Paediatric Research Report
2012-2013
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1. **INTRODUCTION**

In 2011 we produced the first Paediatric Research Report detailing research activity across the Addenbrooke’s campus. The aim of that report was to document the extensive clinical research activity which complements the exceptional translational science, often involving children, which emanates from the research institutes and many academic departments.

Whilst acknowledging the highly productive, but rarely acknowledged paediatric research activity across the Addenbrooke’s campus, the report also highlighted a need to ensure appropriate research governance, paediatric research staff support and to further develop paediatric research within the major Biomedical Research Centre (BRC) themes.

This led to the development of a Paediatric Research Working Group.

2. **PAEDIATRIC RESEARCH WORKING GROUP**

**Remit**

Paediatric Research Working Group reporting to the CUHNHSFT Research Board.

1. Co-ordinating paediatric research strategy, particularly with respect of clinical trials and observational studies. Developing a paediatric research theme over the next 4-5 years.
   - Maximising potential for clinical research
   - Encouraging emerging themes
   - Regional networks

2. Oversight research governance issues in Paediatrics
   - Trained staff
   - Appropriate facilities
   - Suitable study design

3. Review activity
   - Reports
   - Research training
   - Academic development

4. Paediatric Bio-resource

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<tr>
<th>Name</th>
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This group has met 7 times over the last 2 years. Although it has been hard to get everyone to all the meetings, we have overall achieved full participation from all of the Academic/ NHS units involved in paediatric research at some stage of the process. There is a strong feeling, across all disciplines, that a Cross Cutting Theme supporting paediatric research should be an important component of the BRC renewal in 2006.

The 2012-2013 report provides an update of Paediatric Research Activity across the Trust, which demonstrates continued exceptional productivity. We highlight two initiatives, Paediatric studies on the Wellcome Trust Clinical Research Facility and the Evelyn Perinatal Imaging Centre. But we present this report to reflect the extensive academic activity across Paediatrics and suggest that the future potential for Cambridge to become the most important centre for an NHS and Academic translational agendas in paediatrics going forwards.
3. SPECIAL FEATURES

3.1. Evelyn Perinatal Imaging Centre

In 2013 the Evelyn Perinatal Imaging Centre opened in the new Rosie Hospital. Led by Dr Topun Austin, the centre brings together a team of doctors, nurses and scientists in a unique facility to study the developing brain.

Cambridge Centre for Perinatal Neuroscience

The development of the Cambridge Centre for Perinatal Neuroscience brings together key individuals from across different specialties with a common interest in the developing brain. The aim of the centre is to:

− Provide a high quality clinical neurology service for high-risk mothers and babies in the state-of-the-art Fetal Medicine and Neonatal Unit at the Rosie Hospital.
− Develop Cambridge University Hospitals NHS Foundation Trust as the regional centre for neonatal neuroimaging and neuroprotection.
− Create a major programme of research into perinatal brain injury and repair.

The Centre has active collaborations with the Department of Clinical Neurosciences, Autism Research Centre and Brazelton Centre in Cambridge, Department of Medical Physics and Bioengineering, University College London and Department of Neonatology, Copenhagen.

Evelyn Perinatal Imaging Centre

The Evelyn Perinatal Imaging Centre is a unique neonatal functional brain-imaging unit. Funded by the Evelyn Trust, the unit is currently equipped with a physics laboratory and infant scanning room, designed to develop novel optical and electrophysiological imaging technologies to study the developing brain.

Space is also available for a dedicated MRI scanner for women and babies; the intention is to develop this area over the next few years.
3.2. The Addenbrooke’s Clinical Research Centre

The Addenbrooke’s Clinical Research Centre (ACRC) comprises the NIHR Clinical Investigation Ward (CIW) and the NIHR/Wellcome Trust Clinical Research Facility (WTCRF) and supports a wide range of studies currently around 220 are active. 85% are classified as experimental medicine and this includes early phase (phase 0 – IIa) clinical trials of investigational medicinal products (CTIMPs). We have expanded our paediatric nursing team in the last year and now have 2 wte who are able to work across paediatric and adult studies. Figures 1-3 show project type | specialty and study funding source for paediatric studies undertaken on CRF.

Fig 1

![Figure 1: Paediatric Studies 2001 - date project type](image)

Fig 2

![Figure 2: Paediatric studies 2001 - date specialties](image)

Fig 3

![Figure 3: Paediatric Studies 2001 - date Funder](image)
The CRF is one of 19 NIHR funded units in England. In September 2012 we received a 50% increase in our funding (2012-17) allowing us to open a new CRF Satellite unit. The CRF Satellite supports outpatient and day case studies and also provides an outreach service for experimental medicine studies e.g. in Emergency Department, NHSBT. In July 2013, in response to increased demand for inpatient beds, the NIHR/WTCRF converted all outpatient rooms into fully equipped inpatient beds.

In February 2013 we held our first Children’s Board meeting as part of a patient and public involvement initiative. A group of children and young people aged 6-14, comprising current and former research participants and healthy volunteers, volunteered to join our board and were invited to input into a range of service development initiatives. This included designing patient information, choosing entertainment equipment, making art work / photo stories and trying out various metabolic research equipment. A DVD has been made of the event which has subsequently been shared at several forums (CUH board, WACLRN ‘Nippers’ day, UKCRF Network Conference, JDRF Diabetes day, NIHR PPI exemplar).

CRF Children’s Board

Also in progress, are plans to build an extension. The new facilities will include new clinical space for endoscopy research, early phase trials and additional inpatient beds for experimental medicine. This will free up space on the existing NIHR/WTCRF and Clinical Investigation Ward which in turn will enable us to support more paediatric studies.

The ACRC has worked closely with Professor Dunger through the CUH Research Board and NIHR BRC Executive Board to secure infrastructure support for paediatric research activity across the campus.
4. SUMMARY OF RESEARCH ACTIVITY

4.1. Diabetes and Endocrinology

Endocrinology

Through the establishment of a number of large and detailed cohort studies, the Department of Paediatrics provides unique opportunities for translational studies relating to the prenatal and early post-natal determinants of future disease risk, with a particular emphasis on the understanding of key endocrine pathways and potential effects of environmental exposures, including endocrine disrupting chemicals.

