UK-PBC Newsletter

IS003 SPRING EDITION

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Message from Professor Dave Jones

Welcome to the Spring newsletter for UK-PBC. This has again been a wonderful 6 months for PBC patients and for the UK-PBC project as our project goes from strength to strength. Perhaps the highlight has been the work done on the licensing of Obeticholic Acid. UK-PBC has played a key role in both delivering the key trials and in providing the evidence to justify new treatments in PBC. As a result it is likely that the drug will be approved in the USA (by the FDA) in the next few weeks. This is a major step forward for PBC patients. The trials programme goes on however as we look for even better therapies for the disease and its symptoms (2 trials are about to report and 4 are currently recruiting). Another highlight has been the launch of the UK-PBC Risk Score "App" (available to download free from the Apple App Store), which is a tool to help understand risk in PBC and to guide the clinician about the need for better treatments. It has been highlighted by George Freeman, The Minister for Life Sciences, as a wonderful example of digital innovation in healthcare. The data are now also emerging from our health economics programme. This will shed a unique light on the costs of managing PBC and will be invaluable as we move towards NICE approval of new drugs. The next 6 months will be even busier as we will report on a number of major aspects of the project, so watch this space!

Professor David Jones,
Newcastle University

UK-PBC Genetics Study

National Recruitment

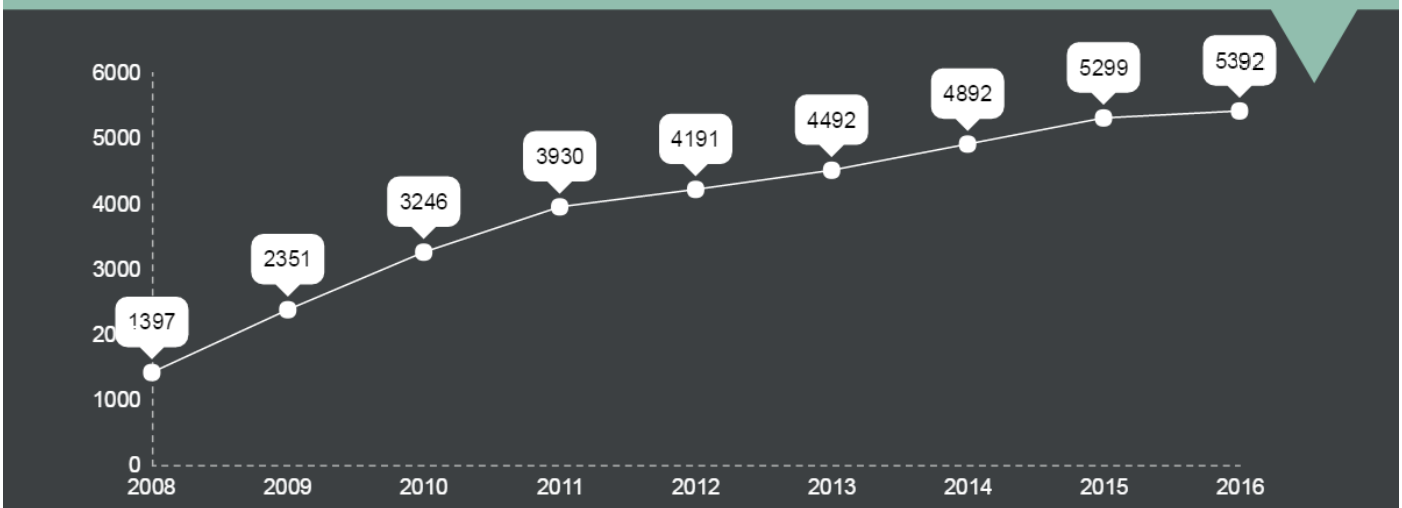
Recruitment to the UK-PBC Genetics Study continues at a steady pace. The recruitment tally now sits at **5,392 participants**. We are grateful to the research teams in all collaborating center's for their hard work, recruiting participants and completing CRFs.

This edition we have provided a more detailed recruitment breakdown. We hope to send out a similar style newsflash every other month to keep PIs and nurses up to date with recruitment progress.

RECRUITMENT

REPORT

RECRUITMENT OVER TIME



DATA CORRECT ON: 22 APRIL-16

TOTAL RECRUITMENT

5392

BREAKDOWN BY YEAR

2008 (4%) 2009 (7%) 2010 (9%) 2011 (11%) 2012 (12%)
2013 (13%) 2014 (14%) 2015 (15%) 2016 (15%)

powered by Piktochart make information beautiful

Recruitment Report Continued...

