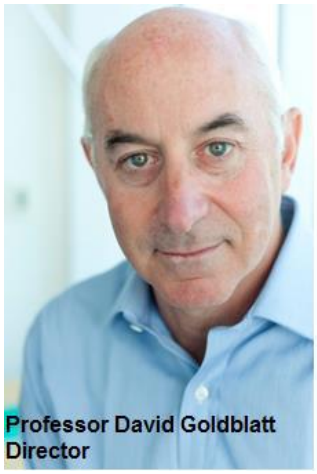
News from the
NIHR Biomedical Research Centre at
Great Ormond Street Hospital for Children NHS Foundation Trust
and University College London

Director's introduction


Professor David Goldblatt
Director

Welcome to the December 2015 edition of our newsletter, highlighting the activity and achievements of our National Institute for Health Research Biomedical Research Centre (BRC) at Great Ormond Street Hospital for Children NHS Foundation Trust (GOSH) and University College London (UCL).

On the 15th December, Chancellor of the Exchequer George Osborne visited Great Ormond Street Hospital (GOSH) to announce a variety of NHS funding developments including an £800 million boost to biomedical research through the NIHR. He was joined by the Secretary of State for Health Jeremy Hunt, Mayor of London Boris Johnson and Chief Executive of NHS England Sir Simon Stevens for the announcement. GOSH and UCL have benefited hugely from having BRC funding since the inception of the scheme in 2007 so the continuation of this scheme with the opportunity for GOSH/UCL to bid again is crucial to our on-going efforts and success in Experimental Medicine which will aid our efforts to continue to translate our research activities into treatments and potential cures for patients with rare and complex conditions from across the UK. Read the full press release here.

We have also received feedback on our BRC annual report submitted earlier in the year to the NIHR. Using this data, the NIHR produces a report that analyses the annual reports received from all 11 NIHR-funded BRCs. We have performed extremely well in a number of categories, especially when we analyse our BRC's activity in the context of our share of funding for the BRC's overall.

Last month, the MHRA (Medicines and Healthcare Products Regulatory Agency) came to review the conduct and management of clinical trials of investigational medicinal products that fall under the clinical trials regulations. This was a routine inspection that ran over three days. The inspectors selected five GOSH sponsored clinical trials. The outcome was very positive; the inspectors commented that much work had been done in improving our processes and remaining compliant since the last inspection in 2011. We are awaiting the final outcome and report but the early indication is that there are no critical findings, one major finding and around 10 "other" findings which are largely recommendations and suggestions to refining our processes. We are expecting a full report before the end of the year to which we will need to respond with our corrective and preventative actions. Thank you to everyone involved in this inspection.

BRC Newsletter – December 2015

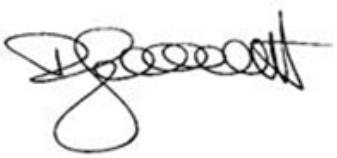
I am pleased to announce that Professors Paolo de Coppi and BRC Deputy Director Bobby Gaspar, who are members of the Gene, Stem and Cellular Therapies Theme, have both been successful in securing Horizon 2020 Collaborative Health grants, as the lead PI, from the European Commission. Professor Lyn Chitty, who is a member of the BRC Diagnostics and Imaging Theme, in collaboration with Karolinska Institutet, Sweden, has also been awarded a H2020 grant. UCL was the most successful university in obtaining EU work programme funding in the period 2014-15. H2020 is the biggest EU Research and Innovation programme ever, with 79 billion euros of funding available over 7 years (2014 to 2020). Well done all!

I would also like to congratulate ICH and hospital teams led by Professors Waseem Qasim and Paul Veys for their outstanding work on being the world's first to treat a baby with 'designer immune cells' manufactured in the GOSH gene therapy facility. Click here to read the full report.

Earlier in the year we commissioned Thomson-Reuters to complete a second bibliometric analysis for the period 2010-2014. You will recall that we presented data two years ago, which showed that in the period 2008-12, in comparison to key international paediatric organisations ICH/GOSH research was third equal in the mean citation index (a measure of quality) of publications. The latest analysis of data from 2010-14, shows ICH/GOSH publications ranked first, in comparison with the other children's academic medical centres, and this is a fantastic accolade and result for our world leading child health research.

Finally, following on from the email sent last month, I would like to remind all researchers to acknowledge the NIHR Great Ormond Street BRC in your published work. We have now developed a one-click system for all researchers to quickly access the correct wording on our website. Click here to be re-directed to this link.