Disorders of sexual development (DSD), including detailed clinical, genetic and functional studies of patients with androgen receptor defects, have been a long-standing interest of the University Department of Paediatrics led by Professor Ieuan Hughes and Dr Carlo Acerini. The Department has a unique collection of clinical, biochemical, genetic and histological data and samples, which has been used to further the scientific understanding of DSD. These data have been integral in securing EU funding for a European-wide DSD register and for the scientific exploration of the causes of DSD and its management. The suggestion that some types of DSD, such as undescended testes and hypospadias, may be related to exposure to environmental chemicals acting as endocrine disruptors also led to the establishment of the Cambridge Baby Growth Study (CBGS) in 2001. The CBGS has recruited over 2600 mothers during pregnancy for the study of their children.

The scope of the CBGS was expanded at its outset to look at the influence of other prenatal exposures, such as maternal blood glucose levels, on the growth and development of offspring. This work includes the study of genetic factors, nutrition, postnatal biomarkers, and prenatal / early postnatal epigenetic changes on infant growth and body composition and the future risk of adult onset metabolic disease. In conjunction with Dr Ken Ong (MRC Epidemiology Unit, Cambridge), the Department of Paediatrics (Dr Clive Petry and Professor David Dunger) collaborate with a number of other research groups in this area including those lead by Dr Miguel Constancia, Dr Sue Ozanne (Institute of Metabolic Science) and Professor Nabeel Affara (Department of Pathology) at the University of Cambridge. International collaborations with Professor Shane Norris (“Birth to Twenty” cohort in South Africa) and Professor Andrew Prentice (MRC Gambia cohorts) have allowed exploration of the relevance of the findings in the CBGS to transitional societies where pregnancy and very early postnatal exposures may underlie the very rapid increases in prevalence of diseases such as type 2 diabetes.

The University Department of Paediatrics has a strong interest in the developmental origins of health and diseases, such as obesity and type 2 diabetes, and Professor David Dunger and Dr Ken Ong have worked with the Avon Longitudinal Study of Parents and Children, in Bristol, and other cohort studies to delineate effects of low birth weight, rapid early postnatal growth and weight gain, and early pubertal maturation on the risk for subsequent obesity and its related co-morbidities, such as type 2 diabetes and cardiovascular disease. These studies have included epidemiological, genetic and physiological studies involving birth cohort studies, adult cohort studies and patients with conditions such as precocious pubarche and polycystic ovary disease (PCOS). An evolving theme for many of these studies has been the potential role of the growth hormone/insulin-like growth factor-1 axis in regulating developmental changes in insulin sensitivity and insulin secretion. The physiology of these interactions has been studied using the model of type 1 diabetes,
and have led to clinical trials of the use of insulin-like growth factor-1 in the treatment of type 1 diabetes, led by Dr Carlo Acerini, and exciting preliminary insulin replacement studies in newborn infants, led by Dr Kathy Beardsall. These studies have also led to the realisation that recombinant human IGF-1, through its insulin sensitising actions, may be the only effective treatment for some children and adolescents with very severe insulin resistance. In collaboration with Professor Steve O’Rahilly and Dr Robert Semple (Institute of Metabolic Science), Cambridge University Hospitals Foundation Trust is the national commissioning centre for the treatment of young people with severe insulin resistance with this service led by Dr Rachel Williams.

**Diabetes**

Type 1 diabetes research at Addenbrooke’s Hospital has been a major strength of the University Department of Paediatrics. Collaboration with Professor John Todd (CIMR) has facilitated the establishment of a unique bio-resource, the “Genetic Resource Investigating Diabetes” (GRID), which comprises over 10,500 DNA samples from young people with diabetes across the UK. These DNA samples underpinned the identification of several novel type 1 diabetes susceptibility genes. These studies continue with further collaborations with Professor Todd’s group and Professor Mark Peakman at Guy’s Hospital (London) that aim to explore the links between type 1 diabetes susceptibility genes and disorders of the immune system that could lead to targeted disease prevention strategies.

Professor Dunger’s work over the last 20 years into the natural history of microalbuminuria, a marker of future cardiovascular and microvascular complications of diabetes, has formed a major part of the research activity within the Department of Paediatrics. The identification of the young type 1 diabetes patients at highest risk of such complications has led to the first multicentre international clinical trial testing the effects of blood pressure (ACE inhibitors) and lipid lowering agents (Statins) in adolescents with type 1 diabetes: Adolescent Type 1 Diabetes Cardio-Renal Intervention Trial (AdDIT). The group are also closely involved in the evaluation of genetic and other biochemical biomarkers of early risk for complications and the data from these studies will be utilised in further long-term clinical trials to improve the prognosis of young people with type 1 diabetes.

The Department of Paediatrics also has extensive expertise in the physiological evaluation of glucose and insulin metabolism and has been involved in the development of new therapeutic strategies for young people with type 1 diabetes. This includes the exploration of potential adjuvant treatments, such as recombinant human insulin-like growth factor-1, led by Dr Carlo Acerini and Dr Rachel Williams, as well as contributing to the evaluation and development of new insulin analogues.

Following the recruitment of Dr Roman Hovorka, an expert in metabolic modelling of glucose homeostasis, the Department of Paediatrics has subsequently led the world in the development of closed loop subcutaneous insulin delivery systems (the “artificial pancreas”). In the last year the Department of Paediatrics has delivered the first home pilot study of the artificial pancreas in young people with type 1 diabetes with a larger multicentre trial expected during 2014/15.
4.2. Gastroenterology

Dr Matthias Zilbauer (University Lecturer) leads a research theme aiming to investigate the role of epigenetic mechanism(s) in regulating immunity (innate and adaptive) with a focus on gastrointestinal (GI) health and disease.

Joint Adult and Paediatric Gastroenterology Research Unit (Level 7)

Just over one year ago, we completed the refurbishment of a previously under-used laboratory based on Level 7. This provides us with a vital infrastructure allowing us to undertake translational basic research in close collaboration with our colleagues from the Adult Gastroenterology Department.

Staff

We currently have a full time Research Assistant as well as two students (both completing a 7 month research project) working in our laboratory. We recently have been awarded a PhD studentship and are in the process of recruiting a PhD student, who will join us in October 2013. Additionally, we shall be recruiting a part-time bioinformatician later this year.

MD – Programme for Witten/Herdecke University, Germany

Over the last year we have established an MD program (i.e. German Dr. med.) for medical students from Witten/Herdecke University (Germany). As Dr Zilbauer is an Honorary Lecturer in Paediatrics at Witten/Herdecke University, he can act as official co-supervisor for the students. In 2012, the first student successfully completed a 6 month laboratory based research project. The second student is currently with us and there are increasing requests for future placements.