Congratulations to research teams at the following sites who recruited participants in the first quarter of 2016.

Site	Investigator	Participants
Addenbrooke's Hospital	Prof Graeme Alexander	4
Basingstoke and North Hampshire Hospital	Dr John Ramage	3
Blackpool Victoria Hospital	Dr Christopher Shorrock	2
Borders General Hospital	Dr Chris Evans	1
Bradford Royal Infirmary	Dr Paul Southern	2
Darent Valley Hospital	Dr Roland Ede	2
Derriford Hospital	Prof Matthew Cramp	5
Dorset County Hospital	Dr Stephen Bridger	1
Fairfield General Hospital	Dr Howard Klass	2
Hemel Hempstead General Hospital	Dr Alistair King	1
Hull Royal Infirmary	Dr George Abouda	2
Ipswich Hospital	Dr Simon Williams	8
James Paget University Hospital	Dr Paul Banim	1
John Radcliffe Hospital	Dr Jane Collier	1
New Cross Hospital	Dr Matthew Brookes	1
Norfolk and Norwich University Hospital	Dr Simon Rushbrook	4
Royal Bolton Hospital	Dr George Lipscomb	3
Royal Cornwall Hospital	Dr Hyder Hussaini	1
Royal Gwent Hospital	Dr Marek Czajkowski	1
Royal Lancaster Infirmary	Dr Andrew Higham	1
Royal Liverpool University Hospital	Dr Martin Lombard	3
South Tyneside District Hospital	Dr Simon Panter	1
St James's University Hospital	Dr Mark Aldersley	4
St Richard's Hospital	Dr Jocelyn Fraser	4
Sunderland Royal Hospital	Dr Harriet Mitchison	1
The Queen Elizabeth Hospital	Prof Gideon Hirschfield	12
The Royal Free Hospital	Dr Douglas Thorburn	3
The York Hospital	Dr Charles Millson	7
Victoria Central Hospital	Dr Amit Singhal	1
Warrington Hospital	Dr Subramaniam Ramakrishnan	6
Worcestershire Royal Hospital	Dr Ian Gee	1
Wycombe Hospital	Dr David Gorard	3

Revisions to the study documentation

Study documentation for the UK-PBC Genetics Study has been recently been revised, including the participant information sheet (PIS) and informed consent form (ICF). By signing the revised ICF, participants in the study consent to the following:

- For health-related information to be obtained from the Health and Social Care Information Centre (HSCIC) or equivalent organisations in the devolved nations;
- Sharing of anonymised data with independent, third parties;
- Sharing of anonymised samples with independent, third party investigators;
- Direct invitation to take part in other studies.

(Continued on page 4)

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This revision is important. Health-related information from the HSCIC includes inpatient and outpatient episodes. This information will dramatically improve the accuracy of prognostic modelling and health economics analysis. Data and sample sharing will ensure that PBC experts throughout the world have access to the unique UK-PBC Bioresource. Direct invitation to other studies will facilitate recruitment to future studies and improve equity of access to clinical trials. For all these reasons, we implore collaborators to support the re-consent process.

The re-consenting process has begun

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. There has been a good response. More than 1,000 participants have already signed and returned their revised ICFs. We anticipate a 50% response rate by the end of April. For UK-PBC to remain successful, however, it is imperative that all participants sign and return the revised ICF. The plan is therefore as follows:

- Mid-May, we will send a reminder to participants who have not yet signed and returned the revised ICF;
- Mid-June, we will provide each collaborating research team with a list of participants recruited from their centre, who have not responded to either mailshot;
- We humbly request that collaborating research teams contact those who have not responded to either mailshot, to address any queries and gently encourage the participants to sign and return their revised ICFs.

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 Nikoletta Varvaropoulou (nv280@medschl.cam.ac.uk).

Forthcoming GWAS of UDCA response

Samples from the UK-PBC DNA collection will be dispatched to the Wellcome Trust Sanger Institute (WTSI) in June 2016 to start genome-wide genotyping using the Illumina CoreExome array. We anticipate that genotype data will be available for analysis by September 2016. Most important, these data will be used for a within-case genome-wide association study (GWAS) of response to treatment to ursodeoxycholic acid (UDCA). These data will also be used for genome-wide survival analysis. Genetic analyses will be led by Professor Heather Cordell in the Institute for Genetic Medicine (IGM) at Newcastle University and Dr Carl Anderson at the WTSI. These are exciting and novel experiments – watch this space!