I hope you enjoy reading this newsletter and as always welcome any thoughts and contributions you would like to make. Please e-mail BRC Newsletter with any future contributions to the newsletter you would like to include.



David Goldblatt Director, NIHR Biomedical Research Centre Director, Clinical Research and Development Professor of Vaccinology and Immunology NIHR Senior Investigator

Visit our website

SPECIAL FEATURE

NIHR Great Ormond Street Biomedical Research Centre Open Day 2015

On 24 October 2015 we held an Open Day in partnership with the Bloomsbury Festival. This was a free event held in UCL Institute of Child Health, which aimed to raise public awareness of medical research and how it can improve child health.

Two hundred and twenty members of the public attended the Open Day, joining almost 90 staff – including Great Ormond Street Hospital (GOSH) volunteers and research staff from ICH and GOSH, and the NIHR Great Ormond Street BRC. The Open Day involved several activities, stands, and seminars, which were aimed at children, young people, and families.

Interactive activities included extracting DNA from a banana, embossing a screen-printed heart on an aluminium sheet, building a model of a cell using Kinder Eggs and Play-Doh, dressing up to 'perform' gene and cell therapy, having a go at muscle testing and measuring movement of the muscle, creating dream sequences inside a zoetrope, and touring lab facilities. Researchers also held stands promoting the activities of the London Young Persons Advisory Group (YPAG), our newly-formed parent and carer research advisory group, Women in Science (organised by our Athena Swan committee), INVOLVE and the Local Clinical Research Network. Seminars explored topics such as the 100,000 Genomes Project, 'How well do you know your brain?', and 'Cells: Keeping them clean and tidy in a messy world'. Zeiss also brought in two microscopes to allow visitors to the study the development of muscle and retinal tissue, and how genetic diseases affect specific cells.

Visitors to the Open Day reported that:

• "We were here from 12-4pm and loved it. Would have been even better if it an hour or two longer. Thanks for a great day."

• "Very enriching and extremely useful to get to speak to researchers about their areas of interest. Very useful to be able to obtain information about various scientific fields as a science student - the lab tour was fab!"

• "Fantastic! It really couldn't be better."

• "Very interesting/my kids enjoyed very much their activities", to give but a few of the comments received.

Similarly, staff felt that:

• "It was a fabulous day. It was inspiring and energising seeing how engaged and interested the children and their families were in all the activities."

• "All of the families were brimming with praise for the whole Open Day event."

• "I was so proud to be part of our team, we were super busy and received brilliant comments from families."

With such positive comments from visitors and staff alike, we look forward to organising and delivering a NIHR Great Ormond Street BRC Open Day again next autumn.

GENERAL NEWS

100,000 Genomes project update: 12 January 2016

Peter Steer and the 100,000 Genomes team would like to invite you to an update on the 100,000 Genomes project on Tuesday 12 January 2016 in the Kennedy Lecture theatre, UCL Institute of Child Health at 1pm. The North Thames Genomic Medicine Centre, which GOSH is leading, is currently recruiting around 20% of the total number of Genomes to the 100,000 Genomes Project. GOSH provided the majority of these whilst our partner Trusts got up and running. We now have four of our six partner Trusts recruiting to rare diseases and the numbers are really beginning to increase. Results from the pilot study are beginning to be returned and we would like to share some of these with you and what this has actually meant for our patients. Please join us for an update and discussion on how we plan to go forward. Refreshments will be provided.

For more information about eligibility criteria and how to refer patients to the project, please go to: 100,000 Genomes Project.

Patient and Public Involvement Lead awarded NIHR Health Technology Assessment (HTA) grant

Dr Erin Walker, Joint Lead for Patient and Public Involvement in Research, has been awarded an NIHR HTA grant as a co-applicant to investigate “Improving the mental health of children and young people with long term conditions: Linked evidence syntheses”. The award of £284,067.41 is awarded to Dr Jo Thompson-Coon at the University of Exeter, and will evaluate, through a review of the evidence base, the effectiveness of interventions aimed at improving the mental health of children and young people with long term physical health conditions and to explore the factors that may enhance, or limit, the beneficial delivery of such interventions.

To read more, please click here.

Qiagen has published a Case Report highlighting the work of GOSgene

The Centre for Translational Genomics GOSgene, a NIHR Great Ormond Street BRC-funded facility designed to help clinicians to identify new genetic causes in rare undiagnosed disorders, has been featured in a report by Qiagen early this year. To read the full report, please follow the link.

