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**Observational Cohort Study Protocol**

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|---|---|
| **Study Title:** | Characterising the burden and clinical trajectory of pruritus in primary sclerosing cholangitis (PSC) and non cholestatic chronic liver disease |
| **Sponsor:** | University of Birmingham (UK) |
| **Indication:** | Chronic liver disease |
| **Protocol Version Date:** | Version 3.0 01 September 2022 |

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# PROTOCOL SYNOPSIS

| | |
|---|---|
| **Study Title:** | Characterising the burden and clinical trajectory of pruritus in primary sclerosing cholangitis (PSC) and non-cholestatic chronic liver disease |
| **Study Centres Planned:** | UK Hospital centres:<br>- University Hospitals Birmingham NHS Trust<br>- Royal Free Hospital London NHS Trust<br>- Oxford University Hospitals NHS Trust<br>- Norfolk and Norwich University Hospitals NHS Trust<br>- Kings College NHS Foundation Trust |
| **Objectives:** | The co-primary objectives of this study are:<br>- Determine the proportion of patients with PSC who suffer with pruritus.<br>- Determine the proportion of patients with non cholestatic chronic liver disease, inflammatory bowel disease (IBD) only and healthy controls who suffer with pruritus.<br>- Quantify pruritus intensity, and how this varies as per the inherent clinical course of the diseases under study.<br><br>The secondary objectives of this study are:<br>- Correlate itch intensity with disease severity, serum liver biochemical parameters, and where possible, serum bile acid values and serum autotaxin activity.<br>- Assess the current unmet need of pruritus in PSC and non cholestatic chronic liver disease with respect to currently available medical therapies. |
| **Study Design:** | This is an observational cohort study, with data collection in line with routine standard of care clinical assessments. The study will consist of both cross-sectional and longitudinal assessments, in patients with PSC (every 12±4 weeks) and in patients with non- cholestatic chronic liver disease, IBD only and healthy controls (minimum two measurements, for up to 48 weeks). |
| **No. of Subjects Planned:** | Approximately 800 subjects; Est. 200-300 with PSC; Est. 500-600 with either non cholestatic chronic liver disease, IBD alone and healthy controls. |
| **Target Population:** | Adults (>16 years of age), men and non-pregnant and non-lactating women, without liver transplantation, and with an established diagnosis of either: PSC, metabolic / non-alcoholic fatty liver disease (MAFLD/NAFLD) with or without steatohepatitis (MASH/NASH), alcohol induced liver cirrhosis, chronic viral hepatitis, drug-induced liver disease, autoimmune hepatitis, genetic disorders of cholestasis, IBD alone and |

healthy controls who have no diagnosis of liver or bowel disease.

**Duration:** 2-year recruitment and follow-up period.

**Primary Outcome:** Quantify pruritus severity in a cross-sectional sample of patients with PSC, non cholestatic chronic liver disease, IBD alone and healthy controls using the Numerical Rating Scale (NRS) and the 5-D itch tool.

**Secondary Outcomes:** 1) Determine the inherent variability of pruritus over time (every 12±4 weeks over a 48-week period, as per the inherent natural history of PSC).

2) Determine the inherent variability of pruritus over time (every 12±4 weeks over a 48-week period, as per the inherent natural history of non cholestatic chronic liver disease, and IBD).

3) Correlate itch intensity to liver disease severity, the distribution of disease, and the extent/activity of concomitant IBD where relevant.

4) Correlate itch intensity AND changes in itch intensity with routinely collected laboratory parameters, serum bile acid values, serum autotaxin activity and disease-specific risk scores.

5) Quantify the proportion of patients with persistent itch symptoms despite currently available anti-pruritic therapies.

6) Where possible, determine the association between pruritus and other domains of quality of life, assessed by EQ-5D, the chronic liver disease questionnaire and the Simple Cholestatic Complaints (SCC) Score

**Diagnosis and Eligibility:**

**Key Inclusion Criteria: PSC Study Group**

a) Diagnosis of PSC with compatible findings on cholangiogram (magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiography (ERCP)) or liver biopsy.
b) Either, subjects attending the Birmingham liver medicine clinic; or registered participants within the nationwide UK-PSC study.

**Key Exclusion Criteria: PSC Study Group**

a) Age <16 years
b) Women who are pregnant or lactating
c) Lack of capacity (as deemed by the investigator) to provide an accurate medical history
d) Non-English speaking

e) Small duct PSC without concomitant inflammatory bowel disease (IBD)
f) Other causes of chronic liver disease including
- IgG4-related disease
- Primary biliary cholangitis (PBC)
- Secondary sclerosing cholangitis
- Fatty liver disease
- Habitual alcohol consumption greater than 21 oz/week for men or 14 oz/week for women
- HIV infection
- Drug-induced liver disease
- Genetic disorders of cholestasis
- Wilson disease
- Alpha-1-antitrypsin deficiency
- Active malignancy
- Cancer chemotherapy in the last twelve months
- Hepatic veno-occlusive disease, including portal vein thrombosis or Budd-Chiari syndrome

