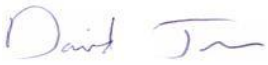
The UK-PBC Project Newsletter Summer 2015

I would like to welcome you all to the summer newsletter for UK-PBC. The project is, thanks to the fantastic work of the team and clinicians and PBC patients across the UK, going from strength to strength. As you will read in the newsletter, recruitment is going very well indeed and UK-PBC is now the largest study of what causes PBC, what makes it a problem in some patients and how we treat it in the world. This has translated into a hugely exciting programme of clinical trials in PBC which will be launched over the next year. I think it is safe to say that we will be treating PBC in completely different and better way within five years (starting with Obeticholic Acid which we anticipate being licensed within the next year). Finally, it has been our great pleasure to support the work of the PBC Foundation and other patient groups to change the name of the condition to **Primary Biliary Cholangitis** to better reflect the fact that the majority of PBC patients do not have cirrhosis and to remove the perceived (but inaccurate) implication of an alcohol component to aetiology. A truly wonderful example of patient power in practice. We look forward to your continued support.



Professor David Jones, Newcastle University

Primary biliary cholangitis (What's in a name?)

The name Primary Biliary Cirrhosis originated in the 1950s when the condition we now recognise as PBC was only rarely diagnosed and when it was, it was in patients who had already progressed to cirrhosis (Stage IV disease). This is no longer the case. Widespread antibody testing nowadays means that more patients are diagnosed, typically in the early stage of the disease (Stage I-III). This means that most cases don't have cirrhosis, making the term primary biliary cirrhosis inaccurate. Over-stating the severity can lead to real problems obtaining health and travel insurance. Furthermore, use of the term cirrhosis can lead to stigmatization because the public inaccurately associates cirrhosis with alcohol.

All in all, Primary Biliary Cirrhosis is a term which is ripe to be changed. Now, owing to the combined efforts of PBC groups across the world (led by Robert Mitchell-Thain from the PBC Foundation) and PBC experts, this is about to happen. Little over a year after the idea was launched, all of the world's professional bodies managing liver disease have agreed to change the term to ***Primary Biliary Cholangitis*** (retaining the still useful abbreviation PBC). The final step is to get the new term adopted into the international directory of diagnostic terms. It will take time for the new term to enter widespread use but this is a very significant step in the right direction. UK-PBC has been delighted to support this patient-driven initiative right the way through

The UK-PBC Research Cohort

National Recruitment

Recruitment into the UK-PBC Research Cohort continues apace! The average rate of recruitment in 2015 has been 33 participants per month. Figure 1 shows overall recruitment in 2014/15. Of note, 694 participants have been recruited since the UK-PBC initiative started, 01.01.2014. A total of 5,155 PBC patients across the UK are now enrolled in the cohort.

We have recently amended our study documentation to allow the UK-PBC research team to send information about third-party studies directly to participants in the cohort. This is part of a broad ambition to improve equity of access to research for PBC patients across the UK. Equity of access is important – and for this reason, we believe that every PBC patient in the UK should be enrolled in the cohort. It is a realistic ambition – but it depends on the ongoing efforts of collaborating teams across the country. We know that collaborating teams work hard to recruit patients; it is worth the effort.

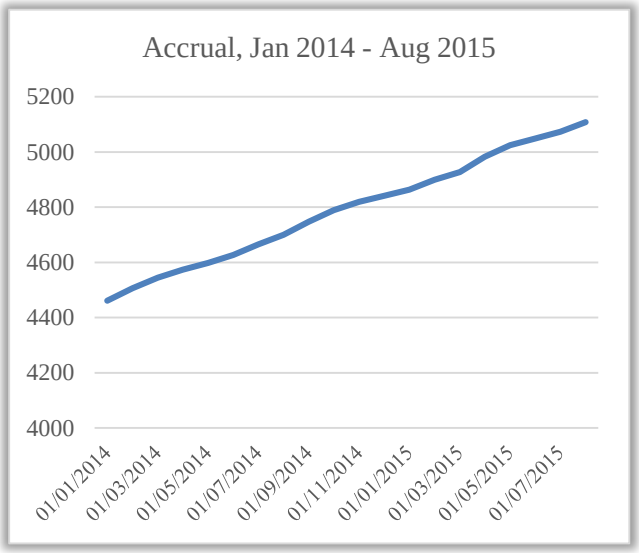


***Figure 1**: Recruitment to the UK-PBC Research Cohort since 01.01.2014. Note steady recruitment at an average rate of 33 participants per month.*

Regional recruitment

Figure 2 shows overall recruitment from regions and hospitals across the UK. It is clear that recruitment is disproportionately high in some regions – and disproportionately low in others. Improving research support in under-recruiting regions is a priority. Please do get in touch if you need our help to obtain additional support for research activity at your centre.

