UK-PBC Newsletter

IS004 / DECEMBER 2016

Inside This Issue

Message from Professor Dave Jones

Time flies and it is already time for the Christmas newsletter for UK-PBC. Things continue to move very rapidly in the world of PBC (and UK-PBC). Following on from the FDA approval of OCA, EMA approval has now be granted and we now move forward towards NICE approval in the Spring. The trials programme continues to move forward at pace, with major presentations at the recent American Association for the Study of Liver Disease (AASLD) meeting on the first new itch treatment in a generation and the first PPAR-delta agonist. Fitting the new therapies together will be an important issue in the future. For those of us who remember empty sessions and no new treatments year after year, the sight of a full room to hear about major innovations in PBC was a true "pinch yourself" moment. I am pleased that the UK-PBC/BSG Treatment Guidelines for PBC are now out for review and will hopefully be published soon. Our work in this area has been further recognized by Gideon Hirschfield, who leads Workstrand 3, being invited to chair the group developing the new EASL guidelines. As for the UK-PBC, we are reaching a critical point (with a year to go) as all the datasets come together. Over the next 6 months we are expecting important and novel findings to emerge to finally shed light on both why some PBC patients have high risk disease and some have fatigue. All this needs, of course, well characterized patients so continuing to recruit patients into the nested cohort is really vital. UK-PBC has always been a team effort and we need a final push from the team to achieve our recruitment goals!

In other news, I am very pleased to announce that RARE-LIVER has been approved as a European Reference Network (ERN). This is great news for European hepatology and for patients in Europe with rare liver disease. I take this opportunity to thank everyone for all their efforts with this. All 28 centres (including a number of UK-PBC sites) sailed through the application process (as did the Network), with no issues arising at all. The quality of the application has been commented on. This reflects, I think, the hard work everyone has put in to getting RARE-LIVER this far. There is more hard work to be done, and I hope to update you in the new year!

Professor David Jones, Newcastle University

UK-PBC Genetics Study

National Recruitment

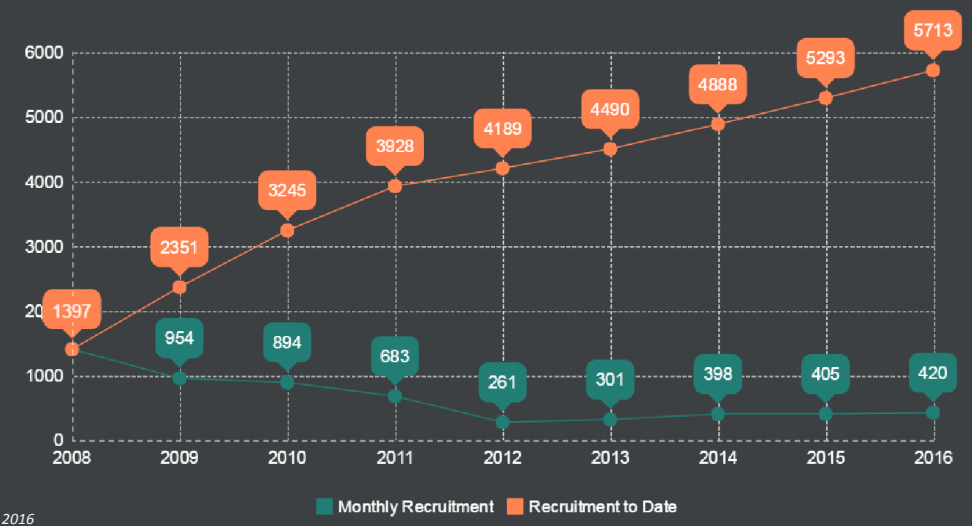
Recruitment to the UK-PBC Genetics Study continues apace. The recruitment tally now sits at 5,608 participants. We are grateful to the research teams in all collaborating center's for their hard work, recruiting participants and completing CRFs.

This edition we have provided a more detailed recruitment breakdown. A recurring newsflash in a similar style is going out every other month to keep PIs and nurses up to date with recruitment progress, and say a big thank you to all for their continuous support.

