UK-PBC Newsletter

IS002 / WINTER EDITION

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"... next year will be a critical one for PBC as we start to move towards true stratified medicine..."

Message from Professor Dave Jones

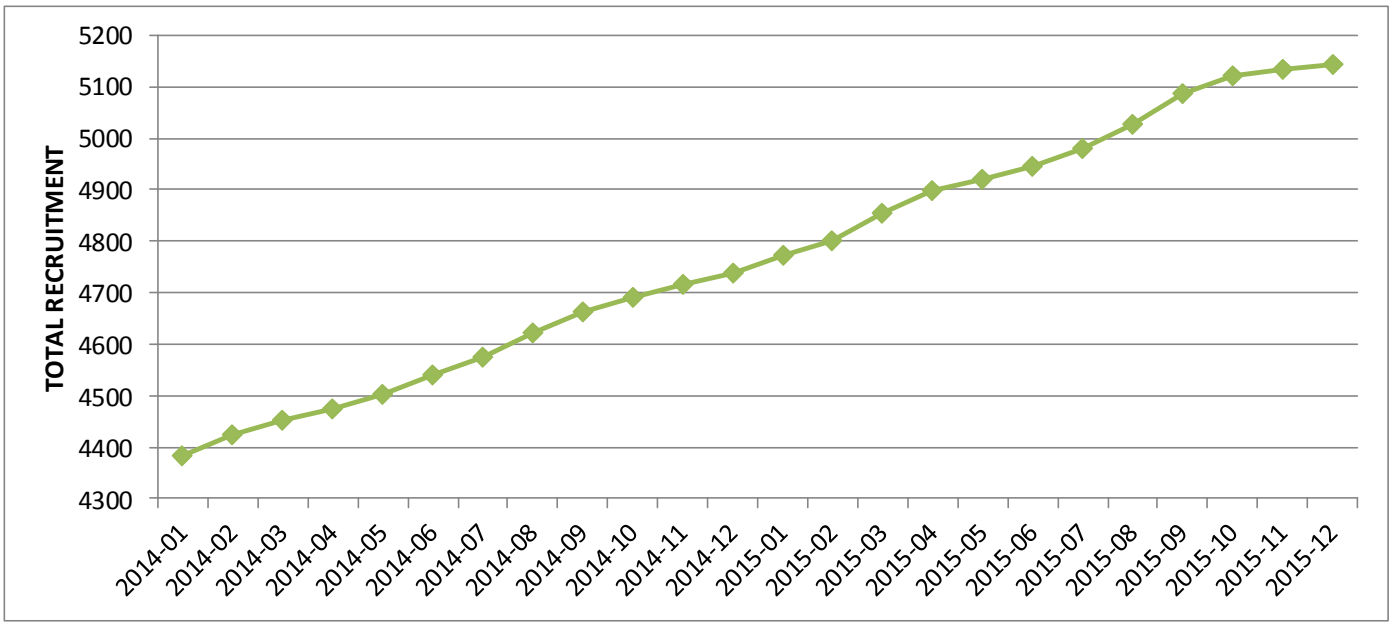
Time is flying by and it is now time for me to welcome you all to the Winter newsletter for UK-PBC. This has been a wonderful 6 months for PBC patients and for the UK-PBC project. The highlight has been the success of all the efforts made by the PBC-Foundation and others to change the name of PBC to **Primary Biliary Cholangitis**. This change, which is supported by UK-PBC, is something that matters hugely to patients with PBC. The other highlight has been the further success for the trials programme. Trials supported by the NIHR and GSK have now finished recruitment and findings are awaited. Trials supported by Intercept, FFPharma, Novartis and Cymabay are either open or about to open early next year. Recruitment to all is supported by UK-PBC. The UK-PBC project is, thanks to the fantastic work of the team and clinicians and PBC patients across the UK, going from strength to strength. 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 the hugely exciting programme of clinical trials. The next year will be a critical one for PBC as we start to move towards true stratified medicine (developing an understanding of the disease as it impacts on individual patients so we can start to target the right treatment to the right patient). This is the ultimate goal of the project and is absolutely attainable. With everyone's continued efforts we can reach the goal.

Professor David Jones,
Newcastle University

UK-PBC Genetics Study
National Recruitment

Research teams in collaborating centres across the country continue to work hard to recruit PBC patients into the UK-PBC Research Cohort. Recruitment between January 2014 to December 2015 has been excellent, with 805 patients being recruited. On average, this equates to 34 patients per month, with our best month being September 2015 (61 patients).