Important developments

The UK-PBC Database

Up to now, the study database has been a Microsoft™ Access database that was designed when the UK-PBC Genetics Study first started in 2007. The old database is no longer fit for purpose. For this reason, we commissioned Dr Tony Bennett of Illuminaries Ltd ® to design a new database that would fulfil the needs of the growing project. The new database is now ready for use.

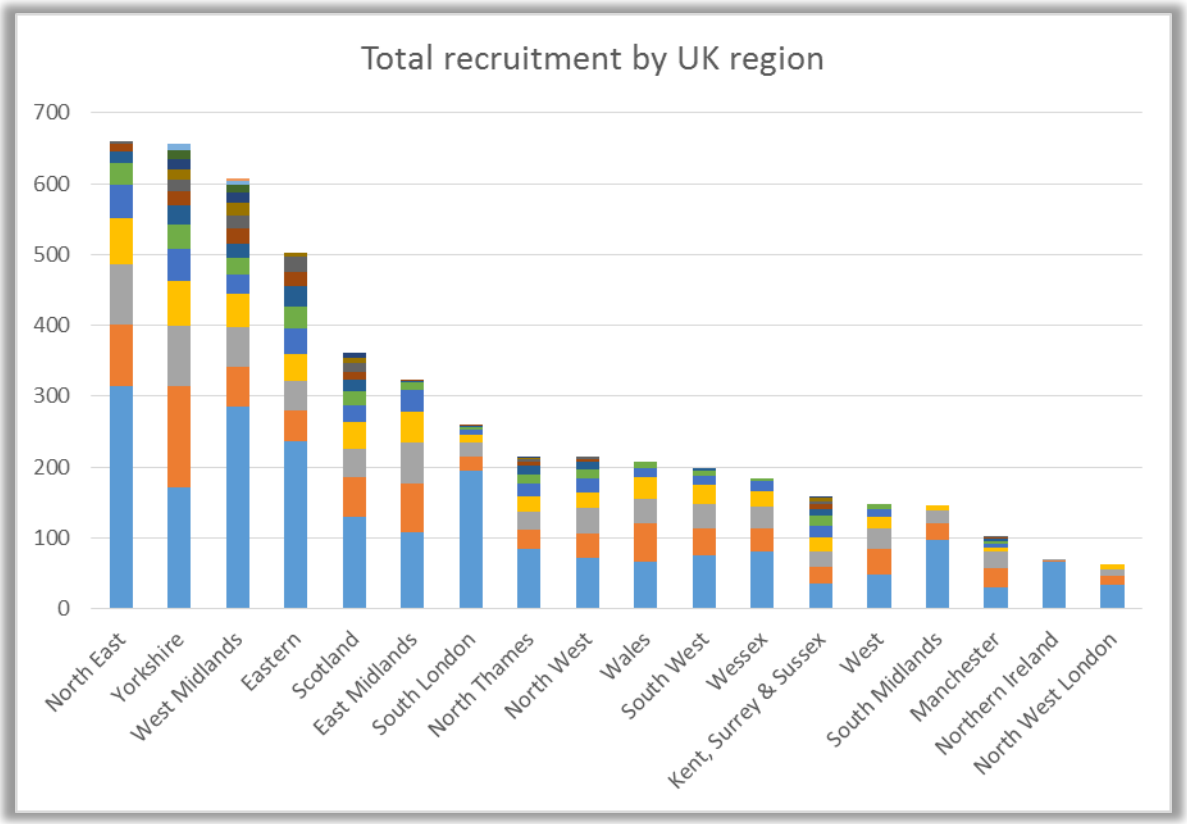


Figure 2: Overall recruitment to the UK-PBC Research Cohort in each CLRN or devolved nation. Recruitment is disproportionately low in some regions. Better support for collaborators in these regions is a priority for UK-PBC.

A major advantage of the new database is that research staff in collaborating centres will be able to log into it from any NHS computer to view information about participants recruited from their own centre. (They will not be able to view information about participants from other centres.) They will also be able to complete Case Record Forms (CRFs) online and upload the results of medical investigations directly into the database.

The new database has been vetted and approved by the information governance (IG) team at Cambridge University Hospitals NHS Foundation Trust. A notification of substantial amendment permitting use of the database has been submitted to the Research Ethics Committee (REC). Once approved by the REC, the amendment will be submitted to the IG and R&D departments of each collaborating centre. Research staff in collaborating centres may start to use the database as soon as local approval has been obtained.