RECRUITMENT

REPORT

RECRUITMENT OVER TIME

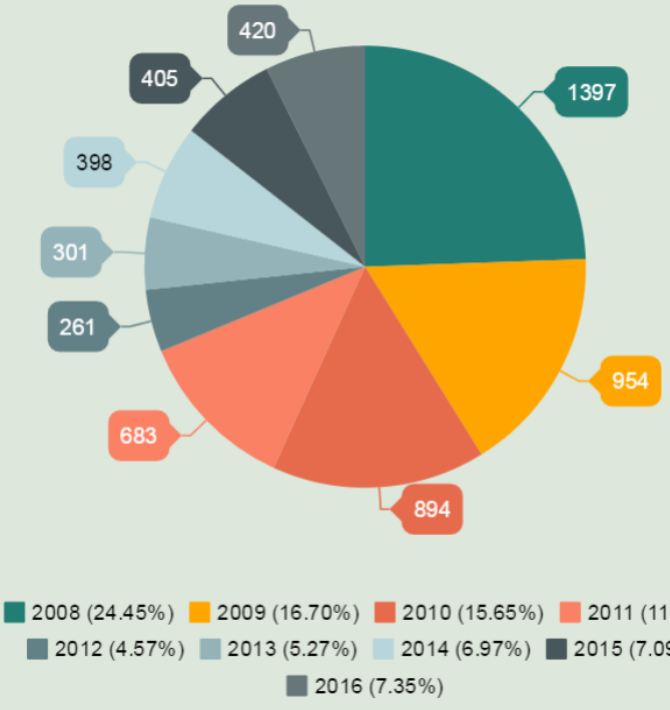


DATA CORRECT ON: 20 Dec 2016

TOTAL RECRUITMENT TO DATE

5713

BREAKDOWN BY YEAR



powered by Piktochart make information beautiful

Recruitment Report Continued...

Congratulations to research teams at the following sites who recruited participants in the **second and third quarter** of 2016.

Site	Investigator	Participants
John Radcliffe Hospital	Dr Jane Collier	13
Freeman Hospital	Professor David Jones	10
Queen Alexandra Hospital	Dr Richard Aspinall	10
Basildon University Hospital	Dr Javaid Subhani	9
Royal Surrey County Hospital	Professor Aftab Ala	8
St James's University Hospital	Dr Mark Aldersley	8
Blackpool Victoria Hospital	Dr Christopher Shorrock	7
Addenbrooke's Hospital	Dr Graeme Alexander	6
New Cross Hospital	Dr Matthew Brookes	6
Queen Elizabeth Hospital (Gateshead)	Dr Andrea Broad	6
The Royal Free Hospital	Dr Douglas Thorburn	6
Bristol Royal Infirmary	Dr Fiona Gordon	5
Southend University Hospital	Dr Gary Bray	5
Chesterfield Royal Hospital	Dr David Elphick	4
Kettering General Hospital	Dr Debashis Das	4
King's College Hospital	Dr Michael Heneghan	4
Lister Hospital	Dr Martyn Carter	4
Warrington Hospital	Dr Subramaniam Ramakrishnan	4
Barnsley Hospital	Dr Kapil Kapur	3
Broomfield Hospital	Dr Chirag Oza	3
Gloucestershire Royal Hospital	Professor Jonathan Brown	3
Hull Royal Infirmary	Dr George Abouda	3
Royal Bolton Hospital	Dr George Lipscomb	3
Royal Liverpool University Hospital	Dr Martin Lombard	3
Royal Stoke University Hospital	Dr Alison Brind	3
St Mary's Hospital, Isle of Wight	Dr Leonie Grellier	3
St Richard's Hospital	Dr Jocelyn Fraser	3
Sunderland Royal Hospital	Dr Harriet Mitchison	3
University Hospital of North Durham	Dr Francisco Porras Perez	3
Warwick Hospital	Dr Jeremy Shearman	3
West Middlesex University Hospital	Dr Carole Collins	3

Re-consent of 65% of the original UK-PBC research cohort

As part of the re-consent process, the revised PIS and ICF were sent to each and every participant at the beginning of April 2016. We sent a reminder in mid-June to all participants who have not responded to the original mailshot. By November 2016, more than 3,364 participants overall had signed and returned their revised ICFs. This is more than 65% of the original cohort, which is a fantastic response!