GEPaedGI study

Genomics and Epigenetics in Paediatric Gastrointestinal and Immune mediated Disease

This study aims to investigate the potential impact of epigenetic mechanisms during intestinal health and disease as well as related immune mediated conditions. In the first instance we are focusing our investigations on children with inflammatory bowel disease (IBD) as well as age and sex matched healthy controls.

Our overall hypothesis is that cell-type specific changes to the epigenome (e.g. DNA methylation) contribute to the onset of IBD and/or are responsible for the observed chronic relapsing inflammatory phenotype.

The role and regulation of DNA methylation during intestinal epithelial development

In addition to GI disease we are also interested in the role of epigenetic mechanisms during physiological gut development. This project particularly benefits from the unique access to human fetal gut samples, allowing us to compare DNA methylation profiles of fetal intestinal epithelium with healthy paediatric tissue. Preliminary results are very exciting pointing towards a major role of DNA methylation during the development of intestinal innate immunity.

The Key collaborators involved: Arthur Kaser and Miles Parkes (Division of Gastroenterology and Hepatology, Department of Medicine), Ken Smith and Paul
Lyons (Cambridge Institute of Medical Research, CIIMR), Alison Coffey (Wellcome Trust Sanger Institute) Andreas Jenke, Jan Postberg and Stefan Wirth (Witten Herdecke University, Germany).

**Cambridge Masterclass in Paediatric Gastroenterology**

In 2013 we will be holding our 3rd Cambridge Masterclass in Paediatric Gastroenterology. This is a 3 day residential course held at Trinity Hall attracting trainees, consultants and other allied health professionals from across Europe and further afield. Following the great success and extremely positive feedback from previous years we are looking forward to this year’s event.

**Workshop on Epigenetics in Gastrointestinal Health and Disease**

In conjunction with the Masterclass, we are organising a half-day workshop in epigenetics with a focus on the GI tract. This workshop is suitable for anyone who is interested in epigenetics including clinicians, scientists and students regardless of their previous experience or knowledge in the field. We will introduce the main principals of epigenetics and highlight the exciting prospects for clinically related research. Lectures and discussions will include currently available cutting edge research methodologies to investigate epigenetic mechanisms in GI health and disease.

**Leading international research into GI epigenetics**

In March 2013 our application to the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) for a working group on epigenetics in paediatric GI and related diseases was approved. The official launch of this working group will take place during the 2013 annual ESPGHAN meeting in London. Dr. Zilbauer will be the chair/lead of this working group and the first meeting of interested members will take place as part of our Masterclass Course in September 2013.

**Current clinical trials**

Drs Robert Heuschkel and Matthias Zilbauer have been lead investigators for the following studies:

The use of Prucalopride in childhood constipation (SHIRE/Movetis) is MCRN approved and recruitment started in December 2011. Due to a complex and restricting protocol, only 3 patients completed the full study. The study is due to close in the next few weeks.

PROCEDE (ESPGHAN / National Society support) is a prospective study of diagnostic criteria in childhood coeliac disease. This a Europe-wide study with 3 UK centres. Addenbrooke’s Hospital achieved ethical and R&D approval in advance of the other UK centres and has completed enrolment of the 25 children required for this 18 month follow up study.
4.3. Neonatology

4.3.1. Neonatal Neuroscience

Dr Topun Austin leads a research group in neonatal neuroscience. Since 2009 this has attracted over £2M of research funding. The themes of the research group are

1. Early identification of infants at risk of brain injury
1. Translating best research into clinical practice

Active collaborations are with the Department of Clinical Neurosciences and Autism Research Centre in Cambridge, the Department of Medical Physics and Bioengineering, University College London and Department of Neonatology, Copenhagen.

Current Studies

Assessment of Cerebral Autoregulation

Funded by a grant from the Evelyn Trust, and in collaboration with Dr Marek Czosnyka in the Department of Clinical Neurosciences, this prospective observational study uses near-infrared spectroscopy and transcranial Doppler ultrasonography to assess cerebral perfusion and oxygenation in preterm infants over the first 72 hours of life. The aim of this work is to define the integrity of autoregulation in different clinical situations and identify the limits of autoregulation on an individual patient basis. It is anticipated that this work will lead to a better understanding of the optimal perfusion pressure for these infants with future studies looking at how manipulation of the circulation, for example with inotropes, may influence autoregulation.

Investigation of Neurovascular Coupling

This is a prospective observational study, funded by a grant from Action Medical Research, to investigate the relationship between cerebral blood flow and cortical electrical activity in neonates and young infants with seizures. The work is being carried out in collaboration with the Department of Medical Physics and Bioengineering at University College London. Previous collaboration with this department resulted in the development of a unique integrated optical topography and electroencephalography system (optical-EEG) with preliminary results showing slow waves of deoxygenation spreading across the brain in infants with brain injury. These results were similar to the phenomena of spreading cortical depolarisation seen in adults following head injury, but not previously described in neonates.

Multiparameter data-fusion analysis

This is another collaborative study with the Department of Medical Physics and Bioengineering at UCL. We have developed an intelligent detection multiparameter model to identify clinical deterioration in preterm infants with the hypothesis that the model will have a higher specificity than conventional single channel alerts. If this pilot study is successful then it will lead onto a larger study comparing multiparameter data analysis with conventional monitoring to improve detection of clinical events in these infants.
SafeBoosC Phase II RCT

The SafeBoosC (Safeguarding the Brains of our smallest Children) trial is a European Collaborative RCT funded by a grant from the Danish Research Council. The overall aim of the SafeBoosC project is to investigate whether cerebral oxygen targeted therapy (monitored using near-infrared spectroscopy) can improve survival and neurodevelopmental outcome in preterm infants. This phase II study involves randomising 150 infants across Europe to receive either standard care (with cerebral oxygenation data collected blindly) or treatment directed at keeping cerebral oxygen levels within a defined range. If this study shows it is possible to keep cerebral oxygen within a targeted range then a much larger study involving over 4000 infants is planned.

Future Studies

The Cambridge Human Imaging and Longitudinal Development (CHILD) study

This is a collaborative study with Professor Simon Baron-Cohen at the Autism Research Centre in Cambridge. Building on their previous work investigating antenatal hormone levels and the risk of autism in later life, this study will focus on understanding the different effects of prenatal and postnatal hormones on brain development and behaviour in typically developing children and in siblings of children with a diagnosis of autism. The overall aim is to hone in on biomarkers that may be predictive of risk for autism.