PLEASE COMPLETE YOUR eCRFs

The GWAS of UDCA response and genome-wide time-to-event analysis depend on the clinical information collected using electronic case report forms (eCRFs) in the UK-PBC Clinical Database. For this reason, we should be very grateful if all outstanding eCRFs were completed by the end of May. We will then begin the arduous process of data cleaning. We aim to have a clean and complete clinical dataset available for analysis by September 2016.

We are immensely grateful to you for your hard work – and we apologise for demanding even more! If you have any questions about the eCRFs or the UK-PBC Clinical Database, please contact Steve Flack (spf36@medschl.cam.ac.uk).

The UK-PBC Nested Cohort Study

The UK-PBC Nested Cohort Study is now running in four regions: North East and North Cumbria, West Midlands, Eastern and North West London. It has taken a considerable time to establish the research networks to support recruitment of participants – but this has finally been achieved. We anticipate rapid recruitment over the next six months.

Amendments to the Nested Cohort Study

Recruitment to the Nested Cohort Study has been sluggish since the start of the study, in part because the eligibility criteria were unnecessarily strict. The Nested Cohort Study has therefore been extensively revised, as follows:

- Any patient with PBC, incipient PBC or PBC/AI overlap is eligible to participate in the study;
- Participants attend a single research visit at their nearest research hub;
- At the research visit, participants provide samples of blood, urine and stool, and complete questionnaires designed to identify environmental exposures;
- A small proportion of participants (mainly those with high-risk PBC) are invited to return to the research hub for a supplementary research visit involving a liver biopsy and/or additional blood samples.

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.

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).

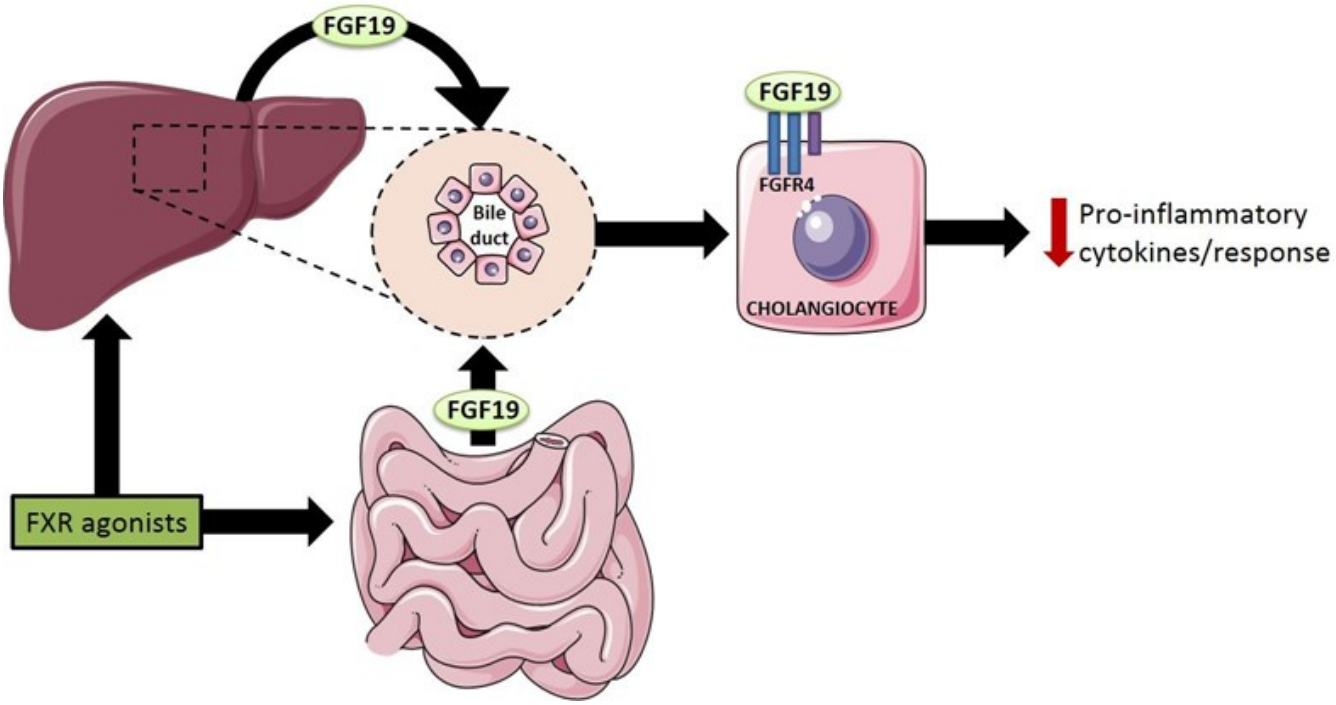
DO YOU HAVE ACCESS TO THE UK-PBC CLINICAL DATABASE?