For UK-PBC to remain successful, however, it is imperative that all participants sign and return the revised ICF. For this reason…

> ...please gently encourage the participants to sign and return their revised ICFs, by contacting them at their next hospital attendance or over the phone.

We recognise that this is a huge task. We are happy to assist collaborators in any way that we can. Please let us know how we can help. If you have any questions about the re-consenting process, please contact Nikki Varvaropoulou (nv280@medschl.cam.ac.uk).

THANK YOU FOR YOUR CONTINUOUS SUPPORT!

A massive thank you for the 3,100 electronic case report forms (eCRFs) completed overall throughout 2016 for the GWAS of UDCA response and genome-wide time-to-event analysis (1,600 only CQ1s). We are immensely grateful to you for your hard work –and your patience during those demanding undertakings.

Steve and Anne have started the process of Quality Checking (QC'ing) the data and may get in touch with simple queries. Thank you for help with this, as well.

If you have any questions about the UK-PBC Clinical Database, the eCRFs or the QC'ing process, please contact Steve Flack (spf36@medschl.cam.ac.uk).

GWAS of UDCA response

The first batch of DNA samples from the UK-PBC collection were dispatched to the Wellcome Trust Sanger Institute (WTSI) in September. The next batch will be sent in December. We anticipate that genome-wide genotyping of 5,000 DNA samples from the research cohort will be complete by January 2017, with analysis commencing shortly thereafter. We are on track for a fabulously large study that will shed light on the mechanisms of UDCA response. Thank you for your continuous efforts to recruit patients into the PBC Genetics Study.

In addition, statisticians in Newcastle and Italy are currently refitting the UK-PBC Risk Score using data from the vastly expanded cohort to improve its accuracy and include measures of precision and bias.

More than 200 FFPE liver biopsy specimens from PBC patients in the cohort have been retrieved and transferred to Newcastle for immunohistochemistry and gene expression profiling, aiming to identify histological markers of risk.

These are exciting and novel experiments – thank you for supporting this initiative!

The NHS (or CHI) number used to obtain data extracts

The IT service of individual collaborating centres will use the NHS (or CHI) number to prepare EPR data extracts for the UK-PBC Genetics Study's re-consented participants. EPR data extracts include results of blood tests, as well as radiology, histopathology and endoscopy reports, collected as part of the UK-PBC Genetics Study. The Queen Elizabeth Hospital, Addenbrooke's Hospital and Royal Derby Hospital have already provided data extracts, and more centres follow suit. The NHS (or CHI) number will also be used to obtain linked datasets from NHS Digital, ISD in Scotland and Wales Informatics Service. Our application to ISD has been submitted and the application to NHS Digital is under preparation.

The data extracts will help research nurses reduce the time spent on completion of eCRFs. Thank you for providing the NHS (or CHI) numbers for this purpose. Your involvement makes this possible.

Ms Nikki Varvaropoulou would be happy to address any further questions regarding the request for NHS numbers (nv280@medschl.cam.ac.uk).

The UK-PBC Nested Cohort Study

The revision of the UK-PBC Nested Cohort Study has broaden the eligibility criteria, and the study now counts 161 participants! The UK-PBC Nested Cohort Study is open in five regions: North East and North Cumbria, West Midlands, Eastern, North West London and East Midlands. It has taken a considerable time to establish the research networks to support recruitment of participants – but this has finally been achieved! Now recruiting at a rate of at 15 – 20 participants per month!

For the majority of participants, the study therefore involves a single research visit and low-risk sample collection. Participants will potentially benefit from detailed clinical characterisation and 'deep phenotyping'.
For these reasons, we encourage collaborating research teams to invite all patients under follow-up for PBC, incipient PBC or PBC/AI overlap syndrome.

On the back of this project, metabonome-wide analysis and microbiome profiling of samples from more than 120 participants is underway at Imperial College, London, and transcriptional profiling of Th1, Th17, Treg and B-cells isolated from 20 participants at the extremes of the treatment response phenotype is underway in Birmingham and the Stratified Medicine Core Laboratory in Cambridge (see Workstrand 2, below).