Three Dimensional Optical Tomography of the Neonatal Brain

This study builds on the collaborative links with the Department of Medical Physics and Bioengineering at UCL and will see the installation of a unique 3D optical tomography system to image regional blood flow and oxygenation in the newborn brain. The overall aim of this study will be to investigate functional brain activation in both healthy newborn infants and infants with evidence of brain injury using conventional neuroimaging. We also intend to use the system to study the development of global cortical networks in the newborn and ultimately to integrate the optical imaging system with MRI to simultaneously assess brain structure and function.

Baseline Resting-state Activity In Newborns – BRAIN study

This is a prospective observational study investigating brain function and behavior in healthy and high-risk infants. Using the optical-EEG system developed by neoLAB, blood flow and electrical brain activity will be measured at rest in order to assess the development of functional brain connections and see if disruption to the development of normal connectivity relates to abnormal behaviour and brain injury. These emerging ‘resting-state functional networks’ will be compared to emerging infant behaviour and structural brain images to test the hypothesis that early functional brain imaging and behavioural assessment is predictive of later neurodevelopmental outcome.

iii) Fast Optical Tomography On Neonates – FOTON study

This study, part of the neoLAB collaboration with UCL-BORL will see the installation of a unique 3D optical imaging system in the Evelyn Perinatal Imaging Centre. Development of the imaging system and clinical studies are funded by a grant from the EPSRC. The imaging system is designed to obtain 3D images of regional blood flow and oxygenation from the developing brain. The overall aim of this study will be to investigate functional brain activation in both healthy newborn infants and infants with
evidence of brain injury and ultimately to integrate the optical imaging system with MRI to simultaneously assess brain structure and function.

**Putting Research into Clinical Practice**

The East of England Neonatal Neuroprotection team, led by Dr Topun Austin, was awarded a grant of £375k by the Health Foundation in 2009 to develop a coordinated, family centred and regional service for infants with hypoxic-ischaemic encephalopathy across the East of England. The project involved engaging all 17 hospitals across the region to ensure that infants eligible for therapeutic hypothermia were identified early and managed in a timely and safe manner. Results from the project showed a significant reduction in the time cooling was started and time to target temperature, with all infants in the last 6 months referred for cooling reaching target temperature within 6 hours of birth. There was also universal adoption of core temperature monitoring across the region with a reduction in the incidence of overcooling. To address the needs of the families an information booklet was produced in collaboration with BLISS and a website for both families and healthcare professionals has been launched [www.BeBop.nhs.uk](http://www.BeBop.nhs.uk). The importance of sustainability was recognised by the East of England Perinatal Networks who have created the UK’s first lead nurse for neonatal neuroprotection. The success of the project was recognised by the National Institute for Health and Clinical Excellence, who presented the team with the 2012 NICE Shared Learning Award at their annual conference in Birmingham.

**Research Responsibilities and Positions outside of Neonatology**

Dr. Topun Austin is on the scientific committee for the European Academy of Paediatric Societies (EAPS), council member of the European Society of Paediatric Research (ESPR) and education committee member of the European Association of Perinatal Medicine (EAPM). He is also on the medical advisory committee for SPARKS, steering committee for the NPEU TOBY Xe study and chairs the MCRN Neonatal Neurology specialty interest group.

4.3.2. Neonatal metabolism and glucose control

Dr Kathryn Beardsall leads on the research in the area of neonatal metabolism and glucose control. The metabolic transition from fetal to independent life involves many adaptive processes, including that of glucose control, and the perinatal period can be critical for programming later metabolic health. This has involved collaborations with Cambridge in the IMS with Roman Havorka as well as leading on the international multicentre randomised controlled trial NIRTURE (Neonatal insulin Replacement therapy in Europe). We are exploring areas to improve our short term clinical management and the long term impact on neurocognitive and metabolic outcomes. The transition from fetal to independent life involves many adaptive metabolic processes and at this time it is not uncommon for babies to have problems with glucose control. In the preterm infant the combination of hyperglycemia, insulin deficiency and catabolism can be a challenge to manage clinically and also has implications for both short and long term health. Infants born following pregnancies complicated by diabetes, often face problems of hypoglycemia which can also be difficult to manage clinically with current methods of glucose monitoring, and has implications for neurological outcomes. Interestingly both these groups of babies are at long term risk of impaired glucose tolerance which is a risk factor for type 2 diabetes. We are interested in exploring, underlying mechanisms, areas to improve our short term clinical management and investigating the long term impact on neurocognitive and metabolic outcomes of these babies.
Current studies

**IMPP – Improving glucose control in the preterm infant.** This involves combining two new technologies, real time continuous glucose monitoring and the development of computer algorithms to individualize the management of glucose control in the extremely preterm infant. Preterm infants <1200g are randomized within 48 hours of birth to one of 3 study arms. This study explores the safety and efficacy of real time glucose monitoring in the preterm infant.

**CBGSII: Cambridge baby growth study II** – To examine the relative changes in body composition from birth to 2 years in small-for-gestational age infants and infants of diabetic mothers. This study will help to determine antenatal, postnatal dietary and genetic influences on growth as well as early biochemical markers (endocrine/metabolic markers) and immunological markers of changes in body composition.

**SABS: Small at Birth Study** - To determine what proportion of babies born small for gestational age (SGA) have shown catch up gains in weight at age 5-7 years and how many remain <2SD for height. To define the relative morbidity associated with being born SGA by assessment of the accumulation of different components of body composition (fat vs. lean mass) and different compartments of body fat (intra-abdominal vs. subcutaneous), as well as insulin secretion and sensitivity at age 5-7 years.

**PREVENT-ROP** The overall objective is to develop a novel preventative intervention for the blinding disease retinopathy of prematurity (ROP) and other complications of prematurity. This work is based on the concept that replacement of critical factor(s), normally provided in utero and reduced due to the disruption of the maternal/fetal interaction, to the infant born prematurely will help prevent the complications of premature birth.

Future Studies

**Real Time CGMs in NICU:** This is a multicentre randomized controlled Trial of Real Time Continuous glucose monitoring in neonatal intensive care. It aims to assess the potential role of real time CGMs to optimize glucose control in preterm infants.

