Limited a Little No, Not Limited at all

PHYSICAL HEALTH PROBLEMS:
During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as
a result of your physical health?
Cut down the amount of time you spent on work or other activities
Yes No
Accomplished less than you would like
Yes No
Were limited in the kind of work or other activities

Yes No
Had difficulty performing the work or other activities (for example, it took extra effort)
Yes No

EMOTIONAL HEALTH PROBLEMS:
During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as
a result of any emotional problems (such as feeling depressed or anxious)?
Cut down the amount of time you spent on work or other activities
Yes No
Accomplished less than you would like
Yes No
Didn't do work or other activities as carefully as usual
Yes No

SOCIAL ACTIVITIES:
Emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?
Not at all Slightly Moderately Severe Very Severe
PAIN:
How much bodily pain have you had during the past 4 weeks?
None Very Mild Mild Moderate Severe Very Severe
During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the
home and housework)?
Not at all A little bit Moderately Quite a bit Extremely

ENERGY AND EMOTIONS:
These questions are about how you feel and how things have been with you during the last 4 weeks. For each
question, please give the answer that comes closest to the way you have been feeling.
Did you feel full of pep?
All of the time
Most of the time
A good Bit of the Time
Some of the time
A little bit of the time
None of the Time
Have you been a very nervous person?
All of the time
Most of the time
A good Bit of the Time
Some of the time
A little bit of the time
None of the Time
Have you felt so down in the dumps that nothing could cheer you up?
All of the time
Most of the time
A good Bit of the Time
Some of the time
A little bit of the time
None of the Time
Have you felt calm and peaceful?

All of the time
Most of the time
A good Bit of the Time
Some of the time
A little bit of the time
None of the Time
Did you have a lot of energy?
All of the time
Most of the time
A good Bit of the Time
Some of the time
A little bit of the time
None of the Time
Have you felt downhearted and blue?
All of the time
Most of the time
A good Bit of the Time
Some of the time
A little bit of the time
None of the Time
Did you feel worn out?
All of the time
Most of the time
A good Bit of the Time
Some of the time
A little bit of the time
None of the Time
Have you been a happy person?
All of the time
Most of the time
A good Bit of the Time
Some of the time
A little bit of the time
None of the Time
Did you feel tired?
All of the time
Most of the time
A good Bit of the Time
Some of the time
A little bit of the time
None of the Time

SOCIAL ACTIVITIES:
During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with
your social activities (like visiting with friends, relatives, etc.)?
All of the time
Most of the time
Some of the time
A little bit of the time
None of the Time
GENERAL HEALTH:
How true or false is each of the following statements for you?

I seem to get sick a little easier than other people
Definitely true Mostly true Don't know Mostly false Definitely false
I am as healthy as anybody I know
Definitely true Mostly true Don't know Mostly false Definitely false
I expect my health to get worse
Definitely true Mostly true Don't know Mostly false Definitely false
My health is excellent
Definitely true Mostly true Don't know Mostly false Definitely false

Appendix 3 5-D Pruritus scale (25):

5-D Pruritus Scale

1. **Duration:** During the last 2 weeks, how many hours a day have you been itching?

Less than 6hrs/day	6-12 hrs/day	12-18 hrs/day	18-23 hrs/day	All day
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. **Degree:** Please rate the intensity of your itching over the past 2 weeks

Not present	Mild	Moderate	Severe	Unbearable
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. **Direction:** Over the past 2 weeks has your itching gotten better or worse compared to the previous month?

Completely resolved	Much better, but still present	Little bit better, but still present	Unchanged	Getting worse
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

4. **Disability:** Rate the impact of your itching on the following activities over the last 2 weeks

	Never affects sleep	Occasionally delays falling asleep	Frequently delays falling asleep	Delays falling asleep and occasionally wakes me up at night	Delays falling asleep and frequently wakes me up at night
Sleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

	N/A	Never affects this activity	Rarely affects this activity	Occasionally affects this activity	Frequently affects this activity	Always affects this activity
Leisure/Social	☐	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Housework/ Errands	☐	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Work/School	☐	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. **Distribution:** Mark whether itching has been present in the following parts of your body over the last 2 weeks. If a body part is not listed, choose the one that is closest anatomically.