**Key Inclusion Criteria: non-PSC/non-PBC Study Group**

a) Subjects attending the liver or gastroenterology clinics
b) Diagnosis of liver disease in keeping with disease-specific clinical guidelines; either:
- Metabolic / non-alcoholic fatty liver disease (MAFLD/NAFLD) with or without steatohepatitis (MASH/NASH) – British Society of Gastroenterology 2020; or
- Alcohol induced liver disease – European Association for Study of the Liver 2018; or
- Chronic viral hepatitis – European Association for Study of the Liver 2020 (hepatitis C) and 2017 (hepatitis B); or
- Drug-induced liver disease – European Association for Study of the Liver 2020; or
- Autoimmune hepatitis without histological or radiological features of biliary disease/cholestasis
- Genetic disorders of cholestasis – confirmed by confirmatory genetic testing, and in the absence of concomitant other causes of acute or chronic liver disease

c) Diagnosis of Inflammatory Bowel Disease
d) Healthy controls who have no present or previous diagnosis of liver disease or inflammatory bowel disease

**Key Exclusion Criteria: non-PSC/non-PBC Study Group**

a) Age <16 years
b) Women who are pregnant or lactating
c) Lack of capacity (as deemed by the investigator) to provide an accurate medical history
d) Non-English speaking
e) Radiological evidence of cholangiography including secondary sclerosing cholangitis
f) Histological evidence of inflammatory bile duct lesions or periductal fibrosis

g) Mixed aetiology of liver disease
h) Other causes of chronic liver disease including
- Primary biliary cholangitis (PBC)
- Primary sclerosing cholangitis (PSC)
- HIV infection
- Wilson disease
- Alpha-1-antitrypsin deficiency
- Active malignancy
- Cancer chemotherapy in the last twelve months.
- Hepatic veno-occlusive disease, including portal vein thrombosis or Budd-Chiari syndrome

**Study Procedures:**

Subjects attending routine hospital outpatient visits will be asked about their current and past history of pruritus as per routine standard-of-care during their clinic consultation. The past history of pruritus will be audited, with patient recall over the preceding 12 months (using routine clinical practice-style questioning: dichotomous yes/no responses, regions in which itch has been noticed, and strategies use to mitigate symptoms). This will be alongside the most recent assessment of pruritus (past 2 weeks) which will be quantified according to specific questionnaires (NRS, 5D itch tool), disease specific quality of life measures (CLDQ), generic health status/utility (EQ-5D), and the partial Mayo score for colitis where appropriate. Disease aetiology, severity of liver disease (cirrhotic/non-cirrhotic disease, compensated/decompensated, MELD score, Child-Pugh score), BMI, past history of acute cholangitis episodes (investigator discretion), extent of disease involvement where appropriate (e.g. small duct/large duct disease, intra-/extra-hepatic ductal disease) and relevant comorbidities (e.g., diabetes; inflammatory bowel disease phenotype, distribution and activity; chronic kidney disease and stage), medication history (including concomitant/past history of anti-pruritic therapies, antibiotics, IBD-specific mediations, curative treatment for chronic viral hepatitis) and routinely collected laboratory parameters, will also be captured. Individuals in the PSC sub-group will be followed-up longitudinally, with clinic visits dictated as per routine standard-of-care (every 8-24 weeks), and the same series of data points will be collected at the aforementioned time points. Individuals in the non cholestatic chronic liver diesease sub-group will be followed-up longitudinally, with clinic visits dictated as per routine standard-of-care (minimum two time points over a 48+/- 4 week period), with the same series of data points collected at the aforementioned time points.

Optional additional test will include quantification of serum bile acid levels.

**Tentative timelines:**

Following approval, the estimated first subject in will be October 1st 2021 (subject to contract approval), with the last subject in by October 1st 2022.

| | |
|---|---|
| **Data collection:** | Birmingham patient data will be collected on a standardised case record form. The data will be entered and stored on a secure REDCAP database hosted by the University of Birmingham servers behind an N3 firewall. (UK).. |
| **Statistical Analysis:** | Analyses will be performed following completion of each respective work-package; namely the cross-sectional and longitudinal overview of the burden of pruritus in patients with PSC and non cholestatic chronic liver disease.<br><br>Depending upon the distribution of data, quantitative variables will be summarised as means (SD) or medians (IQR), and descriptive statistics presented as absolute numbers and frequencies (n (%)).Correlation coefficients (r) will be determined using Spearman's rank correlation test. Chi-square tests or Fisher's exact tests will be used to analyze the difference between proportions. To explore latent groupings within longitudinal trajectories of pruritus, linear mixed-effects models will be developed using the latent class mixed model (LCMM) package in R software. The dependent variable will be the total pruritus domain score under evaluation. Patients will only be eligible in longitudinal analyses if data is available at 3 distinct timepoints, at least 8 weeks apart. The correlation between repeated measures of the dependent variables within participants will be accounted for in a mixed effects model structure. Goodness of fit statistics will be used to determine the optimal number of latent groups within the data. For each participant, a posterior probability associated with each latent group will be calculated, and in subsequent analyses participants will be assigned to the latent group with the highest posterior probability.<br><br>Multinomial logistic regression will be used to assess the association between various clinical and demographic covariates and class membership. The biochemical measures included as covariates will be those routinely used in clinical practice, alongside serum bile acid levels where available. Odds ratios and 95% confidence intervals will be derived for comparison of latent groups. |

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This audit will be conducted in accordance with the guidelines of Good Clinical Practice (GCP) including archiving of essential documents and study data.