**CONCEPTT Neonatal Study:** Continuous Glucose Monitoring in Women with Type 1 Diabetes in Pregnancy Trial This study will use continuous glucose monitoring to compare glucose control in the offspring of mothers recruited to the CONCEPTT randomised controlled trial of CGM in pregnant women with Type 1 diabetes. Mothers currently being recruited

**The Influence Of Paternally-Expressed Foetal Imprinted Genes On Maternal Blood Pressure During Pregnancy** This study will identify potential serum biomarkers of paternal-gene influences on raised maternal BP in pregnancy using candidate (placental protein measurement) and unbiased (metabolomic/lipidomic) analyses of first trimester blood samples. (funding secured)
**NIRTURE Childhood Study: (Neonatal Insulin Therapy in Europe).** (collaboration with Neil Marlow and Stavros Petrou and Sam Johnson). We aim to follow up at 10 years of age the cohort of infants who were initially recruited at birth to this international randomized controlled trial of the use of early insulin in very low birth weight infants. This study will help to define the impact of hyperglycemia and hypoglycemia on neurological and metabolic outcomes in childhood.

### 4.3.3. Perinatal Research: preparing for postnatal life

Dr Gusztav Belteki is using experimental methods to understand the molecular basis of the diseases of preterm infants. Uncovering the molecular mechanisms involved in these conditions will enable identification of novel diagnostic and prognostic biomarkers and could lead to novel therapies. Dr Belteki’s research focuses on three areas:

1. **Fetal lung maturation**

Extremely preterm infants frequently suffer from respiratory distress syndrome (RDS) due to structural and functional immaturity of the lung. Antenatal maturation of the lung is directed by developmental gene expression programs. Working together with Professors Gordon Smith and Steve Charnock-Jones (both in the Department of Gynecology and Obstetrics) we previously used microarray technology to study gene expression in the rat lung and intestine during late gestation (Figure 1). This study has identified novel candidate genes including paraoxonase 3 (PON3), a novel antioxidant. We have shown that paraoxonase 3 is up-regulated during late gestation and induced by antenatal steroids (Figure 2). Disruption of PON3 expression in lung epithelial cells reduces total antioxidant capacity. Knockout of PON3 causes antenatal mortality in mice. We are now using high-throughput RNA sequencing technology to analyse gene expression in the perinatal mouse lung. We aim to discover novel genes including non-coding RNAs dynamically regulated in the perinatal lung. 

![Figure 1. Number of genes changing their expression levels over five-fold in the rat lung and gut during the late fetal period. Microarray analysis.](image1)

![Figure 2. Up-regulation of PON3 transcription in the lung during late gestation.](image2)

2. **Biology of necrotizing enterocolitis**

Necrotizing enterocolitis is a life-threatening emergency affecting preterm infants. Its mortality is as high as 40% and its incidence is increasing. Previously we identified a novel pattern recognition receptor, the NOD-like receptor 6 (NLRP-6) and other components of a pro-inflammatory complex called the “inflammasome” in the rat intestine (Figure 3). Pattern recognition receptors constitute an

![Figure 3. Immunohistochemistry of the inflammasome component Pycard in the rat intestine](image3)
ancient intestinal antimicrobial defence system. Both their inactivation and overactivation can result in intestinal injury. We are planning to use high-throughput genome sequencing to identify novel genetic variants in these genes that contribute to NEC. The other arm of this project is going to study the intestinal microbiome in infants with necrotizing enterocolitis.

3. Discovering novel biomarkers predicting neonatal outcomes.

I am the Chief Investigator of the “Perinatal Markers of Neonatal Outcome” study. In this study we are collecting cord blood samples from very low birth weight (<1500 g) infants and term controls. We will use RNA, protein and metabolomic analysis to identify novel biomarkers in cord blood that predict neonatal morbidity and mortality. These biomarkers may also highlight potential entry points for novel therapeutic interventions.

4.3.4. Neonatal Haematology

Dr Anna Curley’s collaboration with NHS Blood Transplant (NHSBT) has led to a programme of neonatal haematology research. (i) Platelets for Neonatal Transfusion (PlaNeT 2) – is a multicentre randomised controlled trial of platelet transfusion thresholds in preterm neonates. (ii) Development and validation of a bleeding assessment tool (BAT): an international collaboration between 8 neonatal and haematology groups in 3 countries to develop a tool for use in two randomised controlled trials. (iii) A retrospective study of efficacy of neonatal platelet transfusion based on donor platelet response profile. (iv) Transfusion Assessment Tool: a pilot study in Cambridge documenting adverse events associated with neonatal transfusion.

Multicentre studies supported in 2011-2012;

- Probiotics in Premature Infants (PIPS) – PI Kathryn Beardsall; I2S2 (continuing care site); A randomised controlled trial of iodine supplementation in preterm infants
- BOOST II – PI Anna Curley; Down Syndrome Haematology Study – PI Anna Curley.

4.3.5. Other Studies supported in the NICU:

- Impact of Epigenetic mechanisms on regulation and development of GI innate mucosal immunity - PI Robert Heuschkel; MRI fluoroscopy for imaging childhood vesicoureteric reflux - PI Professor David Lomas.

Future Developments

The new NICU was opened in Sept 2012, with a dedicated space created to develop a Perinatal Imaging Centre. The first phase of this development is the creation of a functional brain imaging unit to develop optical and EEG systems to assess the newborn brain. The Evelyn Trust has provided a grant of £0.5M towards the creation of the first phase of the Perinatal Imaging Centre as well as developing a research fellowship in Perinatal Neuroscience. The Perinatal Imaging Centre is due to open early in 2013. Space is also available for a dedicated MRI scanner for women and children which will be installed as part of the second phase of the development.

Research Responsibilities and Positions outside of Neonatology

Dr Jag Ahluwalia is the Trust Executive responsible for research and Dr Kathryn Beardsall is a member of the National MCRN Neonatology Clinical Specialty Group.
4.4. Neurology

There are 5 consultant paediatric neurologists in post (4 FTE) providing tertiary level paediatric neurology services to the population of the East of England and secondary care to the local Cambridge area. We provide outreach clinics to 13 district general hospitals and run active clinical networks in the areas of Epilepsy, neuromuscular disorders and acquired brain injury.

All consultants are NHS clinicians. We do not currently have any funded research time. We have one part-time research assistant, Dr Francine Kieta, funded by the Evelyn Trust.