Mr Jonathan Badrock (project manager for the Nested Cohort Study) will be in touch with collaborating teams to talk them through the amendment and methods to identify and recruit patients. Inviting patients to participate in the Nested Cohort Study is very simple, however, using the Invitation App. If you have any questions about the Nested Cohort Study, please contact Jonathan (Telephone: 01223 769088; Email: jb2069@medschl.cam.ac.uk).

DO YOU HAVE ACCESS TO THE UK-PBC CLINICAL DATABASE?

DO YOU HAVE ACCESS TO THE INVITATION APP?

If not, please contact Steve Flack (spf36@medschl.cam.ac.uk)

Work Strand 2 Update

Further to our research looking at why some patients do not respond to Ursodeoxycholic acid (UDCA) treatment we have now collected retrospective tissue biopsies and explants from our different UK-PBC partners: Newcastle, Nottingham, Sheffield and Cambridge. Initially, we evaluated different cellular markers of T cells and senescent biliary epithelium (BEC) in a small number of non-responders vs responders to UDCA. Now with greater numbers of cases from across the UK our cellular profile of different PBC patients will increase in power once counting is complete. Transcriptomic profile of these same patients in this larger set is also underway allowing us to characterise 'molecular biomarkers'. Together with the immunohistochemistry we hope to determine a mechanism behind non-response to UDCA.

'Profiling' in our nested cohort samples in a similar fashion could potentially be of diagnostic value aiding future therapeutic intervention.

Work Strand 3 Update
Clinical trials supported by UK-PBC

We are continuing to support a number of PBC trials, and the process is starting to get a bit more smoother as more patient start to sign the new 2016 consent form. This new consent form allows the UK-PBC to contact the patient directly regarding clinical trials, as long as the patient has ticked the correct box and provided permission for this. This has been immensely important, as the previous process (which is still simultaneously underway for patients who have not signed the new consent form yet) requires the UK-PBC to approach the patients current clinician and asking him/her to forward study information onto the patient; which often has some delays.

The up-to-date trial sites is as follows:

- **Intercept Pharmaceuticals** (https://clinicaltrials.gov/show/NCT02308111)

  Sites:
  - Newcastle upon Tyne Hospitals NHS Foundation Trust
  - University Hospitals Bristol NHS Foundation Trust
  - Plymouth Hospitals NHS Trust
  - Western Infirmary/Gartnavel General Hospital
  - University Hospitals Birmingham NHS Foundation Trust
  - Cambridge University Hospitals NHS Foundation Trust
  - Nottingham University Hospitals NHS Trust
  - Forth Valley Royal Hospital

- **Novartis Pharmaceuticals** (https://clinicaltrials.gov/show/NCT02516605)

  Sites:
  - Cambridge University Hospitals NHS Foundation Trust
  - Royal Free London NHS Foundation Trust
  - Newcastle upon Tyne Hospitals NHS Foundation Trust
  - University Hospitals Birmingham NHS Foundation Trust

- **Fast Forward Pharmaceuticals** (https://clinicaltrials.gov/show/NCT02193360)

  Sites:
  - Newcastle upon Tyne Hospitals NHS Foundation Trust
  - University Hospitals Birmingham NHS Foundation Trust
  - Royal Free London NHS Foundation Trust

CymaBay MBX8025 Trial

CymaBay Therapeutics looked at the safety of their drug called MBX-8025, and assessed how well it is tolerated by patients and whether it is an effective treatment for patients with PBC. The trial was stopped earlier than anticipated as early review of data showed marked improvements in patients Alkaline Phosphatase blood results for those who were taking the study drug. Twenty-six patients took part in this trial. UK-PBC worked closely with CymaBay Therapeutics throughout the study, including identifying which hospitals to open the study at, by identifying potential patients and also recruiting patients into the study. CymaBay will now investigate the best dose