Re-consenting the cohort

The Participant Information Sheet (PIS) and Informed Consent Form (ICF) in current use were written in 2007; they are inadequate for recent developments in the UK-PBC Research Cohort. For this reason, the PIS and ICF have been extensively revised. In essence, revisions to the PIS and ICF are as follows:

- Consent for ongoing clinical data capture;
- Consent for sharing of pseudonymised data with third party investigators;
- Consent for sharing of pseudonymised samples with third party investigators;
- Consent to receive information about third party studies.

We believe these changes will facilitate global research into PBC, enabling rapid development of better treatments for this condition. Moreover, these changes align UK-PBC with the **NIHR BioResource**, **NIHR BioResource – Rare Diseases** and the **NIHR RD – TRC**.

The revised PIS and ICF have been approved by the research ethics committee (REC). They will now be submitted to the R&D departments of collaborating centres. Following local R&D approval, the UK-PBC research team will begin the huge task of re-consenting every participant in the cohort. This will be coordinated by Ms Nikoletta Varvaropoulou, project manager for the UK-PBC Genetics Study. If you have any questions about this process, please do get in touch with Nikki.

Re-genotyping the cohort

Before the end of the year, we will undertake GWAS-level genotyping of DNA samples from every participant in the UK-PBC Research Cohort (some 5,100 patients with PBC). In addition, we will undertake GWAS-level genotyping of approximately 1,000 samples from an Italian PBC cohort. In the first instance, these genotype data will be used for the following experiments:

- Case-control GWAS of PBC to identify additional susceptibility loci for the disease;
- Within-case, genome-wide time-to-event analysis of PBC to identify risk loci for disease progression;
- Within-case GWAS of UDCA responders versus non-responders to identify risk loci for treatment responsiveness.

All of these experiments require extensive clinical information. Currently, this information is captured using the clinician questionnaire (CQ) and supplementary clinician questionnaires (SCQs). Research teams in collaborating centres have been assiduously completing these questionnaires for several years. In fact, data captured using the CQ and SCQs was used to derive and validate the UK-PBC Risk Score.

With large-scale genetics experiments on the horizon, it is imperative that we complete the clinical dataset in good time. We therefore ask research staff in collaborating centres to complete and return any outstanding CQs and SCQs as soon as possible. We appreciate this is a major undertaking – and we are immensely grateful to everyone in the UK-PBC Consortium for their hard work collecting these data.

The UK-PBC Nested Cohort Study

The Nested Cohort Study is aimed at the molecular and cellular characterization of PBC patients, in particular UDCA responders versus non-responders. Participants in the study attend two or three research visits at UK-PBC Research Centres, when diverse biofluid samples are collected. A proportion of participants undergo a research liver biopsy. The samples are analysed using a number of cutting-edge ‘omic techniques.

The Nested Cohort Study is now running at 22 centres in four regions. A total of 14 participants have been recruited. Recruitment is slightly behind schedule. This is partly because of delays obtaining R&D approval and partly because the eligibility criteria for the study are unnecessarily strict. However, an amendment has recently been drafted that will facilitate recruitment. Briefly, this amendment includes the following changes:

- Any patient with a confirmed diagnosis of PBC will be eligible to join the study;
- PBC patients will attend a single research visit when they will provide biofluid samples;
- At this visit, a proportion of patients will be consented for a research biopsy.

As soon as the amendment has been approved, it will be submitted to the R&D departments of collaborating centres. Changes to the Nested Cohort Study will be implemented as soon as local approval has been obtained. This will be coordinated by Mr Dimitrios Paximadas, project manager for the Nested Cohort Study. **In the meantime, please alert us to any newly-identified PBC patients**. Please contact Dimitrios if you have any queries.

Completed studies

Genome-wide meta-analysis of PBC

The manuscript describing the genome-wide meta-analysis (GWMA) of PBC has now been accepted for publication by *Nature Communications*. Congratulations to Professor Heather Cordell at Newcastle University, who led the analysis on behalf of the UK-PBC Consortium.

The UK-PBC Risk Score

It is well-established that the biochemical response to ursodeoxycholic acid (UDCA) strongly predicts long-term outcomes in PBC. Several prognostic models based on treatment response have been developed (e.g. the Paris I criteria). Increasingly, these models are used to risk-stratify PBC patients and guide their management. However, existing models do not take other prognostic variables into account. Furthermore, they fail to recognise a continuum of risk by dichotomizing PBC patients into responders or non-responders, at low or high risk of progressive liver disease.