Current Research Activity within the department

Dr Alasdair Parker

SPEED study–exome sequencing in child neurological disorders - Co-applicant, PI: Dr Lucy Raymond.
Gene therapy in GM2 - Co-Applicant, PI: Prof Tim Cox
NIHR study on everolimus in childhood tuberose sclerosis (TS) – AP, Principal investigator
NIHR study on everolimus in childhood tuberose sclerosis (TS) with epilepsy - AP, Principal investigator
NIHR study on metformin in childhood tuberose sclerosis (TS) - Chief Investigator: Dr F O'Callghan, Bristol

Dr Anna Maw

Configuration of Rehabilitation services to optimise outcomes in children affected by cancer - Co-applicant, Project lead: Amos Burke
How should the NHS commission and deliver rehabilitation services for children after acquired brain injury?- Co-applicant, Project lead: Rob Forsyth
Cognitive Behaviour Therapy Skills in Children who have sustained an Acquired Brain Injury - Site PI – CUH, Project lead: Anna Adlam/Jessica Ingham
Cognitive outcomes in children with mild TBI. - Principle Investigator and project lead. Research assistant: Francine Kieta

Dr Manali Chitre

International collaborative Infantile spasms study - collaborator
NIHR study: An investigation of neural structure, function and connectivity in Rolandic epilepsy -Site PI – CUH, CI: Anna Smith, Colm McCginnity
SANAD II - RCT comparison of Standard And New Antiepileptic Drugs (SANAD II). - Site PI (Paediatrics CUH)
Identification of the genetic and clinical abnormalities in PEHO syndrome, implications for the treatment of childhood epilepsies and sleep disorders -Project supervisor: Fellow- Dr Apostolos Papandreou, Co-supervisors: Dr A Parker, Prof G Woods
Others activities of the paediatric workstream of the Evelyn project:

- Service use of the children following A&E attendance with Traumatic brain Injury (April to September 2011)
- Service use following admission to Paediatric Intensive Care Unit with Traumatic brain Injury (Jan 2007 to Dec 2011)
4.5. Oncology and Haematology

Members of the department are engaged in a variety of translational research projects in collaboration with other departments within the University of Cambridge and beyond. This is most developed in the area of lymphoid malignancies (Amos Burke) and germ cell tumours (James Nicholson and Matthew Murray)

Lymphoid Malignancies

In addition to leadership roles in clinical trial development in non-Hodgkin lymphoma, Amos Burke is developing collaborative research in the field of lymphoid malignancies with Dr Guy Brown (University department of Biochemistry) and Dr Suzanne Turner (molecular histopathology). Dr Lucy Metayer (Clinical Research Fellow) is undertaking a PhD investigating the role of L-arginine in the survival of lymphoid cells as a potential target for therapeutic intervention (Grant funding: Leukaemia and Lymphoma Research Fund, £199,582).

Working with Dr Anthony Bench (Haematology and Oncology diagnostic Service), Amos Burke is investigating the detection of residual disease detection in Anaplastic Large Cell Lymphoma (ALCL); with a network of 4 labs across Europe led by the Cambridge team. This work will be incorporated into the next International clinical study for ALCL in development.

Germ Cell Tumours (GCTs)

James Nicholson and Matthew Murray are engaged in a programme of clinical and laboratory research in Germ Cell Tumours (GCTs), working with Professor Nick Coleman (Molecular Pathology, University of Cambridge).

Matthew Murray is investigating gene expression in GCTs, a national CCLG biological study based in Cambridge, resulting in the award of a PhD from the University of Cambridge (Grant funding, Medical Research Council, Clinical Research Training Fellowship, £230,961) and a number of national awards, including the RCPCH & SPARKS Young Investigator of the Year (2012) and the NCRI CCLG McElwain Award (2010). Recent focus of this work is based on microRNA (miRNA) expression and both the potential for serum miRNA detection in cancer diagnosis and monitoring, and the development of potential targeted treatment based on common 'seed regions' in upregulated miRNAs across this tumour group. Dr Murray was the first to report the identification of upregulated miRNAs in the serum in malignant GCTs and has extended this work to include other common childhood tumour types. This has identified novel and translational findings, including a panel of serum microRNAs that appear to distinguish MYCN-amplified neuroblastoma from non-MYCN-amplified disease at diagnosis. The work has attracted further grant funding including:


2) “Novel genetic markers for blood-based diagnosis and monitoring of common childhood cancers” Sport Aiding Medical Research for Kids (SPARKS) Innovation Grant, 2012-2013, £44,087, 1 year.

3) “A clinical dataset and tumour bank for malignant germ cell tumours in young people in the UK” Laura Crane Youth Cancer Trust, 2012-2014, £26,883, 2 years.

4) “Novel genetic markers for blood-based monitoring of treatment response in
common childhood cancers” Children with Cancer UK and Great Ormond Street Hospital Children’s Charity (CwCUK/GOSHCC) grant, 2012-2014, £99,840, 2 years.


For the laboratory biological studies, established collaborations are in place with research teams in Montreal, Canada (germline mutations; lead by Dr Will Foulkes), Nottingham, UK (methylation studies; Dr Paul Scotting), Bonn and Dusseldorf, Germany (methylation studies; lead by Dr Stefan Schönberger and Professor Dominik Schneider) and Dallas, TX, US (proposed studies to identify prognostic gene signatures; Professor James Amatruda).

James Nicholson and Matthew Murray are also involved in national and international clinical studies in intracranial and extracranial GCTs. They are leading an international (European) retrospective study of relapsed intracranial GCTs with a view to future study and guideline development. In extracranial GCTs, data is being pooled from recent UK and US studies in collaboration with US colleagues. This has led to refining of risk group stratification for a new study design and one which will, for the first time on both sides of the Atlantic, incorporate young adults as well as children. The planned study will also incorporate biological questions, on which Matthew Murray is leading together with the US GCT biology lead based in Dallas.

Other solid tumours

In a further collaboration between Dr Burke and Dr Suzanne Turner with Dr Liz Hook (clinical pathology) a mouse model for neuroblastoma is being developed [grant funding, Addenbrookes Charitable Trust, £19,995].

Dr Boo Messahel has an established track record in research in Wilms’ Tumour and in particular investigation of the molecular correlates of high risk disease, work which will continue in Cambridge in collaboration with national and international colleagues. She has been instrumental in setting up the UK-based IMPORT study, investigating clinical and biological correlates of high risk disease in renal tumours of childhood, which should result in an improved risk stratification for patients following definitive surgery for the primary disease.

Non Malignant Haematology

Both Myles Bradbury and Mike Gattens are involved in the following studies; BRIDGE - genetic analysis of inherited platelet disorders, ITP study. We are one of four centres in the UK which have recruited patients into two international portfolio adopted commercial studies. These are open-label, Evaluation of the Safety, Pharmacokinetics, and Efficacy of Recombinant Factor VIII Fc Fusion (rFVIIIFc) in the Prevention and Treatment of Bleeding in Previously Treated Subjects with Severe Haemophilia A and the second study looking at Recombinant Factor IX Fc Fusion (rFIXFc) in Severe Haemophilia B.