The UK-PBC Research Cohort now consists of more than **5,300** participants. Congratulations and thank you for your considerable efforts!



Re-consenting the UK-PBC Research Cohort

In the last UK-PBC Newsletter, we reported that documentation for the UK-PBC Genetics Study had been revised with three main objectives:

- To allow large-scale clinical data capture from now into the future;
- To allow sharing of data and samples with independent third-party investigators;
- To allow recall of participants to other research studies.

We revised the study documentation because we believe the problem of PBC will only be solved if investigators across the globe can share their resources, knowledge and expertise.

The revised documentation was approved by the Research Ethics Committee in the summer. The approved documentation was subsequently submitted to the Research and Development Departments of collaborating centres. Having secured R&D approval from most collaborating centres, we will aim to re-consent the entire UK-PBC Research Cohort in the first quarter of 2016. **This process is outlined on the right.**

The mailshot will be a major exercise. To get this done efficiently, we will work with a commercial organisation called Ciconi® (http://www.ciconi.co.uk/) that has all the required NHS permissions in place to generate and dispatch the mailshot, as well as bulk scan the signed ICFs. Furthermore, Dr Tony Bennett from Illuminaries Ltd® (http://www.illuminaries.co.uk/) will revise the UK-PBC Database (see below) to accommodate the new ICF. We are working on a solution to ensure that electronic copies of the signed ICFs are available to the respective local research teams via the UK-PBC Database.

If you have any concerns or queries about the re-consenting process, please contact Ms Nikoletta Varvaropoulou (Email: nv280@medschl.cam.ac.uk; Tel: 01223 746771).

1 We will undertake a test run in which the revised participant information sheet (PIS) and informed consent form (ICF) will be sent by surface mail to participants recruited from Cambridge University Hospital NHS Foundation Trust. The mailshot will be undertaken mid-January. We will evaluate the succesas of postal re-consent in February. Based on this, we will proceed to Stage 2 of the re-consent process.

2 If the response rate to postal re-consent is acceptable, we will send the revised PIS and ICF to the remainder of the UK-PBC Research Cohort by surface mail. This mailshot will be undertaken early March. We anticipate that participants receptive to postal re-consent will return their signed ICFs within one month.

3 If the response rate to postal re-consent is acceptable, we will send the revised PIS and ICF to the remainder of the UK-PBC Research Cohort by surface mail. This mailshot will be undertaken early March. We anticipate that participants receptive to postal re-consent will return their signed ICFs within one month.

The UK-PBC Database

In the last edition of the UK-PBC Newsletter, we reported that a new UK-PBC Database had been developed by Dr Tony Bennett from Illuminaries Ltd®. A major advantage of the new database is that research staff in collaborating centres can log into it from any NHS computer to view information about participants recruited from their own centres (they are not able to view information about participants from other centres). They can also complete Case Record Forms (CRFs) online and upload the results of medical investigations directly into the database.

The database went live towards the end of 2015 and research teams in most collaborating centres have started to use it. So far, we have received very positive feedback. Research teams have found the database easy to use – and better than the previous, paper-based system. Further developments to the UK-PBC Database are planned. We will alert you with each new release.

If you do not have access to the UK-PBC Database or you are struggling to use it, please contact Mr. Steve Flack (Email: spf36@medschl.cam.ac.uk; Tel: 01223 746771).

The UK-PBC Nested Cohort Study

Recruitment to the Nested Cohort Study remains sluggish. However, the study has been completely revised so that any patient with a confirmed diagnosis of PBC, incipient PBC or PBC/AIH overlap syndrome is eligible to join the study. Participants in the study attend a single research visit when they will provide biofluid samples. At this research visit, a proportion of participants are invited to return within one month for a research biopsy. The main reason for revising the Nested Cohort Study is to facilitate development of a large biofluid sample collection for population-level epigenomic, metabonomic and metagenomic studies of PBC.

Previously, the Nested Cohort Study was coordinated by Mr. Dimitrios Paximadas. Dimitrios left the project for a project manager position in the pharma industry at the end of 2015. We thank him for his extraordinary efforts getting the study up and running; we wish him the best of luck in his career. The baton has passed to **Mr. Jonathan Badrock,** who joined the Cambridge research team in January as project manager for the Nested Cohort Study. Jonathan's focus for the first quarter of 2016 is to get the study up and running in Nottingham, Leeds and Norwich, and to substantially improve recruitment across all centres.