# GLOSSARY OF ABBREVIATIONS AND DEFINITION OF TERMS

| | |
|---|---|
| 5D-itch | The 5 dimensional itch scale |
| AIH | Autoimmune hepatitis |
| ALT | Alanine transaminase |
| ALP | Alkaline phosphatase |
| aPTT | Activated partial thromboplastin time |
| AST | Aspartate transaminase |
| BMI | Body mass index |
| CLDQ | Chronic liver disease questionnaire |
| CTP score | Child-Turcotte Pugh score |
| CRP | C-reactive protein |
| EoS | End of study |
| EQ-5D | EuroQoL five dimensions |
| ERCP | Endoscopic retrograde cholangiopancreatography |
| GCP | Good clinical practice |
| GGT | Gamma glutamyl transferase |
| HBV | Hepatitis B virus |
| HCC | Hepatocellular carcinoma |
| HCV | Hepatitis C virus |
| HE | Hepatic encephalopathy |
| Hb | Haemoglobin |
| IBD | Inflammatory bowel disease |
| ICF | Informed consent form |
| IEC | Independent ethics' committee |
| INR | International normalised ratio |
| IRB | Institutional review board |
| ItchRO | Adult Itch-Reported Outcome tool |
| Kg | Kilogram |
| MAFLD | Metabolic associated liver disease |
| MELD | Model for end stage liver disease |
| Mg | Milligram |
| Min | Minute |
| ML | Millilitre |
| Mm | Millimetre |
| MRCP | Magnetic resonance cholangiopancreatography |
| NAFLD | Non-alcoholic fatty liver disease |
| NASH | Non-alcoholic steatohepatitis |
| PBC | Primary biliary cholangitis |
| PI | Principal investigator |
| PRO(M) | Patient-reported outcome (measure) |
| PSC | Primary sclerosing cholangitis |
| PSC-PRO | Primary sclerosing cholangitis patient-reported outcome |
| PTC | Percutaneous transhepatic cholangiogram |
| SCC Score | Simple Cholestatic Complaints Score |
| QoL | Quality of life |
| RBC | Red blood cell |
| TNF | Tumour necrosis factor |
| UDCA | Ursodeoxycholic acid |
| UHB | University Hospitals Birmingham |
| UoB | University of Birmingham |
| ULN | Upper limit of normal |

| | |
|---|---|
| VAS | Visual analogue scale |
| WBC | White blood cell count |

# 1.0 BACKGROUND

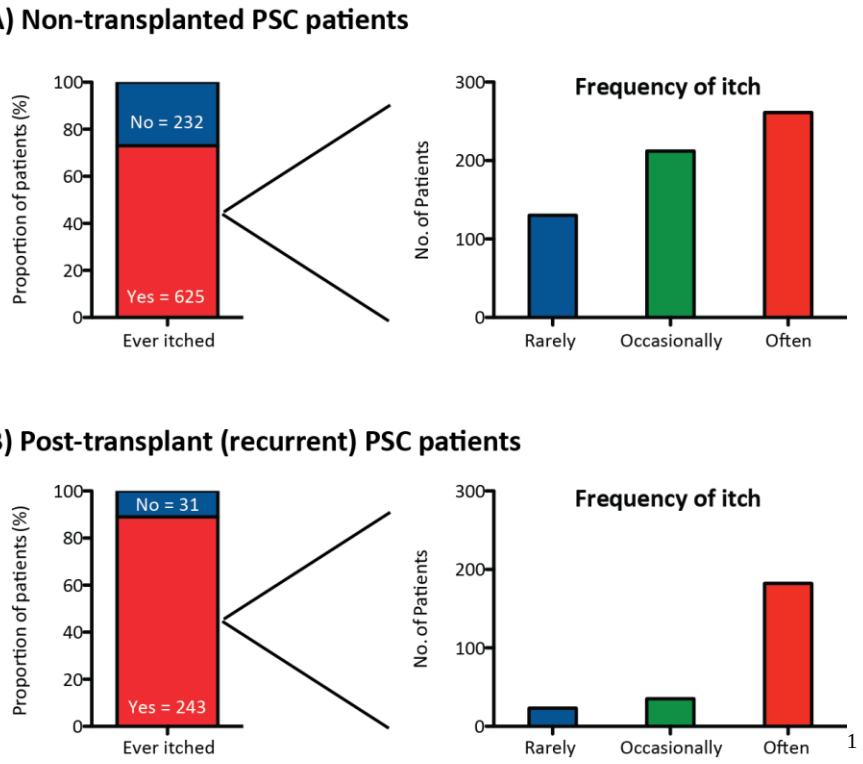
Primary sclerosing cholangitis (PSC) is a chronic, immune-mediated liver disease characterised by multiple strictures that develop throughout the bile ducts.[1] Disease onset may be insidious, but the clinical course is invariably progressive, leading to recurrent bile duct infections, cirrhosis and liver failure, and for some patients, incurable bile duct cancer (cholangiocarcinoma).[2] PSC can strike at any age, but most often between the ages of 20 to 40 years old (60% being men). Our data shows that PSC is associated with approximately 17 years life lost compared to the age- and sex-matched control population of England [3]; and whilst a rare disease (c3,600 people affected in the UK), the incidence is rising (currently 0.58 per 100,000 population).[3] Moreover, PSC now accounts for 10-15% of all liver transplant activity in the UK,[4] and is now the leading indication for transplantation in Europe.[5,6] Indeed, PSC represents the greatest unmet need in modern liver medicine, as no medical therapy has been proven to slow disease progression, and liver transplantation is the only lifesaving intervention for patients.