PBC Clinical Guidelines

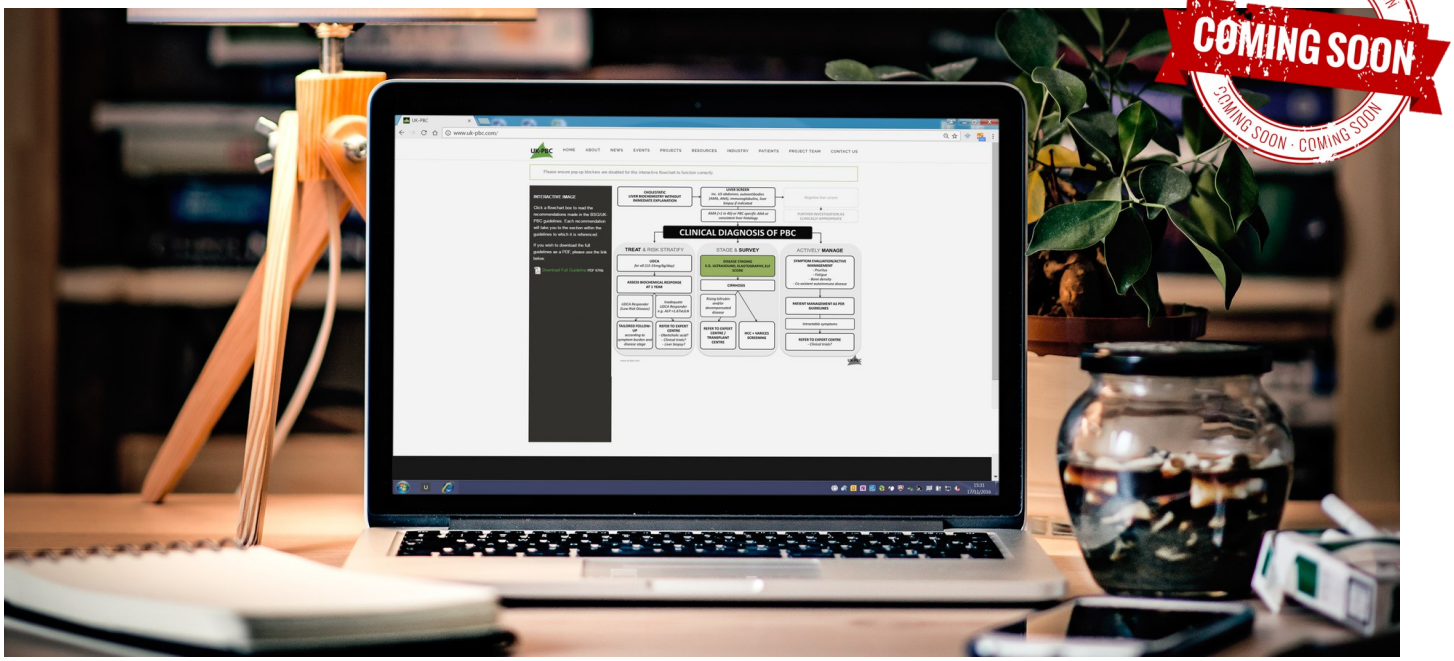
We previously mentioned that the UK-PBC team, in partnership with the British Society of Gastroenterology (BSG) have been working on producing clinical guidelines that can be used to assist clinicians in treating and managing patients with PBC. These guidelines are predominantly targeted towards those Gastroenterologists and Hepatologists leading the care of patients with PBC, usually in secondary care, but may also be of value to primary care physicians, nurses and even patients.

The PBC Foundation has played an invaluable role throughout the development process in producing these guidelines, and CEO of the PBC Foundation, Collette Thain (MBE) was a member of the Guidelines Development Group.

The initial draft of the guidelines was published on the UK-PBC website (www.uk-pbc.com) for a short period, to allow patients and other stakeholders to provide comments. The guidelines were also circulated to various professional bodies including the British Liver Trust, Royal College of General Practitioners, and British Association for the Study of the Liver, as well as the Liver Section of the British Society of Gastroenterology. Feedback was also received from patient group, Liver North.

These guidelines followed the strict criteria set out by the BSG, and have now been submitted for formal review by the BSG. If you are a BSG member, you can access the guidelines under the "draft section" of the website. More information can be found on the UK-PBC website (www.uk-pbc.com).