If you have any queries about the Nested Cohort Study, please contact Mr. Jonathan Badrock (Email: jb2069@medschl.cam.ac.uk; Tel: 01223 769088).

Work Strand 2 Update

In the past 12 months the results produced by scientists engaged in this work strand have greatly exceeded expectations described in our original project proposal. Of particular importance is the definition of key histological differences observed in liver tissue between different groups of patients with Primary Biliary Cholangitis (PBC).

Up to 40% of PBC patients are unresponsive to the only licensed treatment, Ursodeoxycholic acid (UDCA). This highlights the importance of developing sophisticated molecular pathology tools to distinguish responsive and unresponsive patients at an early stage. The laboratories of this work strand have now shown conclusively that certain markers of stressed bile ducts are expressed at a markedly higher level in patients whose disease progresses despite treatment with UDCA. Furthermore, liver samples from these patients showed a greater number of a distinctive form of inflammatory lymphocytes which may play a key role in mediating liver damage.

Work Strand 3 Update
Clinical trials supported by UK-PBC

In the last update we mentioned that trial activity for UK-PBC/PBC patients in the UK is active and underway, and there are planned trials in 2016.

UK-PBC will be supporting on the following four studies this year:

Intercept Pharmaceuticals have a Phase 3 study that will assess the effect of their drug (Obeticholic Acid, OCA) compared to placebo, combined with stable standard care, on clinical outcomes in high risk advanced PBC patients. This is a global study and is already recruiting in the United States, Australia and Canada. The study is currently in the process of being opened in the UK. The proposed sites are as follows:

- University Hospitals Bristol NHS Foundation Trust
- Derriford Hospital, Plymouth Hospitals NHS Trust
- Western Infirmary/Gartnavel General Hospital
- Forth Valley Royal Hospital
- Freeman Hospital, Newcastle upon Tyne Hospitals NHS Foundation Trust
- University Hospitals Birmingham NHS Foundation Trust
- Addenbrookes Hospital NHS Trust
- Nottingham University Hospital NHS Trust

The full details can be found here: https://clinicaltrials.gov/show/NCT02308111

Novartis Pharmaceuticals have a Phase 2 study to assess safety, tolerability and efficacy of their drug (LJN452) in patients with PBC. This study is international and hopefully will be opening in the UK early 2016.

The full details can be found here: https://clinicaltrials.gov/show/NCT02516605

CymaBay Therapeutics have a 12 week Phase 2 study that will evaluate the effects of two doses of their drug (MBX-8025), in subjects with PBC who have an inadequate response to UDCA. The study is currently open in the United States but will be coming to the UK during 2016. Patients must have been on a stable dose of UDCA for the past 12 months.

The full details can be found here: https://clinicaltrials.gov/show/NCT02609048

Fast Forward Pharmaceuticals have a Phase 1/2 trial that is currently open and recruiting already in the UK. The study aims to evaluate the safety, tolerability and pharmacodynamics of the study drug (FFP104). Patients will be on treatment for 12 weeks and then followed up for an additional 12 weeks. The study is open at the following locations:

- Freeman Hospital, Newcastle upon Tyne Hospitals NHS Foundation Trust
- University Hospitals Birmingham NHS Foundation Trust
- Royal Free London NHS Foundation Trust

The full inclusion/exclusion criteria can be found here: https://clinicaltrials.gov/show/NCT02193360

UK-PBC's newly appointed Clinical Trials Project Manager will be working with each site to help identify patients for inclusion into each trial. If you would like further information regarding this process please contact Zohur Miah (Email: Zohur.miah@uhb.nhs.uk; Tel: 0121 371 8116)

Risk Score App

The UK-PBC Consortium have developed a Risk Score Calculator for PBC patients, which uses information from the UK-PBC Research Cohort to estimate the risk (expressed in percentage) that a PBC patient established on treatment with Ursodeoxycholic acid (UDCA) will develop liver failure requiring liver transplantation within 5, 10 or 15 years from diagnosis.

This has been available as a download from the UK-PBC website (http://www.uk-pbc.com) but thanks to efforts by Dr Gwilym Webb, the calculator is now available to download onto you Apple iPhones and Apple Tablets.