	Present		Present
Head/Scalp	☐	Soles	☐
Face	☐	Palms	☐
Chest	☐	Tops of Hands/Fingers	☐
Abdomen	☐	Forearms	☐
Back	☐	Upper Arms	☐
Buttocks	☐	Points of Contact w/ Clothing	
Thighs	☐	(e.g waistband, undergarment)	☐
Lower legs	☐	Groin	☐
Tops of Feet/Toes	☐		

Appendix 4: Short Inflammatory Bowel Disease (SIBDQ)

Patient Name_____ Date_____

This questionnaire is designed to find out how you have been feeling during the last 2 weeks. You will be asked about symptoms you have been having as a result of your inflammatory bowel disease, the way you have been feeling in general, and how your mood has been. Please check the box of your choice below each question.

1. How often has the feeling of fatigue or being tired and worn out been a problem for you during the past 2 weeks?

- ☐ All of the tim
- ☐ Most of the time
- ☐ A good bit of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

2. How often during the last 2 weeks have you delayed or canceled a social engagement because of your bowel problem?

- ☐ All of the time
- ☐ Most of the time
- ☐ A good bit of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

3. As a result of your bowel problems, how much difficulty did you experience doing leisure or sports activities during the past 2 weeks?

- ☐ A great deal of difficulty; activities made impossible
- ☐ A lot of difficulty
- ☐ A fair bit of difficulty
- ☐ Some difficulty
- ☐ A little difficulty
- ☐ Hardly any difficulty
- ☐ No difficulty; the bowel problem did not limit sports or leisure activities

4. How often during the past 2 weeks have you been troubled by pain in the abdomen?

- ☐ All of the time
- ☐ Most of the time
- ☐ A good bit of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

5. How often during the past 2 weeks have you felt depressed or discouraged?

- ☐ All of the time
- ☐ Most of the time
- ☐ A good bit of the time
- ☐ Some of the time

- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

6. Overall, in the past 2 weeks, how much of a problem have you had with passing large amounts of gas?

- ☐ A major problem
- ☐ A big problem
- ☐ A significant problem
- ☐ Some problem
- ☐ A little trouble
- ☐ Hardly any trouble
- ☐ No trouble

7. Overall, in the past 2 weeks, how much of a problem have you had maintaining or getting to the weight you would like to be?

- ☐ A major problem
- ☐ A big problem
- ☐ A significant problem
- ☐ Some problem
- ☐ A little trouble
- ☐ Hardly any trouble
- ☐ No trouble

8. How often during the past 2 weeks have you felt relaxed and free of tension?

- ☐ All of the time
- ☐ Most of the time
- ☐ A good bit of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

9. How much of the time during the past 2 weeks have you been troubled by a feeling of having to go to the bathroom even though your bowels were empty?

- ☐ All of the time
- ☐ Most of the time
- ☐ A good bit of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

10. How often during the past 2 weeks have you felt angry as a result of your bowel problem?

- ☐ All of the time
- ☐ Most of the time
- ☐ A good bit of the time
- ☐ Some of the time
- ☐ A little of the time
- ☐ Hardly any of the time
- ☐ None of the time

Irvine, E. J., et. al. The short inflammatory bowel disease questionnaire: A quality of life instrument for community physicians managing inflammatory bowel disease. Am J Gastroenterology. 1996; 91(8):1571-8 Aug.

Appendix 5: CLDQ-PSC

Supplementary Table 2. The list of questions included in the final version of the CLDQ-PSC instrument.

1. How much of the time during the last two weeks have you been troubled by a feeling of abdominal bloating?
2. How much of the time have you been tired or fatigued during the last two weeks?
3. **How much of the time during the last 2 weeks have you experienced bodily pain?**
4. How often during the last two weeks have you felt sleepy during the day?
5. How much of the time during the last two weeks have you experienced abdominal pain?
6. How much of the time in the last two weeks have you been bothered by having decreased strength?
7. How often during the last two weeks have you felt anxious?
8. How often during the last 2 weeks have you felt a decreased level of energy?
9. How much of the time during the last two weeks have you felt unhappy?
10. How often during the last two weeks have you felt drowsy?
11. How often during the last two weeks have you been irritable?
12. How much of the time during the last two weeks have you had difficulty sleeping at night?
13. How much of the time during the last two weeks have you been troubled by a feeling of abdominal discomfort?
14. How much of the time during the last two weeks have you been worried about the impact your liver disease has on your family?
15. How much of the time during the last two weeks have you had mood swings?
16. How much of the time during the last two weeks have you been unable to fall asleep at night?
17. How often during the last two weeks have you had muscle cramps?
18. How much of the time during the last two weeks have you been worried that your symptoms will develop into major problems?
19. How much of the time during the last two weeks have you felt depressed?
20. How much of the time during the last two weeks have you been worried about your condition getting worse?
21. How much of the time during the last two weeks have you had problems concentrating?
22. How much of the time have you been troubled by itching during the last two weeks?
23. How much of the time during the last two weeks have you been worried about never feeling any better?
24. How much of the time during the last two weeks have you been concerned about the availability of a liver if you need a liver transplant?