Contemporary estimates show that 20.2%, 37.0% and 52.3% of patients will either need a liver transplant or die within 5-, 10- and 15-years, respectively; with a further 7.1%, 10.9% and 16.0% of patients developing hepatobiliary cancer across the same time points.[7] Moreover, a recently completed nationwide study in the UK demonstrated that the incidence rate of liver transplantation and PSC-related deaths was greatest among patients age <40 years, highlighting the disproportionate impact of PSC among younger individuals.[3] Our understanding of the clinical course of disease has advanced significantly in recent years, with a wealth of data yielded through multicentre observational cohort studies. To this effect, the horizon for new treatments is also encouraging, with a wealth of phase III interventional programmes currently underway.

Patients also suffer with a large burden of symptoms, relating to pruritus, fatigue and abdominal pain, with significant and negative impact on emotional wellbeing.[8,9]. In a nationwide survey conducted by the charity PSC Support (n=636), pruritus was described as a "persistent and major problem," "a cause of sleep problems and associated fatigue," and a symptom "having major impact on quality of life."[10] To this effect, patients ranked the need for effective symptom control as being just as important as preventing cancer, or developing treatments that delay transplantation. A snapshot from the UK-PSC multicentre study cohort, which encompasses >2,000 participants nationwide, indicates that the majority of PSC patients have experienced pruritus at some point in their lifetime (**Figure 1**).

Current available treatments for cholestatic pruritus focus on the interrelationship between cholestasis, bile acids, and pruritus and include bile acid sequestrants, antihistamines, antibiotics, opioid antagonists,[11] and more recently, fibric acid derivatives.[12] However, data regarding the proportion of PSC patients who actually experience pruritus, the duration of symptoms, its impact of on day-to-day activities, and the inherent variability as per the natural history of the disease, are currently lacking. This is critically important with regards' the design of interventional studies and identifying the minimum important change for treatment efficacy that is meaningful for patients. Moreover, a comparative evaluation of the burden of pruritus in non-cholestatic chronic liver disease, particularly those of imminent public health impact (fatty liver disease/steatohepatitis, alcohol-induced liver disease and viral hepatitis) has not been presented.

Figure 1: Prevalence of pruritus across the UK-PSC cohort circa 2013-2019




Snapshot of patient-reported pruritus symptoms, and the impact on sleep quality (data indicative of *n* = 1,131 who returned an itch questionnaire; from a total of 2,333 UK-PSC participants).

# 2.0 OBJECTIVES AND OUTCOME MEASURES

The principled intent of this study is to characterise the prevalence of pruritus and its severity, how this varies over time as per the clinical course of PSC, and assess the use and effectiveness of current therapeutic interventions. In parallel, the project will detail pruritus behaviour across a comparator cohort which will include those with chronic liver disease (other than PBC and PSC), IBD alone, and healthy controls, wherein patients attending the University Hospitals' Birmingham liver unit will be screened for the presence of pruritus, including symptom severity. This will include individuals attending liver outpatients as well as those admitted for ward-based care who meet pre-specified inclusion / exclusion criteria.

## 2.1 Study Population

The objectives of this study will be evaluated in patients with PSC, alongside those with non cholestatic chronic liver diseases; namely: non-alcoholic fatty liver disease/metabolic liver disease (with/without steatohepatitis, NASH), chronic HBV infection, chronic HCV infection, alcohol-induced liver disease, AIH, drug-induced liver injury, confirmed genetic disorders of cholestasis, IBD alone and healthy controls.

### 2.1.1 Core Study Primary

Quantify the past history (dichotomous yes/no questioning), distribution, and current prevalence and severity of pruritus. The latter will be according to the 5D-itch scale and the Numerical Rating Scale (NRS)

### 2.1.2 Core Study Secondary

1) Assess how pruritus intensity varies over a 48-week period, as per the inherent natural history of the diseases under study, according to the 5D-itch and NRS (baseline and at 48w for all patients, and additionally at 12w, 36w and 48w for those with PSC).

2) Correlate itch intensity with liver disease severity at baseline and at 48w according to the Child-Turcotte Pugh score, the Model for End Stage Liver Disease (MELD), and for PSC patients, the distribution of ductal disease (small duct disease, isolated intrahepatic disease, intra- and extra-hepatic disease) and extent/activity of concomitant IBD.