The score may be used to identify high-risk patients for closer monitoring and second-line therapies, as well as low-risk patients who could potentially be followed-up in primary care.

To use the UK-PBC Risk Score calculator, enter the laboratory test measurements and upper limits of normal (ULN) for the total bilirubin (BIL12); alanine transaminase or aspartate transaminase (TA12), and alkaline phosphatase (ALP12) after at least 12 months of UDCA, and the laboratory test measurements and lower limits of normal (LLN) for the serum albumin and platelet count in the same timeframe.

Download the App now and try for yourself. Scan the QR code below with your mobile, or visit the following link: https://goo.gl/5vPlgD

UKELD Score App

The United Kingdom Model for End-Stage Liver Disease or UKELD is a medical scoring system used to predict the prognosis of patients with chronic liver disease. It is used in the United Kingdom to help determine the need for liver transplantation.

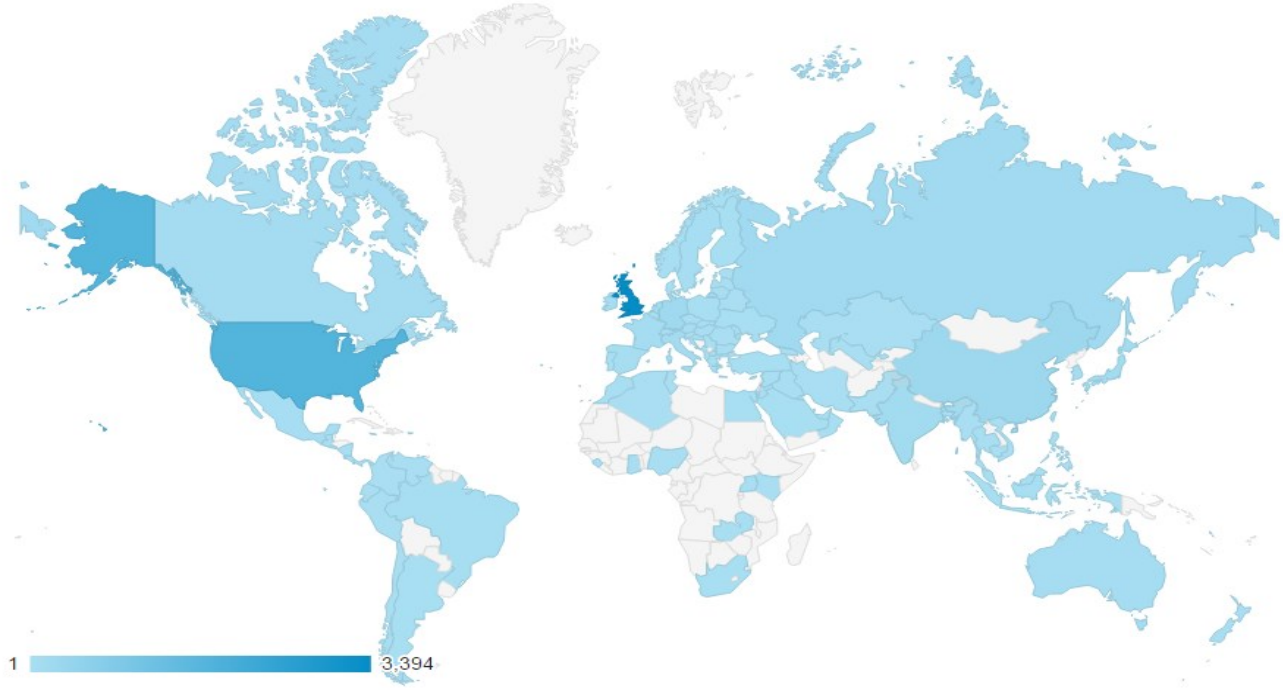
Dr Gwilym Webb, who originally converted the UK-PBC Risk score formula into an App has now done the same for the UKELD score. This is now available from the Apple App store for free.