Appendix 6: PRO-2

Please indicate how you perceive your stool frequency (Based on the last 3 days)
□ Normal
□ 1–2 more stools than normal
□ 3–4 more stools than normal
□ 5 + more stools than normal
Please indicate the severity of your rectal bleeding (Based on the last 3 days)
□ No blood seen
□ Streaks of blood seen with stools for half of the time
□ Obvious blood with stool most of the time
□ Blood alone passed (with no stool)

Appendix 7:COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS Version 5.0 (CTCAE)

Toxicities will be recorded according to CTCAE version 5.0. The full documents is available from the National Cancer Institute (NCI) website and the quick reference can be viewed via the following link:
https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

Appendix 8: TOKYO GUIDELINES 2018 DEFINITION OF ACUTE CHOLANGITIS[31]

Diagnosis is made on account of a combination of clinical, biochemical and radiological parameters as established on the basis of the consensus reached in the International Consensus Meeting held in Tokyo 2018.

Evidence of	Parameters	Thresholds
A. Systemic Inflammation	• Fever/Rigors • Biochemic evidence of inflammatory response	• Temperature >38℃ • Leucopenia (<4 x1000 µl), leucocytosis (>10 x 1000µl) or elevated CRP (>1mg/dl)
B. Cholestasis	• Jaundice • Abnormal liver function tests on biochemistry	• Elevated bilirubin (>2g/dl) • Elevated ALP/AST/ALT/GGT > 1.5x ULN
C. Imaging (Ultrasound, endoscopic ultrasound, MRCP)	• Dilated biliary system • Organic pathology seen on imaging	• Bile duct >7mm • Evidence of Stone, stricture, or obstruction

Tokyo Guidelines score Interpretation:

Definite diagnosis	**one item in A, one item in B and one item in C**
Suspected diagnosis	one item in A + one item in either B or C

Appendix 9: Bristol Laboratories Ltd SmPC Version 10, January 2021

Side effects are grouped on the basis of System Organ Class. Within each system organ class the frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000) and not known (cannot be estimated from the available data).

Blood and lymphatic system disorders	*Common:* Increased bleeding tendencies. *Rare:* Thrombocytopenia, granulocytosis, aplastic anaemia.

Not known:
Cases of bleeding with prolonged bleeding time such as epistaxis and gingival bleeding.
Symptoms may persist for a period of 4–8 days after acetylsalicylic acid discontinuation. As a result there may be an increased risk of bleeding during surgical procedures.
Existing (haematemesis, melaena) or occult gastrointestinal bleeding, which may lead to iron deficiency anaemia (more common at higher doses).

Immune system disorders	*Rare:* Hypersensitivity reactions, angio-oedema, allergic oedema, anaphylactic reactions including shock.
Metabolism and digestive system disorders	*Not known:* Hyperuricemia.
Nervous system disorders	*Rare:* Intracranial haemorrhage *Not known:* Headache, vertigo
Ear and labyrinth disorders	*Not known:* Reduced hearing ability; tinnitus
Vascular disorders	*Rare:* Hemorrhagic vasculitis.
Respiratory, thoracic and mediastinal disorders	*Uncommon:* Rhinitis, dyspnoea. *Rare:* Bronchospasm, asthma attacks.
Reproductive System and mammary disorders	*Rare:* Menorrhagia
Gastrointestinal disorders	*Common:* Dyspepsia. *Rare:* Severe gastrointestinal haemorrhage, nausea, vomiting *Not known:* Gastric or duodenal ulcers and perforation, diarrhoea