Interactive Care Pathway



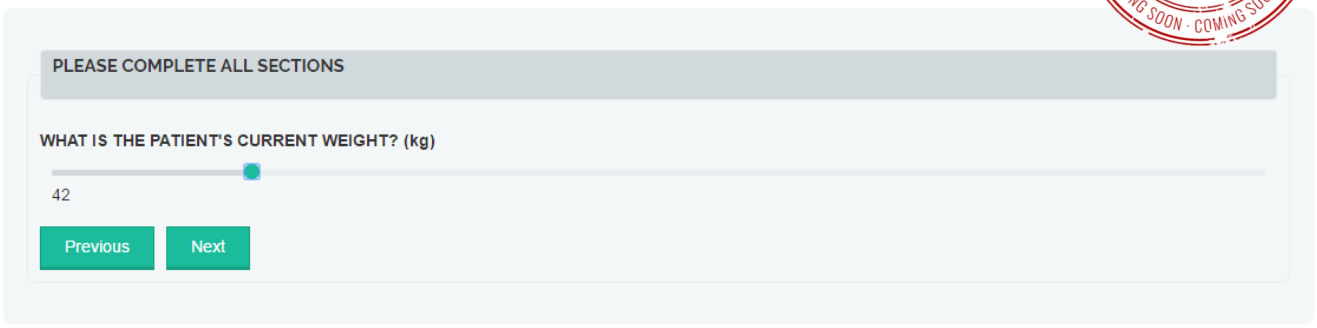
To further help assist health care professionals in treating and managing patients with PBC, the UK-PBC has created an interactive care pathway. The interactive care pathway allows clinicians, nurses and even patients to easily understand what to expect once a diagnosis of PBC has been made. Each step is linked back to the British Society of Gastroenterology/UK-PBC Primary Biliary Cholangitis Treatment and Management Guidelines. The interactive care pathway will be available on the UK- UK-PBC website (www.uk-pbc.com) in the coming weeks.

In the interim, a standard non-interactive version is available to view and download immediately. A high resolution 300 DPI version is also available if you wish to use this image for presentations. P

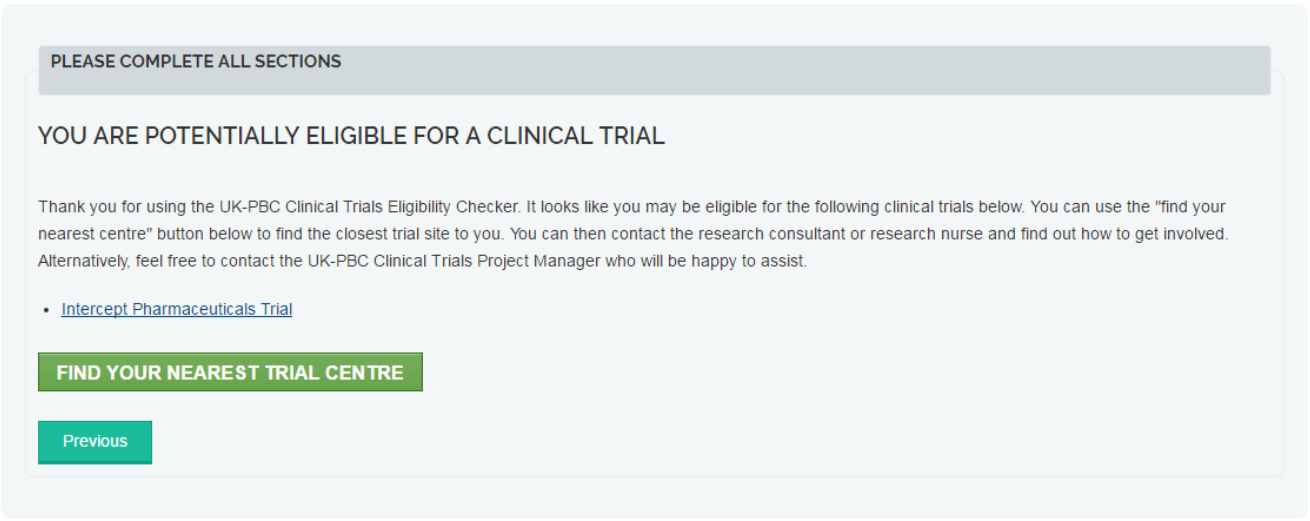
You can view and download this by visiting the following link: http://www.uk-pbc.com/resources/tools/care-pathway/

UK-PBC Clinical Trials Eligibility Checker

There are three clinical trials currently taking place in the UK for patients with PBC. We want to be able to help patients find clinical trials that they may be suited for. The UK-PBC team are also proud to announce another online tool aimed at helping patients do exactly this!



