

Briefly summarise the main changes proposed in this amendment. Explain the purpose of the changes and their significance for the study.

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1. New study database

The UK PSC Study is launching a new online study database, to replace the current Access system, called the UK PSC Database. This is a bespoke Microsoft SQL database designed by Dr. Tony Bennett of Illuminaries® Ltd. (<http://www.illuminaries.co.uk>). The UK PSC Database enables electronic data capture in collaborating centres using a secure web-based interface, as well as the import of bulk data obtained from electronic medical record systems (see point 2 below).

The database is hosted on a dedicated server on the network of the Cambridge University Hospitals NHS Foundation Trust, linked to the N3 network. The N3 network is used for electronic data transfer. Access to the UK PSC Database is restricted to members of the UK PSC and NIHR Bioresource research teams and to regulatory authorities, such as the Research and Development (R&D) Department at the study sponsor or the patient's own hospital.

The database will be supported by Illuminaries® for the duration of the study. Identifiable information about participants will be destroyed ten years after the end of the study. Non-identifiable information will be retained indefinitely for use in future, ethically-approved studies.

This database offers significant improvements to the efficiency of study administration and data management. Sites will log on to generate patient invitation letters, input clinical data and source real-time recruitment information.

2. Data Capture from electronic medical records, centralized data repositories and NHS data centres

Sourcing accurate, comprehensive clinical data sets, with annual updates, is a key priority for the UK PSC Study, as it facilitates long-term monitoring of patient outcomes. We therefore wish to automate this process, by linking to electronic medical records held on systems at the patient's hospital and at the following NHS data centres:

- [NHS Digital](#) (participants in England)
- [The Information Services Division, NHS National Services Scotland](#)
- [NHS Wales Informatics Service](#)
- [The Health and Social Care Board Northern Ireland](#).

We have secured support for our plans from PSC patients and clinicians, who understand the importance of high quality, up-to-date data for the delivery of UK PSC strategic objectives. Automating this process would reduce the workload for collaborating centres, who currently complete paper or online CRFs, and prevent data transcription errors.

We have edited the *Informed Consent Form* (version 4) and *Parent/Guardian Consent Form* (version 2) accordingly and outlined the process that we will follow in the *UK PSC PIS* (version 7), *UK PSC Parent/Guardian PIS* (version 2) and the *UK PSC Protocol* (version 5). The datasets that we plan to source are listed in a new document (*Appendix E - UK PSC Data Collected from EMRs*).

3. Participant opt-out system for new data capture process

UK PSC has recently undertaken a large-scale reconsenting and resampling initiative with 80% of the cohort, using ICF version 3 (which includes provisions for data and sample sharing). The patient response rate was very high (approximately 53%).

Due to the limited funding for UK PSC, it is not possible to screen patients again and co-ordinate further, large-scale mailshots, to re-consent the cohort on Informed Consent Form version 4.

We therefore propose to inform current participants on Informed Consent Form version 3 of our plans to access electronic medical records. We will communicate via comprehensive information in plain English on dedicated webpages (<http://www.uk-psc.com/patients/obtaining-health-data-on-uk-psc-participants/>) and by sending them a letter. The letter will outline the process we plan to follow and ask them to contact us with any queries. It will offer them the opportunity to opt out of this data capture process, or to withdraw from the study entirely.

The patient charity PSC Support will inform patients of this process and will seek their feedback. They will also communicate via features in their regular e-newsletter and promotion on their website and on social media.

In devising this plan we have consulted patients and teams running similar prospective cohort studies. One such study is BLISS, a long-term cohort study funded by the NIHR. We have adopted their ethically-approved approach to informing patients of this data collection method, offering them the opportunity to raise questions, and to opt out of this process or to withdraw from the study.

BLISS has obtained REC and NHS Digital approval to source participant datasets from NHS Digital on this opt-out basis. They have provided us with invaluable guidance on best practice relating to comprehensive, plain English patient information on this data collection process and participation options. Reference documents relating to the opt-out letter and website promotion communication by the BLISS Study are supplied for your information.

PSC Support endorses this approach and has written a Letter of Support, which is supplied with this amendment.