3) Correlate itch intensity AND changes in itch intensity with clinical laboratory parameters (AST, ALT, ALP, bilirubin, albumin, INR and platelet count) measured at baseline and 48w, and additionally for PSC patients taken at 12w, 24w and 36w.

4) Where possible, itch intensity will also be correlated against serum bile acid values, serum autotaxin activity and objective risk scoring systems (the UK-PSC risk score, the Amsterdam-Oxford risk score).

5) Capture the use of anti-pruritus medication, and quantify the proportion of patients with persistent itch symptoms despite existing treatment paradigms (taken at baseline and 48w for all patients, and additionally for PSC patients at 12w, 24w and 36w).

6) Where possible, determine the association between pruritus and other domains of quality of life and health status, as determined by CLDQ, EQ-5D (5L), and SCC score and where appropriate, the partial Mayo colitis score (measured at baseline and 48w for all patients, and additionally for PSC patients at 12w, 24w and 36w).

## 3.0 STUDY DESIGN

This is a multi-stage observational cohort study with cross-sectional and longitudinal components. The cross-sectional component will evaluate pruritus amongst individuals attending the Birmingham liver clinic (patients with PSC as well as those with non-PSC/non-PBC chronic liver disease, IBD alone and healthy controls), together with the national UK-PSC patient population. The longitudinal component will collect data at 8-to-12-weekly intervals (up to 48 weeks) for PSC patients, and as a minimum at baseline and at 48 weeks for those with non-PBC, non-PSC-associated chronic liver disease.

### 3.1 Cross-sectional study component

Patients attending the hospital clinic will be approached during routine clinic visits, and the presence and severity of pruritus documented; together with disease aetiology, disease severity and activity (as appropriate), treatment regimens, and routinely collected clinical, laboratory and radiological data.

In parallel, all active (pre-consented) UK-PSC registrants will be sent a patient information sheet and invitation letter to participate in this sub-study through their local hospital. In kind,

local PIs will complete the required case record form, with minimal required data and optional data points.

*Minimal required data (* applies to PSC patients only)*:
a) Patient ID
- Hospital No.
- Date of birth/age
- Sex
- BMI
b) Disease diagnosis
- Date/age at diagnosis
- Sub-type: small duct disease, isolated intra-hepatic disease, intra- and extra-hepatic disease*
- Overlapping features of AIH*
c) Interventional history
- Previous endoscopic biliary intervention: 1x / >1x; date of last intervention
- Previous percutaneous biliary intervention: 1x / >1x; date of last intervention
- Previous surgical resection: free text details
d) Current medications, dosages and frequency and indications
- UDCA
- Oral prednisolone
- Oral budesonide
- Oral 5-aminosalicylic acid
- Topical prednisolone
- Topical 5-aminosalicylic acid
- Azathioprine
- Vedolizumab
- Infliximab
- Adalimumab
- Tofacitinib
- Ustekinumab
- Colestyramine
- Other bile acid sequestrants (specify)
- Rifampicin
- Naltrexone
- Sertraline
- Gabapentin
- Bezafibrate
- Fenofibrate
- Antihistamine (specify)
- Topical anti-pruritus therapy (specify)
- Antibiotics (specify)
- Other treatments, including over the counter and non-prescription drugs (specify)
e) History of acute cholangitis (investigator discretion)
- Current
- Last 12 months: 1x, >1x
f) History of antibiotic therapy in the last 12 months
- Outpatient
- In-patient
- Last 3 months
- >1x
g) IBD history and extent
- Concomitant IBD and diagnosis date

- Partial Mayo colitis score
- Colitis extent
- Ileitis
- More extensive small bowel disease
- Perianal disease
- Stricturing disease
- Penetrating disease

h) Bowel resection and date
- Subtotal colectomy
- Ileostomy
- Ileal pouch anal anastomosis
- Pouch reversal
- Ileorectal anastomosis
- Other bowel surgery (specify)

i) Laboratory parameters
- ALT
- AST
- ALP
- γGT
- Bilirubin
- Albumin
- Creatinine
- CRP
- INR
- Platelet count
- Hb
- White blood cell count
- Na

j) Child-Turcotte Pugh score
k) MELD score
l) Liver cirrhosis status (investigator discretion)
- Non-cirrhotic
- Cirrhotic
- Decompensated

n) NRS and 5D-itch
o) CLDQ
p) EQ-5D (5L)
q) SCC score

*Optional data*
a) Transient elastography score, date
b) Spleen size
c) Serum bile acid levels
d) serum autotaxin activity

## 3.2 Longitudinal study component

Individuals in the cross-sectional study will undergo longitudinal data collection in line with routine clinic visits, at baseline and 48 weeks thereafter (minimum requirement for all patients), alongside interim measurements taken at 12(+4) weekly intervals for those with PSC. At each time point, the following parameters will be collected:

*Minimal required data (* applies to PSC patients only)*:
a) Patient ID
- Hospital No.
- Date of birth/age
b) Disease diagnosis
- Sub-type: small duct disease, isolated intra-hepatic disease, intra- and extra-hepatic disease*
- Overlapping features of AIH*
c) Interventional history
- Interim endoscopic biliary intervention: 1x / >1x; date of last intervention
- Interim percutaneous biliary intervention: 1x / >1x; date of last intervention
- Interim surgical resection: free text details
d) Current medication, dosage and frequency and indication
- UDCA
- Oral prednisolone
- Oral budesonide
- Oral 5-aminosalicylic acid
- Topical prednisolone
- Topical 5-aminosalicylic acid
- Azathioprine
- Vedolizumab
- Infliximab
- Adalimumab
- Tofacitinib
- Ustekinumab
- Colestyramine
- Other bile acid sequestrants (specify)
- Rifampicin
- Naltrexone
- Sertraline
- Gabapentin
- Bezafibrate
- Fenofibrate
- Antihistamine (specify)
- Topical anti-pruritus therapy (specify)
- Antibiotics (specify)
e) Interim episodes of acute cholangitis (investigator discretion)*
- 1x, >1x
f) Interim antibiotic therapy (specify)
- Outpatient
- In-patient
- >1x
g) Interim bowel resection and date
- Subtotal colectomy
- Ileostomy
- Ileal pouch anal anastomosis
- Pouch reversal
- Ileorectal anastomosis
- Other bowel surgery (specify)
i) Laboratory parameters
- ALT
- AST
- ALP

- γGT
- Bilirubin
- Albumin
- Creatinine
- CRP
- INR
- Platelet count
- Hb
- White blood cell count
- Na

j) Child-Turcotte Pugh score
k) MELD score
l) Liver cirrhosis status (investigator discretion)
- Non-cirrhotic
- Cirrhotic
- Decompensated

m) NRS
n) 5D itch
o) Partial Mayo colitis score*
p) CLDQ
r) EQ-5D (5L)
s) SCC Score

*Optional data*
a) Transient elastography score, date
b) Spleen size
c) Serum bile acid levels
d) Serum autotaxin activity

# 4.0 ELIGIBILITY CRITERIA

Subjects who meet all of the following criteria may be included.

## 4.1 PSC Study Group

### 4.1.1 Inclusion Criteria

a) Diagnosis of PSC with compatible findings on cholangiogram (magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiography (ERCP) or liver biopsy.
b) Either, subjects attending the Birmingham liver medicine clinic; or registered participants within the nationwide UK-PSC study.

### 4.1.2 Exclusion Criteria

a) Age <16 years
b) Women who are pregnant or lactating
c) Lack of capacity (as deemed by the investigator) to provide an accurate medical history
d) Non-English speaking
e) Small duct PSC without concomitant inflammatory bowel disease (IBD)
f) Other causes of chronic liver disease including
- IgG4-related disease
- Primary biliary cholangitis (PBC)

- Secondary sclerosing cholangitis
- Fatty liver disease
- Habitual alcohol consumption greater than 21 oz/week for men or 14 ox/week for women
- HIV infection
- Drug-induced liver disease
- Genetic disorders of cholestasis
- Wilson disease
- Alpha-1-antitrypsin deficiency
- Hepatic veno-occlusive disease, including portal vein thrombosis or Budd-Chiari syndrome

g) History of liver transplantation
h) Current or prior history of cholangiocarcinoma, pancreatic or hepatocellular cancer
i) Gallbladder cancer in the previous twelve months
j) Colorectal cancer (or evidence of active metastatic disease) in the previous twelve months
k) Chemo- or radiotherapy in the previous twelve months
l) Chronic kidney disease, defined by the use of renal replacement therapy or a urea >20mmol/L
m) Other known dermatological, haematological or extrahepatic disorder, including iatrogenic causes (e.g. excessive opioid use) associated with pruritus; investigator discretion

## 4.2 Non cholestatic chronic liver disease Study Group

### 4.2.1 Key Inclusion Criteria

a) Subjects attending the Birmingham liver medicine clinic
b) Diagnosis of liver disease in keeping with disease-specific clinical guidelines; either:
- Metabolic / non-alcoholic fatty liver disease (MAFLD/NAFLD) with or without steatohepatitis (MASH/NASH) – British Society of Gastroenterology 2020; or
- Alcohol induced liver disease – European Association for Study of the Liver 2018; or
- Chronic viral hepatitis – European Association for Study of the Liver 2020 (hepatitis C) and 2017 (hepatitis B); or
- Drug-induced liver disease – European Association for Study of the Liver 2020; or
- Autoimmune hepatitis – European Association for Study of the Liver 2015; or
- Genetic disorders of cholestasis – confirmed by confirmatory genetic testing, and in the absence of concomitant other causes of acute or chronic liver disease
- c) Diagnosis of Inflammatory Bowel disease only, with no diagnosis of present or past liver disease
- d) Healthy controls who have no past or present diagnosis of liver or bowel disease