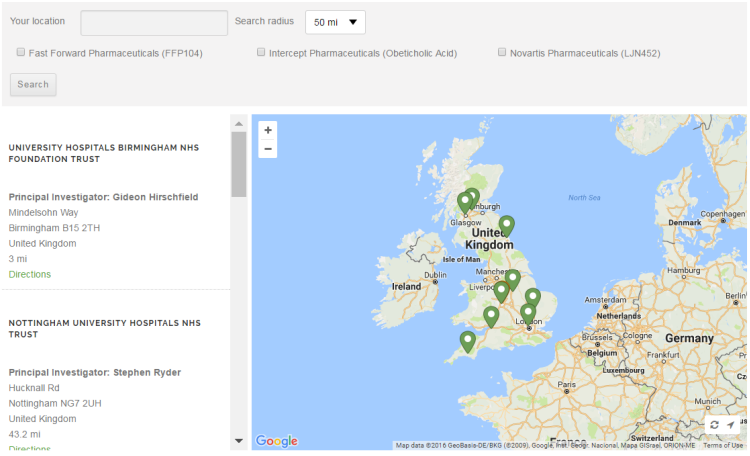
By simply answering some questions on their health status, such as current weight (see image above) the tool will show which of the three studies they are eligible for (see image below). The patient will require a copy of their latest blood results in order to use this tool.



A "Find Your Nearest Trial Centre" button will appear, which then takes the user to the next tool, the UK-PBC Clinical Trials Locator.

UK-PBC Clinical Trials Locator

The UK-PBC Clinical Trials Locator can be used in conjunction with the UK-PBC Clinical Trials Eligibility Checker or independently. This tool simply allows a user to enter their post code, and it will locate all UK trial sites taking part in the three current PBC clinical trials. The user can filter results by a certain trial, or by a certain radius.



AASLD Update

The American Association for the Study of Liver Diseases (AASLD) annual Liver Meeting® took place on the **11-15th November 2016** and was held at the John B. Hynes Veterans Memorial Convention Center in the heart of downtown **Boston**. The UK-PBC team delivered key presentations on a number of clinical trials which the UK-PBC supported and recruited to this year.

Professor David Jones, Professor of Liver Immunology at the Institute of Cellular Medicine, Newcastle University, delivered a late-breaking presentation on behalf of CymaBay Therapeutics, describing results from a phase 2 proof-of-concept study of MBX-8025 - an orally administered potent and selective peroxisome proliferator-activated receptor delta (PPARδ) agonist. The UK-PBC has worked closely with CymaBay Therapeutics throughout the study, including preliminary site identification, recruitment into the study and the utilisation of the UK-PBC Genetics Study Research Cohort and Consortium for potential patient identification. CymaBay Therapeutics stopped the study early, due to top line efficacy and safety data clearly demonstrating proof-of-concept by showing marked improvements in biochemical markers of cholestasis. The abstract, entitled "A phase 2 proof of concept study of MBX-8025 in patients with Primary Biliary Cholangitis (PBC) who are inadequate responders to ursodeoxycholic acid (UDCA)" is published on the AASLD website at www.aasld.org.

UK-PBC has consistently worked alongside Intercept, including preliminary site identification, recruitment into clinical trials and the utilisation of the UK-PBC Genetics Study Research Cohort and Consortium for potential patient identification. More recently, the UK-PBC investigators have been heavily involved in the FDA approval process for Ocaliva®. Data from the UK-PBC played a key role in convincing the committee to vote 17 to 0 to support FDA approval of Ocaliva®, which will is now the first new drug approved for use in PBC in 20 years. Professor Gideon Hirschfield, Professor of Autoimmune Liver Disease at the University of Birmingham, delivered a oral presentations on behalf of Intercept Pharmaceuticals, on Ocaliva's® (brand name for Obeticholic Acid, OCA) effects on non-invasive fibrosis measurements in patients with PBC. The abstract for the presentation entitled "Long-Term Effect of Obeticholic Acid on Transient Elastography and AST to Platelet Ratio Index in Patients with PBC" can be found on the AASLD website at www.aasld.org.