4. Changes to participant withdrawal options

We are offering greater choice to participants withdrawing from the UK PSC Study regarding the use of their data and samples. They can now choose from the following options:

- **Withdrawal and data deletion** – the UK PSC team will delete all participant data, apart from name, address, date of birth and NHS/CHI number. The participant's samples will also be destroyed. We cannot remove the participant's data from completed research. It will not be possible to destroy samples that have already been prepared for testing or distributed to other laboratories collaborating in the study.
- **No further participation, but retain data** – UK PSC will retain and use any data and samples already collected for the participant.

Previously, participants withdrawing from the UK PSC Study could not request the deletion of information about them held on the research database. This new withdrawal option also provides an additional safeguard against data or samples being used in research without the subject's consent.

We are also providing more comprehensive information on withdrawal options and the process on www.uk-psc.com

5. New resampling documents

As we are now able to resample the cohort annually, we have compiled a new *UK PSC Clinical Data Update Questionnaire* (for adults and children). This will be sent to sites no more frequently than once every 12 months, via the new study database.

We have also compiled separate letters for adult blood resampling, with a document seeking blood for serum extraction and one requesting blood for DNA extraction, to replenish participant research samples ('UK PSC Participant Resampling letter – DNA' and UK PSC Participant Resampling letter – serum').

Paediatric centres will approach their patients for further blood samples at routine clinic appointments, so these letters are not required.

6. Alignment with new international guidelines for PSC database elements

A small number of new questions have been added to the *UK PSC Clinician Questionnaire* and *UK PSC Participant Questionnaire*, along with additional answer options to existing questions. These are as a result of an international initiative to standardise PSC patient registry databases, to facilitate data sharing for international research.

7. Paediatric Inclusion Criteria

We plan to open up the study to children with Autoimmune Hepatitis, with or without possible biliary disease. This will enable us to profile PSC across all ages, alongside childhood autoimmune liver disease, and to offer all patients the chance to participate in research seeking effective therapies. The new paediatric inclusion criteria will therefore be:

- Primary Sclerosing Cholangitis
- Autoimmune Sclerosing Cholangitis
- Autoimmune Hepatitis with possible biliary disease
- Autoimmune Hepatitis with no biliary disease at time of recruitment

Due to this change, the title of the study will now be *A Research Study to determine the Genetic Causes of Primary Sclerosing Cholangitis **and Childhood Autoimmune Liver Disease*** (additional wording in bold).

8. Paediatric recruitment processes and documentation

We are no longer seeking saliva samples for DNA extraction from children, on the advice of our paediatric colleagues. As blood is already being taken for the serum sample, paediatric participants will now have two blood samples taken, one for DNA and one for serum extraction.

Two additional statements have been added to the *Parent/Guardian Informed Consent Form* (version 2). Statement no. 9 covers monitoring of the database by the research team and R&D departments at the collaborating centre or sponsor institution, and is already included on the current adult *UK PSC Informed Consent Form* (version 3). We have also added statement 7, which relates to linkage to electronic medical records from the participant's hospital or NHS Data Centres. This process is outlined in more detail in point 2 above.

We have also made changes to and introduced new paediatric participation documents:

- Working in consultation with our paediatric co-investigator, we have developed a new *UK PSC Paediatric Clinician Questionnaire*, based on the adult document. This features additional questions to log paediatric-specific phenotypes, investigations and medications.
- We have also reviewed the *UK PSC Participant Questionnaire* and added a small number of paediatric-specific questions. This document will be used for both adult and paediatric participants, with a separate version (*UK PSC Paediatric Participant Questionnaire*) being produced, featuring the same questions, but for parent/guardian completion (on behalf of younger children).
- We have amended the age ranges of the following paediatric Participant Information Sheets:
 - *UK PSC PIS age 11-17 years*: the age range is now 11-15 years
 - We have developed a new *UK PSC PIS age 16-17 years*. This reflects the fact that children of this age can consent to join the study themselves and without parent/guardian involvement.

9. Processes for paediatric reconsent and resampling in clinic

On request from UK PSC, the recruiting site will ask the child (consulting the parent /guardian of children aged 0-15 years) to provide an additional blood sample (for DNA or serum extraction). This will occur no more frequently than once every 12 months. These samples will be taken at a routine clinic appointment.

UK PSC will also ask the recruiting site to complete the *UK PSC Clinical Data Update Questionnaire*, no more frequently than every 12 months. We will also ask participants (or the parent/guardian of younger children) to complete the *UK PSC Participant Questionnaire* again, no more frequently than every 12 months.