### 4.2.2 Key Exclusion Criteria

a) Age <16 years
b) Women who are pregnant or lactating
c) Lack of capacity (as deemed by the investigator) to provide an accurate medical history
d) Non-English speaking
e) Radiological evidence of cholangiography including secondary sclerosing cholangitis
f) Histological evidence of inflammatory bile duct lesions or periductal fibrosis
g) Mixed aetiology of liver disease
h) Other causes of chronic liver disease:
- Primary biliary cholangitis (PBC)
- Primary sclerosing cholangitis (PSC)
- HIV infection
- Wilson disease
- Alpha-1-antitrypsin deficiency

- Hepatic veno-occlusive disease, including portal vein thrombosis or Budd-Chiari syndrome
i) History of liver transplantation
j) History of liver transplantation
k) Current or prior history of cholangiocarcinoma, pancreatic or hepatocellular cancer
l) Gallbladder cancer in the previous twelve months
m) Colorectal cancer (or evidence of active metastatic disease) in the previous twelve months
n) Chemo- or radiotherapy in the previous twelve months
o) Chronic kidney disease, defined by the use of renal replacement therapy or a urea >20mmol/l
p) Other known dermatological, haematological or extrahepatic disorder, including iatrogenic causes (e.g. excessive opioid use) associated with pruritus; investigator discretion

# 5.0 JUSTIFICATION FOR TIME POINTS

This study will evaluate the prevalence of pruritus in a large population of patients with chronic liver disease; and in those with PSC, how this varies over longitudinally. The time points under assessment have been selected given their alignment with routine standard of care clinic visits, as requested by our patient and public involvement (PPI) group. Importantly, the patient organisation PSC Support highlight the need for new anti-pruritus therapies to be tested and validated long-term (>3 to 6 months as a minimum), given that contemporary trials of anti-pruritus therapy in cholestatic liver disease have only demonstrated short-term efficacy.[12,13] The studied timelines will therefore provide a reference upon which to power interventional studies at a later date.

# 6.0 STUDY DISCONTINUATION AND CENSORING

Given the observational nature of the study (without testing of an investigational medicinal product), the concept of study drug discontinuation is irrelevant. However, patients will be censored at the point of liver transplantation or death. No censoring will be applied in the event of hepatopancreatobiliary or colorectal malignancy, however those individuals with active cancers at the time of screening will be excluded. In a similar vein, active pregnancy is a study exclusion criteria, and women who become pregnant during the course of study will be censored from results.

# 7.0 STUDY ASSESSMENTS

Protocol waivers or exemptions are not allowed. Immediate safety concerns (with regards existing therapy outside of study requirements) should be discussed with the sponsor immediately upon occurrence or awareness, in line with the MHRA yellow card system. All screening evaluations must be completed prior to the clinic visits and reviewed to confirm that potential participants meet eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

## 7.1 Informed consent

Formal informed written consent for the study will be obtained from each participant. This will be carried out by the investigator. Firstly capacity will be assessed. Only participants deemed to have capacity will be invited to participate and consent.

Potential participants will be provided with a Patient Information Sheet and invitation letter. The participant will be given the opportunity to ask any questions at any point during the process. Any questions or queries will be addressed. The participants will be free to refuse to

take part and this will not impact their routine clinical care. The investigator will then obtain consent from those who choose to participate.

## 7.2 Inclusion/exclusion criteria

At each study visits (in-person or telephone), all inclusion and exclusion criteria will be reviewed by the investigator, who is a qualified physician, to ensure that the participant still qualifies for audit evaluation.

## 7.3 Demography

Participant demographic information including sex, age (year and month), and race, as allowed per local regulations, will be collected during screening, and verified during the index visit.

## 7.4 Prior and Concomitant Treatments

Specific prior and concomitant treatments and therapies administered for underlying liver disease or treatment of pruritus will be collected at each visit.

## 7.5 Medical History

A medical history will be recorded as per routine standard of care by the investigator and their study team All clinically or medically relevant information will be recorded, including liver disease history, regardless of how much time has elapsed since the date of diagnosis.

## 7.6 Assignment of Identification Numbers

All participants will be assigned a unique number on the audit case record form, that will be used to identify the participant for all future subject visits. Each participant will be assigned only 1 subject number for each screening. Subject numbers must not be re-used for different participants. For participants who rescreen, a new Subject ID number will be generated.

## 7.7 Study Visits

Study visits are expected to be conducted at clinical study sites; either through face-to-face consultations as per routine standard of care, via video consultation, or televisit, at the discretion of the investigator, and in line with routine standard of care (**Table 1**).

**Table 1: Schedule of Assessments**

| | Week 0 | Week 12±4 | Week 24±4 | Week 36±4 | Week 48±4 |
|---|---|---|---|---|---|
| | Baseline/V1 | V2 | V3 | V4 | EoS /V5 |
| Medical history (inc. interventions) | • | | | | |
| Medication history | • | | | | |
| Review inclusion/exclusion criteria | • | | | | |
| Body weight/BMI | • | | | | |
| Liver disease severity status | • | • | • | • | • |
| PSC risk stratification * | • | • | • | • | • |
| Pruritus and NRS | • | • | • | • | • |
| CLDQ | • | • | • | • | • |
| EQ-5D | • | • | • | • | • |
| IBD history** | • | | | | |
| IBD activity | • | • | • | • | • |
| Spleen size (and date) *** | • | | | | |
| MRCP report/ductal disease extent (and date)* | • | | | | |
| Fibroscan report (and date) *** | | | | | |
| Interim clinical event recording | | • | • | • | • |
| ***Laboratory panels*** | | | | | |
| Chemistry | • | • | • | • | • |
| Haematology | • | • | • | • | • |
| Bile acids *** | • | • | • | • | • |
| Autotaxin activity *** | • | • | • | • | • |