Successful applications by BRC researchers to funding administered by the Translational Research Office (TRO)

In a recent round of calls, the Translational Research Office received 22 applications for **UCL's Therapeutic Innovation Fund (TIF)** and 56 applications to the **MRC-funded UCL Confidence in Concept (CiC) fund.**

We are pleased to report that NIHR Great Ormond Street BRC researchers at ICH have been awarded 1 out of 7 TIF awards and 2 out of 8 CiC awards. We congratulate the TIF award recipient: Dr Francesco Conti (Project: Repair of duplications in dystrophin using CRISPR/Cas9 nucleases); and the CiC award recipients: Dr Dagan Jenkins (Project: Testing a novel drug treatment for craniosynostosis) and Professor Nicholas Greene (Project: Diseases of the Glycine Cleavage System: Understanding the causes and development of novel therapies).

The TIF awards are supported by funds from all three NIHR BRCs at University College London. The award provides seed funding to support biomedical innovations at their earliest stage of discovery research.

The CiC awards are funded by the MRC to support UCL's translational research projects. The aim of the fund is to support preliminary work or feasibility studies to establish the viability of a novel approach. This should accelerate the transition from discovery research to translational development projects which will be suitable to apply for main stream translational funding such as the MRC DPFS.

BRC Faculty member, Professor Shamima Rahman wins prize at the Study of Inborn Errors of Metabolism (SSIEM) Annual Symposium 2015

Professor Shamima Rahman, part of the Molecular Basis for Childhood Diseases theme, won the prize for the "Best Free Research Communication" at the Society for the Study of Inborn Errors of Metabolism (SSIEM) Annual Symposium 2015. This annual conference, which was hosted in Lyon, France this year, is the biggest metabolic meeting in the world with more than 2,000 delegates attending the event.

MedCity launches cell therapy campaign at BioJapan

MedCity, a collaboration between the Mayor of London and the capital's three Academic Health Science Centres - Imperial College Academic Health Science Centre, King's Health Partners, and UCL Partners, has led a delegation of SMEs, scientists and industry to promote partnerships in cell therapy and regenerative medicine between Japan and the greater south east. The new campaign, developed with London & Partners and the GREAT Britain campaign, brings together figures including Life Sciences Minister George Freeman, UCL's Professor Chris Mason, and the Cell Therapy Catapult's Keith Thompson. Professor Adrian Thrasher, Lead of our NIHR Great Ormond Street BRC's Gene, Stem and Cellular Therapies Theme, attended the event on behalf of UCL.

The intended outcomes for the MedCity delegation are to initiate engagement with the Japan market, start relationships with new companies and, enhance relationships with existing partners. Japan, after the US, has the second largest healthcare, pharmaceutical and medical devices markets in the world. Total medical expenditure is over £250 billion a year and the Japanese pharmaceutical market is bigger than both France and Germany's combined. UK bio companies are in a strong position to supply Japan's healthcare market where unique, sophisticated, and highly technical products are sought after to assist the growing population.

To read more about the event and MedCity, please click here.

Gene, stem and cellular therapies theme news

World first use of gene-edited immune cells to treat 'incurable' leukaemia

A new treatment that uses 'molecular scissors' to edit genes and create designer immune cells programmed to hunt out and kill drug resistant leukaemia has been used at Great Ormond Street Hospital (GOSH).

The treatment, previously only tested in the laboratory, was used in one-year-old, Layla, who had relapsed acute lymphoblastic leukaemia (ALL). She is now cancer free and doing well.

This breakthrough comes from GOSH and UCL Institute of Child Health's (ICH) pioneering research teams with support from the National Institute for Health Research (NIHR) Great Ormond Street Biomedical Research Centre, who together are developing treatments and cures for some of the rarest childhood diseases.

Chemotherapy successfully treats many patients with leukaemia but it can be ineffective in patients with particularly aggressive forms of the disease where cancer cells can remain hidden or resistant to drug therapy. Recent developments have led to treatments where immune cells, known as T-cells, are gathered from patients and programmed using gene therapy to recognise and kill cancerous

cells. Multiple clinical trials are underway, but individuals with leukaemia, or those who have had several rounds of chemotherapy, often don't have enough healthy T-cells to collect and modify meaning this type of treatment is not appropriate.