DO YOU HAVE ACCESS TO THE INVITATION APP?

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

Work Strand 2 Update

Following on from our earlier demonstration that bile duct cells in PBC patients who are unresponsive to treatment with Ursodeoxycholic acid (UDCA) show increased signs of function-limiting stress, we have just concluded a further series of experiments to assess whether these cells can be protected from stress by enhanced drug treatment. Our initial idea was to stimulate stressed bile duct cells with molecules termed "FXR agonists" which can activate a specific receptor on the cell surface. This turned out to provide only marginal support for the cells. We determined that one reason for this minimal effect is that the drug target receptor is actually lost during periods of cell stress. However, we did notice that other cells in the body (mainly the gut) produce a further chemical in response to stimulation of FXR. This chemical, called FGF19, can itself stimulate bile duct cells (cholangiocytes) and mediate a powerful anti-inflammatory action which may mitigate against further cell damage. Results from this exciting new study were presented in Barcelona by research students supported by UK-PBC at the April 2016 meeting of International Liver Congress (EASL).



Work Strand 3 Update
Clinical trials supported by UK-PBC

In the previous update, we mentioned that UK-PBC will be supporting a number of clinical trials. There are a few sites still in the process of being set-up, but we are excited to announce that all four trials (see below) are now active.

UK-PBC has started identifying patients for these trials/sites and research nurses/investigators have been provided with a list of patients that have been pre-screened from their own site. It is important for each site to review their list of patients as soon as possible . Depending on how many patients are shortlisted, the UK-PBC team will start identifying and approaching patients from feeder/referral sites. If you wish to start approaching feeder/referral site patients sooner, please contact the WS3 Clinical Trials Project Manager, Zohur Miah (Zohur.miah@uhb.nhs.uk).

The studies we are support are 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

- **CymaBay Therapeutics** (https://clinicaltrials.gov/show/NCT02609048)

  Sites:
  - Plymouth Hospitals NHS Trust
  - University Hospitals Birmingham NHS Foundation Trust
  - Cambridge University Hospitals NHS Foundation Trust
  - Hull and East Yorkshire Hospitals NHS Trust
  - Newcastle upon Tyne Hospitals NHS Foundation Trust
  - Nottingham University Hospitals NHS Trust
  - Royal Free London 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

PBC Clinical Guidelines

Gideon Hirschfield, Dave Jones and Jessica Dyson have worked to bring the BSG guidelines to a very advanced stage. The guidelines have been circulated amongst the Cholestasis Guidelines Development Group for final comments. The guideline will also be circulated to other stakeholders such as the Royal College's and patient groups. A copy of the guideline has also been uploaded onto the UK -PBC website for a limited time for comments. This can be accessed here: http://www.uk-pbc.com/category/news/

If you have any comments, please send these across to Zohur Miah (Zohur.miah@uhb.nhs.uk) before the **31st May 2016.**

SCREENED/RECRUITED A UK-PBC PATIENT?

If you have screened or recruited a UK-PBC patient, either from the list provided to you by Zohur Miah or from your own local list, please notify Zohur Miah. It is essential we can log how many UK-PBC patients have gone onto clinical trials so we can demonstrate the efficiency of the platform. Please contact Zohur Miah in all instances, (zohur.miah@uhb.nhs.uk).

New Website

There is now a new UK-PBC website. The website can still be accessed by the same URL (http://www.uk-pbc.com). All of the content within the new website has been migrated over from the previous website.

The new website has the following features:

- Mobile/tablet compatible
- Dynamic event section
- Updated news section
- Newsletter subscribe section
- Online forms

Over the coming months, we will start on the next phase of the website, which would include updating all the content and team profiles.

If you have any comments or suggestions for the website, please contact Zohur Miah (Zohur.miah@uhb.nhs.uk).

UK-PBC Smartphone App

We previously mentioned that the UK-PBC Consortium have developed a Risk Score Calculator for PBC patients and clinicians, 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.

The iPhone app was recently featured in a visit by George Freeman MP, Minisiter for Life Sciences, to Newcastle University. Full information on the visit can be found the UK-PBC website (http://www.uk-pbc.com/2016/04/uk-pbc-smartphone-app-gains-media-attention-and-award/

The iPhone app has also won the University of Birmingham Student Mobile App Competition 2015-2016 (https://intranet.birmingham.ac.uk/it/innovation/Student-Mobile-App-Competition/StudentMobileAppCompetition2015-2016.aspx).