* PSC patients only
** Applicable to individuals with IBD only; includes surgical history
*** Optional

# 8.0 STATISTICAL CONSIDERATIONS

Analyses will be performed following completion of the cross-sectional overview of the burden of pruritus in PSC patients, the longitudinal overview of the burden of pruritus in PSC patients, the cross-sectional overview of the burden of pruritus in patient with non-PSC/non-PBC chronic liver disease and the longitudinal overview of the burden of pruritus in non-PSC/non-PBC patients. Importantly, a detailed statistical analysis plan will synthesised following ethics' submission, and evolve as the study progresses. Given that this is an observational cohort study, the choice of statistical methodology is neither fixed nor hypothesis driven at this stage.

Depending upon the distribution of data, quantitative variables will be summarised as means (SD) or medians (IQR), and descriptive statistics presented as absolute numbers and frequencies (n (%)). Correlation coefficients (r) between itch intensity/severity and continuous variables at baseline (and those over time) will be determined using Spearman's rank correlation test. Chi-square tests or Fisher's exact tests will be used to analyze the difference between proportional estimates.

To explore latent groupings within longitudinal trajectories of pruritus within workpackage II, linear mixed-effects models will be developed using the latent class mixed model (LCMM) package in R software. The dependent variable will be the total pruritus domain score under evaluation. Patients will only be eligible in longitudinal analyses if data is available at 3 distinct timepoints, at least 8 weeks apart. Correlation between repeated measures of the dependent variables within participants will be accounted for in a mixed effects model structure. Goodness of fit statistics will be used to determine the optimal number of latent groups within the data. For each participant, a posterior probability associated with each latent group will be calculated, and in subsequent analyses participants will be assigned to the latent group with the highest posterior probability.

Multinomial logistic regression will be used to assess the association between various clinical and demographic covariates and class membership. The biochemical measures included as covariates will be those routinely used in clinical practice, alongside serum bile acid levels where available. Odds ratios and 95% confidence intervals will be derived for comparison of latent groups.

The above illustration is to provide insight into the magnitude of the burden of pruritus and its inherent variability over time, that can be quantified with reasonable error rates. However, the study will aim to make more efficient use of all outcome data through the use of modelling, and will consider the totality of all data points with regards the primary/secondary outcome evidence in making inference. This means that our study will not be solely reliant upon a single outcome measures taken at a single timepoints.

# 9.0 REGULATORY, ETHICAL, AND STUDY OVERSIGHT

## 9.1 Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines

- Applicable International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

Given that a large proportion of data collection herein is in accordance with local audit standards, informed consent will only be required in the event data collection is beyond the remit of routine standard of care.

With regards mechanistic sample collection, the protocol, protocol amendments and informed consent forms and other relevant documents must be submitted to an IRB/IEC by the investigator and reviewed and approved before these aspects of the study can begin. Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants. The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
- Notifying the authorities of any incidental significant safety findings as required by IRB/IEC procedures.
- Providing oversight of the conduct of the study at the site and adherence to requirements of ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

## 9.2 Financial Disclosure

Not applicable

## 9.3 Data Protection

All subjects under study will be assigned a unique identifier. Any participant records or datasets that are transferred offsite will contain the identifier only; participant names or any information that would make the participant identifiable will not be transferred. Patients must be informed that his or her personal study-related data will be used by the sponsor in accordance with local data protection law, and for auditing of clinical care only, unless appropriate written consent has been obtained. The level of disclosure must also be explained to the participant. Where relevant, the participant must be informed that his or her medical records may be examined by Quality Assurance auditors or other authorized personnel appointed by the sponsor, and by inspectors from regulatory authorities.

## 9.4 Publication Policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the funder before submission. This allows protection of proprietary information and to provide comments. The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicentre studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement. Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

## 9.5 Data Quality Assurance, Data Handling, and Data Record Keeping

All subject data relating to the study will be recorded on dedicated eCRFs. The investigator is responsible for verifying that data entries are accurate and correct manual cross-checking against patient medical notes. The investigator must maintain accurate documentation (source data) that supports the information entered into the eCRF. The Chief Investigator is responsible for the data management of this study including quality checking of the data. The Chief Investigator assumes accountability for actions delegated to other individuals. Local Principal Investigators and Sub-Investigators will perform ongoing source data verification to confirm that data entered into the eCRF are accurate, complete, and verifiable from source documents; and that the study is being conducted in accordance with the currently approved protocol and other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents pertaining to the conduct of this study must be retained by the investigator for a period of 15 years following the date of publication. No eCRFs may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor and Chie Investigator. To ensure compliance with GCP and all applicable regulatory requirements, the sponsor may conduct a quality assurance audit.

# 10.0 REFERENCES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