Current NCRN portfolio studies actively recruiting

During April 2012-March 2013 we saw 128 new patients in our department with malignancy. For 45% of these patients there was an NIHR NCRN portfolio study open. Of those patients eligible 58% were recruited to a trial. Myles Bradbury is the Clinical trials lead for Paediatric Haematology and Oncology at Addenbrookes.
Leukaemia trials;

UKALL2011 – PI Myles Bradbury (Acute Lymphoblastic Leukaemia >1ys <25yrs of age)

LK2006 10 Infant ALL – PI Mike Gattens (Acute Lymphoblastic Leukaemia under age of 1 years),

AML17 – lead sub-investigator Myles Bradbury (Acute Myeloid Leukaemia),

UKALLR3- PI Mike Gattens (relapse ALL study),

Dasatinib CA180/372 – PI Mike Gattens (Philadelphia positive Acute Lymphoblastic Leukaemia)

Oncology trials;

NB 2002 06 High risk neuroblastoma- PI James Nicholson,
HD 2007 10 Euronet Hodgkins closed 01/2013- PI Amos Burke,
Herby (CNS) PI James Nicholson
GeDDis (TYA)
ET 2000 03 Euro-Ewings- PI James Nicholson,
LT 2007 03 SIOPEL 6 (hepatoblastoma)-PI Amos Burke,
STS 2006 03 Non-rhabdo soft tissue sarcomas –PI Denise Williams
STS 2006 04 RMS 2005 Rhabdomyosarcomas– PI Denise Williams,
FACT – PI Amos Burke
PK studies - PI Amos Burke

The 1.5WTE research nurses are actively involved in the portfolio studies. In addition they recruited 153 patients to; 5 PK studies, tumour and leukaemia cell banking and the FACT study (genetics and causation of cancer).

Trial governance has been a major strength of the Addenbrooke’s team and several processes have been developed that have become nationally adopted; most notably Trust-to Trust agreements covering research governance in Paediatric malignant Haematology and Oncology. These have been used by the designated trials unit for Children’s cancer and Leukaemia (CR-UK Clinical Trials Unit, Birmingham) in collaboration with the National Institute for Health Research cancer Research Network (NCRN) as a model for the development of shared care governance across England.

Chief investigators or co-investigators on national and international trials

Inter B-NHL Ritux Amos Burke (UK Chief Investigator and International Steering Committee member; Dr Denise Williams UK Co-Investigator) - CRUK grant (University of Birmingham) - in set up

SIOP CNS GCT II James Nicholson (UK Chief Investigator & International Co-chair) – CRUK grant £147,000 (University of Birmingham) - in set up

CCLG Germ Cell 3 study for extracranial germ cell tumours, closed to recruitment 2010, in active follow-up James Nicholson (Co-Investigator)
Analysis of the genome and transcriptome in primary paediatric malignant germ cell tumours (CCLG 2002 BS 03) James Nicholson (Chief Investigator)

ALCL 99. First line for anaplastic large cell lymphoma (closed June 2009) Denise Williams (Chief investigator)

ALCL-R. Relapse protocol for anaplastic large cell lymphoma (closed Sept 2009) Denise Williams (Chief investigator) Amos Burke (Co-investigator)

BS 2007 02. Detection of minimal or residual disease in ALCL Amos Burke (Chief Investigator)

BS 2002 03. Study of gene expression of paediatric malignant germ cell tumours using micro-arrays James Nicholson (Chief investigator)

**Locally Sponsored Research**

Learning from the experts: A research study looking at children’s experiences of being diagnosed with cancer. PI Dr Amos Burke (research project for MSc of Dr Jill Mant – University of London, completed 2012).

With Dr Rachel Williams, Consultant Paediatric Endocrinologist, in the University Department of Paediatrics, and Mike Gattens, Matthew Murray has lead a retrospective single-centre study of changes in height, weight and BMI in non-irradiated childhood acute lymphoblastic leukaemia survivors, leading to publications in the *British Journal of Cancer* (2011) and the *British Journal of Haematology* (2013).

**Additional research responsibilities and positions**

Amos Burke took on a new position in 2011 as national Institute for Health Research Cancer Research Network (NCRN) Associate Director for CCL (Children’s Cancer and Leukaemia).

James Nicholson is chair of the Intracranial Germ Cell Tumour Working Group of the SIOP (International Society of Paediatric Oncology) -Europe Brain Tumour Group, and is a member of the SIOP Scientific Programme Advisory Committee. He also chairs the Germ Cell Tumour Subgroup of the NCRI CCL CSG (National Cancer Research Institute Children’s Cancer and Leukaemia Clinical Studies Group).

Denise Williams chairs the European Intergroup Collaboration for Childhood Non-Hodgkin Lymphoma (EICNHL), of which Amos Burke is also a member. Amos Burke is a member of the NCRI Lymphoma CSG and chairs the Paediatric Non-Hodgkin Lymphoma Subgroup.

**Developments within the department in 2012 impacting on future research activity**

Our centre has recently been accepted to recruit patients on ITCC phase I and phase II haematology and oncology studies, joining 9 other centres in the United Kingdom.
4.6. Paediatric Intensive Care Unit (PICU)

The Paediatric Intensive Care Unit (PICU) is an 11 bedded mixed (medical and surgical) unit staffed by 6 consultants (2 full-time + 4 part-time). It is the referring centre for critical illness in the east of England and admits more than 600 critically ill children per year. The PICU contributes to the national paediatric intensive care database and has collaborative research with other PICUs in the UK and in South America. The main research themes within PICU are Inflammation and Immune Response, Nutrition and Metabolism, Brain Injury, Endocrinology of critical illness, and blood conservation.

Dr Nazima Pathan has been appointed as University of Cambridge Lecturer in Paediatric Intensive Care, with an honorary contract with Addenbrooke’s as Consultant in PICU. She comes from Imperial College London and the Royal Brompton Hospital where she was a HEFCE funded clinical academic for 5 years. She has an interest in inflammation and nutrition. She is a member of the PICANet clinical advisory group.

Dr Roddy O’Donnell leads research into the immune response to respiratory infection. His research focus is on the immune response to severe respiratory viral infections in children.

Dr O’Donnell is involved with the PICAnet national audit on both the clinical advisory group and steering group and is chair of the acute respiratory failure sub group of the Paediatric Intensive Care Society.