FDA Support for Obeticholic Acid (OCA)

UK-PBC team helps new PBC drug to the point of licensing. UK-PBC investigators have been heavily involved in the FDA approval process for Obeticholic Acid, a novel drug for use in PBC patients unresponsive to UDCA.

On Thursday 7th April an independent Advisory Committee voted 17 to 0 to support FDA approval of OCA which will now be the first new drug approved for use in PBC in 20 years. Data from the UK-PBC played a key role in convincing the committee that there is significant unmet need in PBC and thus a need for new drugs.

Further information will be available on the UK-PBC website, when available.

Publications

Professor Gideon Hirschfield from University of Birmingham has published a article in Hepatology journal looking at Ustekinumab for patients with primary biliary cholangitis who have an inadequate response to ursodeoxycholic acid. Open-label ustekinumab therapy, while associated with a modest decrease in ALP after 28 weeks of therapy, did not otherwise appreciably change ALP and overt proof-of-concept was not established as per pre-specified primary endpoint of proposed efficacy. No new ustekinumab safety signals were observed (http://www.ncbi.nlm.nih.gov/pubmed/26597786).

Hegade et al. has published the findings of a retrospective European study aimed to evaluate the safety and efficacy of nasobiliary drainage in the treatment of refractory cholestatic pruritus. The study reports nasobiliary drainage is effective in relieving cholestatic pruritus in most patients and has favourable effect on biomarkers of cholestasis. Nasobiliary drainage may be associated with high risk of adverse events, especially pancreatitis. Prospective studies are needed to confirm our findings. The article has been published in Alimentary Pharmacology and Therapeutics (http://www.ncbi.nlm.nih.gov/pubmed/26526892).

Mroz et al. has submitted an abstract for American Society for Mass Spectrometry (ASMS) conference titled 'DESI-MSI-based diagnostics of cirrhotic liver diseases'.. The project aims to use DESI-MSI to understand the metabolic hallmarks of primary biliary cirrhosis and other liver diseases and use this information to augment diagnostics.

VISIT THE UK-PBC WEBSITE FOR LATEST PUBLICATIONS:

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

Upcoming Events

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: Prof Gideon Hirschfield
More Info: Visit: http://goo.gl/VDIzDI

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7-9 September 2016 | BASL Annual Meeting 201 6

The BASL Annual Meeting is the highlight of the BASL calendar and the main liver meeting in the UK. This year we hope to attract in excess of 500 delegates, bringing together clinicians, nurses, scientists and all those interested in liver disease.

Eminent UK and overseas speakers converge to deliver an informative and exciting meeting over three days, which for September 2016 will take place at Manchester Central.

Location: Manchester Central, Manchester
More Info/Provisional Programme: Visit http://www.baslannualmeeting.org.uk/

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7 September 2016 | UK-AILD Meeting at BASL Annual Meeting

A progress/update meeting for all UK-PBC, UK-PSC and UK-AIH investigators, taking place at BASL. This meeting is not part of the BASL agenda, but a separate meeting.

Location: Manchester Central, Manchester (Meeting room/time to be confirmed)
More Info: Email Zohur.Miah@uhb.nhs.uk

Contact Details

UK-PBC Project Manager

Nancy Rios
Newcastle Clinical Trials Unit
Newcastle University
Room M3046 3rd Floor Leech Building
Framlington Place
Newcastle upon Tyne
NE2 4HH
Phone: +44 (0)191 208 2420/7138
E-mail: Nancy.Rios@newcastle.ac.uk

FOR COMMENTS, SUGGESTIONS OR QUERIES REGARDING ANY PART OF THIS NEWSLETTER, OR IF YOU WANT TO JOIN THE CIRCULATION LIST PLEASE EMAIL ZOHUR.MIAH@UHB.NHS.UK

Genetics Study Manager

Nikki Varvaropoulou
Academic Department of Medical Genetics
University of Cambridge
Box 238, Addenbrooke's Hospital
Hills Road
Cambridge
CB2 0QQ
Phone: +44 (0) 1223 746771
E-mail: nv280@medschl.cam.ac.uk

Nested Cohort Study Manager

Jonathan Badrock
Academic Department of Medical Genetics
University of Cambridge
Box 238, Addenbrooke's Hospital
Hills Road
Cambridge
CB2 0QQ
Phone: +44 (0) 1223 769088
E-mail: jb2069@medschl.cam.ac.uk

Clinical Trials Project Manager

Zohur Miah
Institute of Translational Medicine
Level 1, East Wing, Office 12
University Hospitals Birmingham NHS Foundation Trust
Birmingham
B15 2GW
Phone: +44 (0) 121 371 8116
E-mail: Zohur.Miah@uhb.nhs.uk