The GMP facility that manufactured the modified T-cells is funded directly through our NIHR Great Ormond Street BRC. Professor Waseem Qasim is a NIHR professor and Professor Adrian Thrasher is the 'Gene, Stem and Cellular Therapies' Theme Lead.

Read the full press release here.

Funding to develop immunotherapy for childhood sarcomas

BRC-supported Professor John Anderson has been awarded funding from Children with Cancer UK to investigate new immunotherapy approaches for childhood sarcomas. If successful, the team plan to develop a new clinical trial to test this treatment. Such a trial will increase the treatment options for young sarcoma patients at relapse, where chemotherapy has failed.

Professor Anderson and his team plan to use an approach called adoptive immunotherapy – first, doctors take a sample of a patient's own blood cells. In the lab, these cells are then genetically modified to recognise a particular target (called an antigen) and then injected back into the patient. Once these genetically modified cells, called chimeric antigen receptors (CARs), come into contact with the antigen, these cells activate the patient's immune system to fight the cell.

The team have already successfully used this approach to treat chemotherapy-resistant neuroblastomas, and a trial is now underway at Great Ormond Street Hospital to investigate this treatment option for sarcoma, solid tumours that can occur in the bone or soft tissue, which include Ewing sarcoma**,** osteosarcoma and rhabdomyosarcoma. These cancers have a dismal prognosis if they relapse or metastasise. Only about 1% of adults with cancer suffer from sarcoma, but 15% of children with cancer suffer from sarcoma.

Molecular basis of childhood diseases theme news

A new, genetic diagnostic service for ciliopathy disorders has been launched

In a collaboration between GOSH North-East Thames Regional Genetics and the UCL Institute of Child Health, a new genetic diagnostic service for ciliopathy disorders has been launched for service delivery to the NHS.

Ciliopathies are rare inherited conditions caused by defects of cilia, hairlike microscopic extensions present on most cells in the human body. Cilia play important roles in development and disease through a diverse number of cell motility and signalling functions. Collectively, ciliopathies cause a significant number of complex and often lethal syndromes with

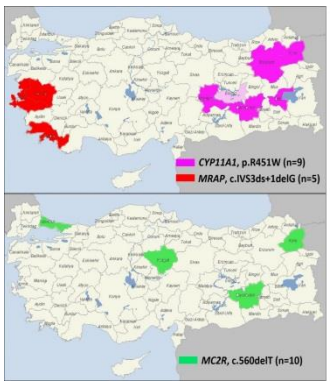
diverse features that include skeletal anomalies, cystic kidney disease, retinal degeneration, obstructive respiratory disease, polydactyly, neurological defects, and problems in left-right axis determination of the internal organs that are associated with heart defects.

A panel of over 120 causal ciliopathy disease genes is now available for screening in affected individuals – in a recent pilot study, more than 60% of well-defined ciliopathy cases were diagnosed using this panel. In parallel, these genes form part of a larger gene panel currently in use in Dr Hannah Mitchison's lab at ICH for further discovery of new ciliopathy genes. They also form the basis for pre-screening patients prior to entry into the Genomics England 100,000 Genomes Project.

This research was funded by Action Medical Research and GOSH Children's Charity. Dr Hannah Mitchison is a BRC-supported researcher.

Photo: Ciliopathy diagnosis team (Tom Cullup, Lucy Jenkins, Hannah Mitchison, Mitali Patel, Mahmoud Fassad, Jane Hayward, Chris Boustred)

High throughput screening identifies the genetic cause underlying a rare disease in a large nationwide cohort



A collaborative study between ICH and the Turkish Pediatric Endocrinology Society has used high-throughput DNA analysis to identify the genetic cause of primary adrenal insufficiency in more than 80% of affected children.

Primary adrenal insufficiency (PAI) is a rare condition that can be difficult to diagnose and is life-threatening if not treated with steroid replacement. Several genetic causes of PAI have been found in recent years but it can be difficult to know which genes to look at first as there is often great overlap in clinical and biochemical features.

This collaborative study was undertaken between Professor John Achermann's group at ICH, Dr Tulay Guran and 19 paediatric endocrinology centres in Turkey covering approximately 15 million children. A total of 95 patients were identified with rare forms of PAI where the cause was not known. A high-throughput Haloplex DNA capture approach was developed by Dr Federica Buonocore to analyse many genes simultaneously. A specific genetic diagnosis was reached in 81% (77/95) of children.