10. Clinical trial invitation letters

We have developed a template UK PSC Clinical Trial Invitation letters for adult participants (*UK PSC Participant Clinical Trials Invitation – adults*). When participants are identified as being potentially suitable for a PSC clinical trial, this letter will be posted to them (if they have signed *UK PSC ICF v3* or higher).

11. New HRA Statement of Activities and Schedule of Events documents

We have completed *Statement of Activities* and *Schedule of Events* documents (with versions for adult sites and paediatric sites), working in consultation with our sponsor, Cambridge University Hospitals NHS Trust.

12. Logging of participant information

If patients are willing, they will provide their phone no and email address on the reply slip that they return requesting a study pack. This information will be optional. It will enable us to contact patients more efficiently about their ongoing participation in the UK PSC study and resolve any queries. This data would not be released to third parties.

Participants will continue to return ICFs and questionnaires by post.

We will log patient NHS or CHI no.s, via the Clinician Questionnaire and on the invitation reply slip. This will enable us to access patient electronic medical records, as outlined above. NHS or CHI no.s will also be used to check patient status and contact details via central NHS systems, including NHS Spine – a much more efficient system than the current manual checks with individual collaborating centres.

All participant data is logged on the UK PSC Database. This system has the same level of protection as confidential information stored by the patient's own hospital. Identifiable information (such as patient name, address and NHS or CHI number) will be destroyed ten years after the study has ended.

13. New Documentation

The above changes have necessitated the development a number of new documents:

- *Appendix D: UK PSC Paediatric Reconsent and Resampling*
- *Appendix E: UK PSC Data collected from EMRs*

Resampling

- *UK PSC Clinical Data Update Questionnaire– Adults and Children*
- *UK PSC Participant Resampling letter – DNA*
- *UK PSC Participant Resampling letter – serum*

Paediatrics

- *UK PSC PIS age 16-17 years*
- *UK PSC Paediatric Clinician questionnaire*

Clinical Trials

- *UK PSC Participant Clinical Trial Invitation – Adults*

HRA Documents

- *UK PSC 196928 Statement of Activities – Adult Recruiting Sites*
- *UK PSC 196928 Statement of Activities – Paediatric Recruiting Sites*
- *UK PSC 196928 Schedule of Events – Adult Recruiting Sites*
- *UK PSC 196928 Schedule of Events – Paediatric Recruiting Sites*

NHS Data Centres opt-out communications

- *UK PSC Participant Information letter – England*
- *UK PSC Participant Information letter – Scotland*
- *UK PSC Participant Information letter – Wales*
- *UK PSC Participant Information letter – Northern Ireland*
- *UK PSC NHS Digital - Opt out form*

- *UK PSC NHS National Services Scotland – Opt out form*
- *UK PSC NHS Wales Informatics Service - Opt out form*
- *UK PSC Health and Social Care Board Northern Ireland - Opt out form*
- *PSC Support Letter of Support*

UK PSC Opt out Information webpages

<http://www.uk-psc.com/patients/obtaining-health-data-on-uk-psc-participants/>

Password 041217

Renamed documents

The names of these existing documents have been changed as follows and assigned version number 1:

Current doc name	Previous Name
UK PSC Pruritus questionnaire A	UK PSC Pruritus questionnaire pre OLT
UK PSC Pruritus questionnaire B	UK PSC Pruritus questionnaire post OLT
UK PSC PIS – children age 11-17 years	UK PSC PIS – children age 11-15 years
UK PSC Paediatric Participant Questionnaire – aged 0-10 years	UK PSC Paediatric Participant Questionnaire

14. Study team changes

Claire Barrett has left the UK PSC study and her replacement is Sajeep Grewal, UK PSC Data Manager. The UK PSC administrative team is now based at the University of Birmingham. The study registered address and sponsorship remains in Cambridge. The study contact details have changed to tel: 0121 371 8101 and email ukpsc@uhb.nhs.uk.

Dr David Lomas is no longer a Co-Investigator. Dr Palak Trivedi of the University of Birmingham and paediatrician Dr Marianne Samyn of Kings College London have joined as Co-Investigators and DR Trivedi is also Cohort Utilisation Lead. Chief Investigator Gideon Hirschfield is now a Professor of Autoimmune Liver Disease.

15. Site and PI changes

Eighteen study sites (NHS Trusts or Health Boards) have had a change of Principal Investigator. Nineteen sites have closed; three paediatric sites and one adult site have opened. A list of these changes is attached with the submission.