Download the App now and try for yourself. Scan the QR code above with your mobile, or visit the following link: https://goo.gl/EEKH5e

Website Statistics

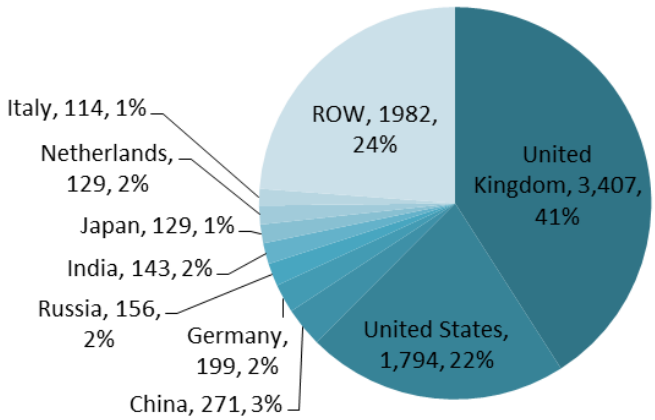
UK-PBC.COM has proved to be a very effective communication tool. Since launching the website in February 2015, the number of visits to the website has steadily increased. We hope that this upward trend continues to grow as does UK-PBC. This section highlights the key stats that some of you may find interesting.

Sessions by Geography



This map explorer above shows the number of sessions between **February 2015 to 18th December 2015.** The countries with the larger number of sessions are indicated by a darker colour, whilst the countries with the smaller number of sessions are in a lighter shade. The number of hits per country along with the respective percentage is shown in the adjacent pie chart.

NOTE: A session is defined as any period of time a user is active with the website. This is sometimes defined as "hits". The stats on the right also include multiple visits from the same person/ PC. This is **not** the number of pages visited.



Publications

Recruitment for the RITPBC trial (the first trial to investigate a treatment for fatigue in PBC) has now come to a close . The study is currently ongoing, and the findings will be reviewed in the coming future. The protocol for the trial design has been published in BMJ Open (http://www.ncbi.nlm.nih.gov/pubmed/26297361). The protocol will be valuable to research groups planning clinical trials targeting fatigue in PBC and also transferrable to other conditions associated with fatigue.

Professor Heather Cordell from Newcastle University has published a International genome-wide meta-analysis which identifies new primary biliary cholangitis risk loci and targetable pathogenic pathways . The article has been published in Nature Communications (http://www.ncbi.nlm.nih.gov/pubmed/26394269).

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).

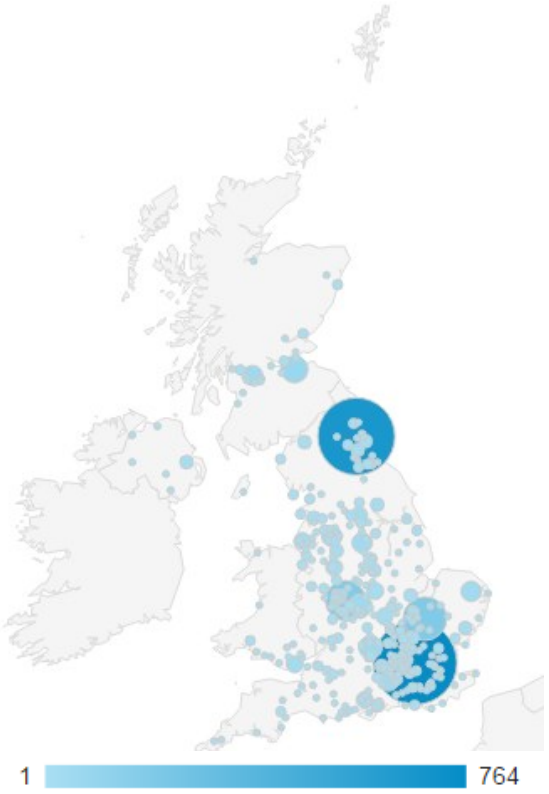
Those interested in PBC therapy will be excited to know that a new therapy may be on the market within the next 12-24 months. The new agent is obeticholic acid (OCA) (Hirschfield et al. Gastroenterology 2015, http://www.ncbi.nlm.nih.gov/pubmed/25500425), which is under review by the regulators in Europe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

VISIT THE UK-PBC WEBSITE FOR LATEST PUBLICATIONS:

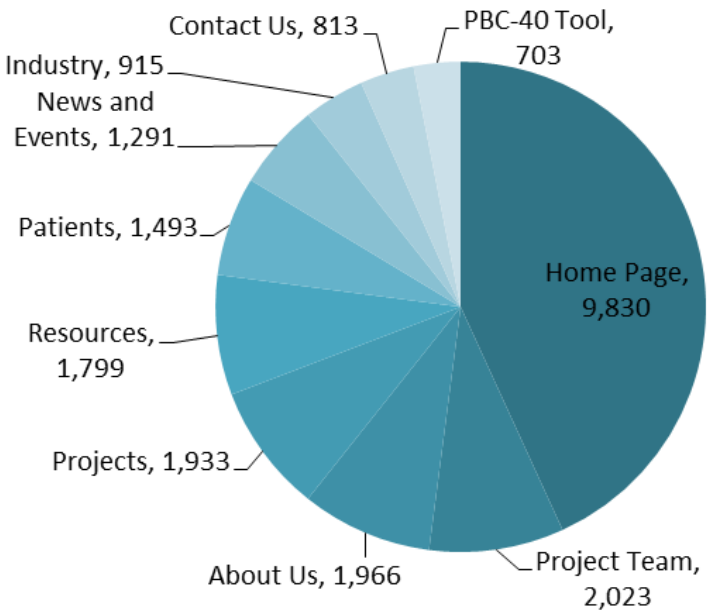
HTTP://WWW.UK-PBC.COM/RESOURCES/PUBLICATIONS/

Regional data by city can be seen in the Map Explorer on the right. The cities with the most number of sessions are **London**, **Newcastle upon Tyne**, **Cambridge** followed by **Birmingham**. The top 10 cities are shown below:

City	Sessions
London	764(22.51%)
Newcastle upon Tyne	665(19.59%)
Cambridge	190(5.60%)
Birmingham	181(5.33%)
Edinburgh	72(2.12%)
Oxford	52(1.53%)
Coventry	50(1.47%)
Glasgow	46(1.36%)
Farnham	43(1.27%)
(not set)	46(1.36%)



Sessions by Pages



Sessions can be broken down into specific sections of the website. The home page will naturally have the most number of views, as is the case here. The breakdown of the views can be seen on the adjacent chart. Acquisition stats shows 34% of visitors found the website via a search engine such as Google, with 64% of visitors coming in directly. Interestingly, we had a small number (101), 3%) of visitors come via Facebook. No other social media has forwarded on visitors. This is an area we will be looking at utilising more.

Upcoming Events

23 February 2016 | HepNet West Midlands

The WM CRN will be putting on another Specialty Group Meeting to discuss current and upcoming Hepatology trials in the UK. Speakers will include Dr Gideon Hirschfield, Dr Esther Unitt and Professor Philip Newsome.

Time: 18.30 – 21.00
Location: Malmaison, The Mailbox, Wharfside St, Birmingham B1 2JR

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3-4 March 2016 | AASLD/FDA Conference on Trial Design and Endpoints for Clinical Trial in Adults and Children with Primary Sclerosing Cholangitis

This workshop promotes successful and meaningful clinical trials and drug development in PSC by identifying and clarifying what is currently known to determine the best trial designs, populations and endpoints.

Location: FDA White Oak Campus Silver Spring, Maryland
More Info: Scan QR or visit: Scan QR or visit: http://goo.gl/4gZVam

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26th (09:30) – 27th (13:00) May 2016 | Birmingham Liver Course

The University of Birmingham and Queen Elizabeth Hospital are pleased to welcome you to the Birmingham Liver Course. During this one and a half day meeting we will cover practical and pressing issues in the management of advanced liver disease with speakers from around the country who are experts in their field. Using an interactive approach, we are sure this course will prove to be very popular and of interest to trainees, consultants, nurses and allied health professionals.

Location: Centre for Professional Development, Medical School, University of Birmingham
Fee: £150
More Info: Scan QR or visit http://goo.gl/LKXkNC

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2-3 September 2016 | Symposium 204 | Clinical Hepatology Practice in 2016: From Science to Therapy

A two day international liver meeting in Birmingham that spans the relevant scientific and clinical aspects of Hepatology, needed for those practicing liver medicine in 2016.

Featuring an international group of speakers well placed to deliver state-of-the-art talks, covering the full range of liver disease encountered in hospital and clinic practice around the world.

In keeping with previous Symposia, the meeting combines science with practice, and in particular translational aspects of liver disease. As is the tradition at Symposia of the Falk Foundation we invite clinicians in training, as well as established clinicians, to attend, and in particular present their work during our poster sessions.

Location: The ICC Birmingham
Organiser: Dr Gideon Hirschfield
More Info: Scan QR or visit: http://goo.gl/VDIzDI

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