This study – published in the Journal of Clinical Endocrinology and Metabolism – has translational impact for counselling families, diagnosing and treating affected children before symptoms occur, predicting potential associated features and for targeting genetic analysis where local founder effects are known. Professor John Achermann is a Wellcome Trust Senior Research Fellow in Clinical Science.

Novel therapies for translation in childhood disease theme news

Less intensive chemotherapy avoids irreversible side effects in some childhood cancers

Children with a kidney cancer known as Wilms' tumour, who are at low risk of relapsing, can have their chemotherapy reduced. This finding comes from a European-wide trial that studied the drug doxorubicin.

The 10-year study, led by BRC-funded Professor Kathy Pritchard-Jones, followed 583 children with stage II or stage III Wilms' tumour of intermediate risk type, which is the commonest. The results showed that 96.5 per cent of children whose treatment included doxorubicin – which has been linked to irreversible heart problems later in life – survived for five years or more, compared with 95.8 per cent of children who did not receive the drug. Even though there was a slight increase in the risk of patients relapsing if they did not receive doxorubicin, these patients were successfully treated subsequently, meaning that overall survival rates were the same. The standard treatment for this type of Wilms' tumour has now been changed to not give doxorubicin. This means that the majority of children now avoid the risk of long term heart problems.

The results have been published in the Lancet. Kathy Pritchard-Jones is a BRC funded researcher.

Treatment of the central nervous system as well as the peripheral organs proves beneficial in severe cases of Spinal Muscular Atrophy (SMA)

A pre-clinical study investigating treatment options for a severe form of Spinal Muscular Atrophy (SMA) has demonstrated that optimal treatment of a morpholino antisense oligonucleotide drug is achieved when the drug reaches the central nervous system as well as the peripheral organs. In addition, this study has better defined the window of therapeutic response after chronic therapy, information that will prove very important when considering therapeutic intervention in patients with SMA.

SMA is a genetic neuromuscular disease, which means it is inherited and affects nerve cells responsible for muscle function. Although classified as rare, SMA is the leading genetic killer of infants and toddlers, with approximately 95% of the most severely diagnosed cases resulting in death by the age of 18 months. Children with a less severe form of SMA face the prospect of progressive muscle wasting, loss of mobility and motor function.

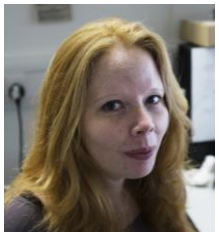
The information of the role of targeting the peripheral organs comes at a crucial time when clinical trials in SMA patients are in their infancy. Current clinical trials focus on delivering the antisense drug treatment to the central nervous system only. Based on these findings, the team has joined forces with Professor Matthew Wood (Oxford) and Dr Mike Gait (Cambridge) to study a new class of antisense oligonucleotide drugs which can be delivered systematically and retain activity in both the central nervous system and the periphery.

The study findings were published in Human Molecular Genetics. NIHR Great Ormond Street BRC-funded Senior Research Associate Dr Haiyan Zhou, who is the first author in this study, was awarded the annual Léa Rose Spinal Muscular Atrophy Prize for the most outstanding contribution to spinal

muscular atrophy (SMA) research at the 20th international World Muscle Society Congress in Brighton.

Diagnostics and Imaging in Childhood Diseases theme news

BRC researchers develop a new rapid test for Alzheimer's and Lewy Body Dementia



NIHR Great Ormond Street BRC researchers, working in collaboration with the Biomedical Research Centre at NIHR Queen Square Dementia and the Wolfson Biomarker Dementia consortium at ION, have developed a new test to diagnose different types of dementia, which they hope will allow for more reliable and accurate diagnosis of the neurodegenerative conditions of Lewy Body Dementia and Alzheimer's disease. These findings have just been accepted for publication in the Journal, Molecular Neurodegeneration.

Currently there are no effective treatments/cures for many neurodegenerative diseases. Reliable biomarkers for identifying and stratifying these diseases will be important in the development of future novel therapies. Lewy Body Dementia (LBD) is considered an under diagnosed form of dementia for which markers are needed to discriminate LBD from other forms of dementia such as Alzheimer's Disease (AD).

Using a very small amount of Cerebral Spinal Fluid (CSF), the team identified several new protein biomarkers that are increased in LBD patients when compared to healthy controls. Using this, as well as previously identified protein markers, the team developed a 10 minute 'one-pot' diagnostic test to observe the levels of 46 different key biomarkers. This test was validated using two separate dementia centre cohorts.