Hepatobiliary disorders	*Not known:* *Hepatic insufficiency*
Skin and subcutaneous tissue disorders	*Uncommon:* *Urticaria.* *Rare:* *Steven-Johnsons syndrome, Lyells syndrome, purpura, erythema nodosum, erythema multiforme.*
Renal and urinary tract disorders	*Not known: Impaired renal function, salt and water retention.*

Drug interactions

Interaction with Other Medicinal Products and Other Forms of Interaction
Contraindicated combinations
Methotrexate (used at doses >15 mg/week):
The combined drugs, methotrexate and acetylsalicylic acid, enhance haematological toxicity of methotrexate due to the decreased renal clearance of methotrexate by acetylsalicylic acid. Therefore, the concomitant use of methotrexate (at doses >15 mg/week) with Aspirin 75 mg tablets is contraindicated (
Not recommended combinations:
Uricosuric agents, e.g. probenecid and sulfinpyrazone
Salicylates reverse the effect of probenecid and sulfinpyrazone. The combination should be avoided
Combinations requiring precautions for use or to be taken into account:
Anticoagulants e.g. coumarin, heparin, warfarin and phenindione:
Increased risk of bleeding due to inhibited thrombocyte function, injury of the duodenal mucosa and displacement of oral anticoagulants from their plasma protein binding sites. The bleeding time should be monitored
Anti-platelet agents (e.g clopidogrel and dipyridamole) and selective serotonin re-uptake inhibitors (SSRIs; such as sertraline or paroxetine):
Increased risk of gastrointestinal bleeding
Salicylics may increase the hypoglycaemic effect of sulphonylureas.
Digoxin and lithium:
Acetylsalicylic acid impairs the renal excretion of digoxin and lithium, resulting in increased plasma concentrations. Monitoring of plasma concentrations of digoxin and lithium is recommended when initiating and terminating treatment with acetylsalicylic acid. Dose adjustment may be necessary
Diuretics and antihypertensives:
NSAIDs may decrease the antihypertensive effects of diuretics and other antihypertensive agents. As for other NSAIDs concomitant administration with ACE-inhibitors increases the risk of acute renal insufficiency.
Diuretics: Risk of acute renal failure due to the decreased glomerular filtration via decreased renal prostaglandin synthesis. Hydrating the patient and monitoring renal function at the start of the treatment is recommended.
Carbonic anhydrase inhibitors (acetazolamide):
May result in severe acidosis and increased central nervous system toxicity.

Systemic Corticosteroids:
The risk of gastrointestinal bleeding and ulceration is increased when acetylsalicylic acid and corticosteroids are co-administered
Methotrexate (used at doses <15 mg/week):
The combined drugs, methotrexate and acetylsalicylic acid, may increase haematological toxicity of methotrexate due to decreased renal clearance of methotrexate by acetylsalicylic acid. Weekly blood count checks should be done during the first weeks of the combination. Enhanced monitoring should take place in the presence of even mildly impaired renal function, as well, as in elderly.
Other non-steroidal anti-inflammatory drugs (NSAIDs):
Increased risk of ulcerations and gastrointestinal bleeding due to synergistic effects.
Ibuprofen:
Experimental data suggest that ibuprofen may inhibit the effect of low dose aspirin on platelet aggregation when they are dosed concomitantly. However, the limitations of these data and the uncertainties regarding extrapolation of ex vivo data to the clinical situation imply that no firm conclusions can be made for regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use
Ciclosporin, tacrolimus:
Concomitant use of NSAIDs and ciclosporin or tacrolimus may increase the nephrotoxic effect of ciclosporin and tacrolimus. The renal function should be monitored in case of concomitant use of these agents and acetylsalicylic acid.
Valproate
Acetylsalicylic acid has been reported to decrease the binding of valproate to serum albumin, thereby increasing its free plasma concentrations at steady state.
Phenytoin (Anti-epileptics):
Salicylate diminishes the binding of phenytoin to plasma albumin. This may lead to decreased total phenytoin levels in plasma, but increased free phenytoin fraction. The unbound concentration, and thereby the therapeutic effect, does not appear to be significantly altered.
Alcohol:
Concomitant administration of alcohol and acetylsalicylic acid increases the risk of gastrointestinal bleeding.
Metamizole:
Metamizole may reduce the effect of acetylsalicylic acid on platelet aggregation, when taken concomitantly. Therefore, this combination should be used with caution in patients taking low dose aspirin for cardioprotection.