Dr Vinod Hegade, Clinical Research Fellow at Newcastle University, presented the results of a phase 2 clinical trial of Ileal Bile Acid Transporter Inhibitor GSK2330672 in patients with PBC and with symptoms of pruritus. The aim of the trial was too investigate the safety, tolerability and effect of GSK672 administration. The trial was conducted at two specialist centres in the United Kingdom (Newcastle and Birmingham), with a double-blind, randomised, placebo controlled design. A total of 21 patients, were enrolled. The finding concluded that two weeks of oral twice daily GSK672 was well tolerated and reduced itch intensity in PBC patients with pruritus. The full abstract and results can be downloaded on the AASLD website at www.aasld.org.

GSK are now planning the next phase of the clinical trial for this study drug and details will appear on ClinicalTrials.gov.

Publications

A Placebo-Controlled Trial of Obeticholic Acid (Ocaliva) in Primary Biliary Cholangitis

The New England Journal of Medicine (NEJM)

Nevens F, Andreone P, Mazzella G, Strasser SI, Bowlus C, Invernizzi P, Drenth JP, Pockros PJ, Regula J, Beuers U, Trauner M, Jones DE, Floreani A, Hohenester S, Luketic V, Shiffman M, van Erpecum KJ, Vargas V, Vincent C, Hirschfield GM, Shah H, Hansen B, Lindor KD, Marschall HU, Kowdley KV, Hooshmand-Rad R, Marmon T, Sheeron S, Pencek R, MacConell L, Pruzanski M, Shapiro D; POISE Study Group

Nevens *et al.* on behalf of Intercept Pharmaseuticals have published the key results of the Intercept Phase 3 POISE trial of Ocaliva (Obeticholic Acid) for the treatment of patients with PBC. Ocaliva, given as a monotherapy or in combination with standard of care met the primary endpoint of the POISE trial and improved multiple biochemical disease markers as compared to placebo with high statistical significance. The full paper can be read on the NEJM website: http://www.nejm.org/doi/full/10.1056/NEJMoa1509840

Early Molecular Stratification of High-risk Primary Biliary Cholangitis

EBioMedicine

Hardie C, Green K, Jopson L, Millar B, Innes B, Pagan S, Tiniakos D, Dyson J, Haniffa M, Bigley V, Jones DE, Brain J, Walker LJ

Using long-term follow-up data to define risk at presentation, 6 high-risk PBC patients and 8 low-risk patients were identified from biopsy, transplant and biochemical archival records. Findings suggest high- and low-risk PBC are biologically different from disease outset and senescence an early feature in high-risk disease. Identification of a high-risk 'signal' early from standard FFPE tissue sections has clear clinical utility allowing for patient stratification and second-line therapeutic intervention. The full paper can be read here: https://www.ncbi.nlm.nih.gov/pubmed/27913155

The inter-relationship of symptom severity and quality of life in 2055 patients with primary biliary cholangitis.

Alimentary Pharmacology & Therapeutics

Dyson JK, Wilkinson N, Jopson L, Mells G, Bathgate A, Heneghan MA, Neuberger J, Hirschfield GM, Ducker SJ, UK-PBC Consortium, Sandford R, Alexander G, Stocken D, Jones DE

Dyson *et al.* studied the impact of age at presentation on perceived QoL and the inter-related symptoms which impact upon it. Of the 1990 patients reporting a global PBC-QoL score, 66% reported good/neutral scores and 34% reported poor scores. Each 10-year increase in age at presentation was associated with a 14% decrease in risk of poor perceived QoL The full paper can be accessed here: https://www.ncbi.nlm.nih.gov/pubmed/27640331

VISIT THE UK-PBC WEBSITE FOR LATEST PUBLICATIONS:

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