Dr Wendy Heywood who led the study is funded by the NIHR Great Ormond Street BRC as a Senior Research Associate in Translational Biomarker Discovery.

PATIENTS AND THE PUBLIC

Research awareness survey

Our PPI/E leads are working in partnership with GOSH Patient Involvement and Experience Team and hospital volunteers to conduct a research awareness survey with patients and families during November 2015. The aim of the survey is to find out what people think about research and findings will help us improve the way we communicate and engage with patients, families and the public about the research we carry out. We will report on the findings in the next newsletter.

Parent/Carer Research Advisory Group

Our newly formed group with parents/carers had their second meeting in early November. We have 21 group members, with a range of experiences; about 80% have experience of parenting a child

with a health condition and/or have had a premature baby, some have research experience and some have been involved in PPI previously. Three researchers attended the meeting to consult with the group and gain advice and a parent/carer perspective on different aspects of their research projects. Any researcher at GOSH/ICH looking for PPI can consult with the group, it's a free resource and consultation can take place through attendance at a meeting and/or virtually.

Please get in touch with us via research.ppi@gosh.nhs.uk if you would like any information or advice about PPI/E.

TRAINING

Young Faculty Day – Wednesday 25 November 2015

Last month, 12 young researchers joined together to share their research topics and their visions for the NIHR Great Ormond Street BRC funding for 2017-22. This day comprised of a number of short talks and then was followed up by a breakout session, where young researchers covered a number of topics directly relating to their career progression, including how the future NIHR Great Ormond Street BRC could help to implement this.

It is expected that future BRC funding will incorporate the views of the Young Faculty, through each theme having direct representation from individuals at this level.

2nd Residential National Paediatric Academic Trainee Weekend – October 2016

Following the success of the September 2014 Residential Paediatric Academic Trainee Weekend in September 2014, we are pleased to announce that we will be hosting a similar event on the 1st and 2nd October 2016, which will be open to clinicians, nurses and AHPs.

This weekend aims to provide a unique opportunity to develop research skills, from encouraging the involvement of young people in the design of your research to reviewing grant proposals, as well as networking with peers and senior academics.

More information will be available on our website early next year.

EVENTS

Upcoming Events

ESRC Research Methods Festival 5-7th July 2016

University of Bath

National Centre for Research Methods is organising the 7th ESRC Research Methods Festival at the University of Bath.The programme will be available early 2016. Delegate registration will open in March 2016.

Please visit the website for more information.

RCN International Nursing Research Conference 6-8th April 2016

Edinburgh International Conference Centre, Edinburgh, Scotland, UK

The Royal College of Nursing is hosting their annual Research Conference. This conference aims to:

- bring together researchers from diverse clinical and academic settings from around the world to participate in critical debate
- promote and advance a body of knowledge with relevance to nursing
- facilitate sharing and collaboration between health care researchers.

For more details and to register for this event, please follow the link.

Past Events

AHSN Children and Young Person (CYP) Event: Transforming Research Into Practice For Improved Child Health - 10 November 2015 13.00-18.30

UCLPartners recently hosted the AHSN Integrated Children, Young People and Maternal Health (CYM) Programme event, bringing together a wide-range of child health professionals and charities in London. Meradin Peachey, Director of Public Health Newham Borough Council, said: "I enjoyed seeing the challenges of child health across London, and how other cities like New York are raising the priority of child health and using innovative approaches." While Dr David Masters, Children's Lead, Haringey CCG, commented: "The update on the i-Thrive model was really thought provoking for my role both as a clinician and commissioner."

Read Dr Amit Bali's blog on the event here.

The next UCLPartners CYP meeting will be held on the afternoon of 20 April 2016.

'Introduction to PPI in Paediatric Research' training - 24 September 2015 9.00-13.00

GSTT Biomedical Research Centre, 16th Floor, Tower Wing, Guy's Hospital, SE1 9RT

In collaboration with the NIHR BRC at Guy's & St Thomas' NHS Foundation Trust and King's College London, we ran a half day training session for child health researchers interested in finding out about PPI. 17 researchers attended the session and participated in discussions about values, principles, and resources in PPI; heard case study examples of successful PPI and had the opportunity to develop PPI for their own research projects. Feedback from attendees was positive, *"it was a brilliant morning and makes you think about PPI at all stages. Good to meet people working in the same area and hearing different ideas"*. We plan to run similar training again in 2016.