Using data from 3,165 participants in the UK-PBC Research Cohort, Dr Marco Carbone and colleagues from the University of Cambridge have derived and validated a risk scoring system that overcomes these limitations. The UK-PBC Risk Score uses the patient's bilirubin, transaminases, ALP, albumin and platelet count to evaluate his or her absolute risk of developing liver failure within a defined time-frame. The scoring system is highly accurate and well-calibrated, achieving AUCs (area under receiver operating characteristic curve) above 0.9 in the validation cohort (**Figures 3 & 4**).

The UK-PBC Risk Score can be used guide management of PBC patients. For example, patients with higher risk scores despite treatment with UDCA may prioritized for second-line or experimental treatments. Conversely, those with low risk scores may be followed-up less frequently. A description of the UK-PBC Risk Score has been accepted for publication by *Hepatology* (http://www.ncbi.nlm.nih.gov/pubmed/26223498). The risk score calculator is available at the UK-PBC website (http://www.uk-pbc.com/resources/tools/riskcalculator/).

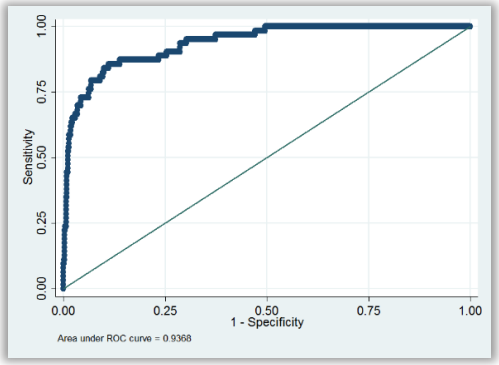


Figure 3: Receiver operating characteristic (ROC) curve for the 15-year UK-PBC Risk Score, showing AUC = 0.94

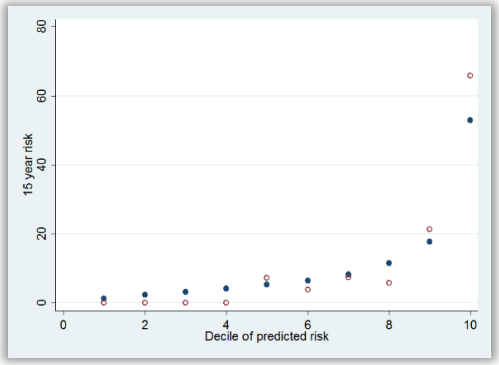


Figure 4: Observed versus expected risk per decile of the 15-year UK-PBC Risk Score showing that the risk score is well-calibrated.

Recent publications

For those interested in understanding more about risk stratification, Dr Palak Trivedi at the University of Birmingham has written a helpful review of the topic, something of value given the explosion of interest in this area! Palak's article in *Hepatology*, "Risk Stratification in autoimmune cholestatic liver diseases: Opportunities for clinicians and trialists" is now on Pubmed (http://www.ncbi.nlm.nih.gov/pubmed/26290473).

Those interested in PBC therapy will be excited to know that a new therapy may be on the market within the next 12-24 months. The new agent is obeticholic acid (OCA) (Hirschfield *et al*. Gastroenterology 2015, http://www.ncbi.nlm.nih.gov/pubmed/25500425), which is under review by the regulators in Europe and America at the time of writing.

Clinical trials supported by UK-PBC

Trial activity for UK-PBC/PBC patients in the UK is active and very exciting. Centres with an interest in PBC and trials have been working hard on existing studies and new ones are planned for the end of 2015, through into 2016.

As an update, **FF Pharma** are recruiting to a study of anti-CD40 in UDCA treatment non-responders; **Intercept** are soon to open a study of obeticholic acid in high risk advanced PBC, and **Novartis** have PBC studies en route to the UK, as does **Cymabay**, an American company interested in new therapies for PBC. The **Lumena** ASTBi study of itch in PBC is being analysed, as is an exciting **GSK** study of another ASTBi for use in itch. **RitPBC** continues to recruit in Newcastle targeting fatigue and the UK-PBC team itself are thinking ahead about investigator initiated studies that would benefit UK-PBC patients.

The UK-PBC team now has a Project Manager working towards our goal of fully engaging in PBC trials across patient, hospital, industry and CRN platforms: welcome Mr Zed Miah who is based in the Institute of Translational Medicine in Birmingham. Please do contact Zed if you have any questions about clinical trials and whether your patients might be eligible for them.

Thank you!

UK-PBC continues to make excellent progress. None of this would be possible without the support of every member of the UK-PBC Consortium. Once again, we thank you for your dedication to this unique research endeavor.

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