Dr Sarah Morley leads research in Blood conservation. Dr Morley is a consultant for the PICU and for the National Blood Services. Her special interest and research is in coagulation disorders and strategies for blood conservation. She chairs the education and science committee for the Paediatric Intensive Care Society.

Dr Anke Top led research into microcirculation until her departure in 2012. Her research line is on the evaluation of the microvasculature using orthogonal polarization spectral imaging. Her work includes microcirculatory changes during the neonatal period and microcirculatory adaptation to critical illness. Dr Top is involved in research collaboration with the Erasmus Medical Center-Sophia Children’s hospital in the Netherlands.

Dr Ricardo Branco has established a research theme on the endocrinology of critical illness, with focus on critical illness-related corticosteroid insufficiency (CIRCI), insulin therapy, and somatotropic resistance. Dr Branco also has an interest in the endocrine response to cardiac surgery in children. He has a strong collaboration with PICUs in South America.
4.7. Respiratory, Allergy and General Paediatrics

4.7.1. Respiratory

We have participated in several NIHR studies. This has included studies in CF (TIDES, TORPEDO), wheeze (WAIT), bronchiolitis (LIBSS) and empyema (ESPE). Other studies (ACOUSTIC, TRUMPET) are under review as potential future studies. Recruitment has been generally good with around 50 children recruited in total over the last year.

Dr Rob Ross Russell has continued in his role as CLRN representative, also sitting on the Respiratory Clinical Specialty Group (CSG) determining national priorities in respiratory research.

Non-invasive assessment of respiratory function

*Structured light plethysmography*

Dr Richard Iles is continuing his award winning work with Structured Light Plethysmography (SLP) in conjunction with the Department of Signal Processing, Cambridge University. Over 2012-13 there have been active studies in several areas, including COPD, NICU, Adult ITU and the Cambridge Rowing squad. Physiological outputs have been extended to include regionalisation of chest and abdomen, and left and right. Further work is ongoing to assess the entropy of the respiratory pattern. Abstracts submitted to RCPCH and ERS 2013.

*Oxygen diffusion index*

Dr Ross Russell has been working on the assessment of oxygenation in adult and paediatric patients. Collaboration with the University Department of Engineering and Anaesthetics Department at Addenbrooke’s Hospital continues. An algorithm has been developed which enables the percentage of ambient oxygen to be related to the measurement of arterial oxygen saturation from a standard pulse oximeter. This enables the calculation of pulmonary shift and shunt to be calculated non-invasively (without the need of an arterial blood gas). New studies in the Neonatal Unit, to assess infants with chronic lung disease, and in children with CF or scoliosis are being planned and will start shortly.

Other projects

A joint project with the MRC Nutrition Unit has been developed to look at bone health in CF children using the PQ CT scanner, that analyses bone mineral content in great detail. Dr Ross Russell has been developing this in conjunction with Dr Kate Ward and the project will start recruiting in May 2013.

Work on the care of children with bronchiolitis has led to several successful abstracts at international meetings. A paper on the effect of admission rates on length of stay has recently been submitted by Dr Ross Russell.
4.7.2. Allergy

The childrens' allergy research programme at Addenbrooke’s is led by Dr Andrew Clark.

Study of Tolerance to Oral Peanut (STOP) Oral immunotherapy for severe food allergy was a pilot study (n=22) set up in 2008 looking at peanut oral immunotherapy. This was funded by the Evelyn Trust, and led to the NIHR Efficacy and Mechanism Evaluation programme awarding funding for a phase II efficacy study of peanut OIT (STOP II; n=104). This study is underway and was completed in March 2013. Manuscripts and final reports have been submitted. CI - Dr Clark.

The Study of Extrinsic Factors in Food Allergy (TRACE). This multi-centre food challenge study led by Cambridge (Cambridge, Imperial and Manchester) looks at food thresholds in the population. It aims to explore the challenge thresholds of peanut allergic patients with and without extrinsic factors (exercise and sleep deprivation). Cambridge is the lead centre CI - Dr Clark (n=100; CLRN portfolio study).

Study of T cells in Allergy and Resolution (STAR) n =100. This is a clinical study of natural resolution of egg allergy egg allergic children and involves performing sequential challenges to well cooked and then raw egg in each child, allied to mechanistic immunophenotyping laboratory assays. The study was completed in 2011, 2 publications were produced and the study contributed to a national guideline.

The development of novel diagnostic techniques for food allergy involves a pilot study of thermographic imaging used in peanut challenges. It will lead to development of Phase II dose-ranging study of nasal peanut challenges and infrared thermography in preparation.

Mechanism of tolerance induction, both naturally and through oral immunotherapy – Development of a panel of mechanistic immune blood assays to monitor changes occurring during resolution of allergy. These are applied throughout our studies and include allergen specific T cell proliferation, IgE, IgG and subclasses, basophil responsiveness and tryptase.

*Important collaborations – internal/external*

Cambridge is the lead centre in an FSA funded thresholds study. Subcontractors include Imperial College (St Mary’s Hospital and Royal Brompton), University of Manchester (Professor Iaian Buchan and Professor Clare Mills).

The TRACE study forms a platform for a £1M MRC study at Imperial examining physiological mechanisms involved in anaphylaxis (local PI Paul Turner).

We are collaborating with Dr Jo Kosmala-Anderson at the University of Coventry to provide an e-learning package for teenagers with anaphylaxis and will perform an efficacy study of this intervention. An application is in progress.

4.7.3. Acute and General Paediatrics

Acute and General Paediatrics are in the process of developing a research infrastructure which goes beyond supporting recruitment of patients in the clinical setting. There are close working relationships with the Emergency Department and other, more research active paediatric sub-specialties.

NIHR portfolio studies
Peter Heinz is Principal Investigator for PREDNOS and PREDNOS 2. PREDNOS is a national multicentre randomised double blind trial of long-term tapering versus standard prednisolone (steroid) therapy for the treatment of the initial episode of childhood nephrotic syndrome.

PREDNOS 2 is a national multicentre double blind randomised controlled trial of short course daily prednisolone therapy at the time of upper respiratory tract infection in children with relapsing steroid sensitive nephrotic syndrome (SSNS).

Dr Helen Bailie is Principal Investigator for PYCES: a prospective longitudinal, randomised clinical trial of trauma-focussed cognitive behavior therapy for posttraumatic stress disorder (PTSD) in young children aged 3-8 years (PYCES).

She has also been Chief Investigator in a study correlating spinal canal depth with body weight in children which has been presented at a national conference and accepted for publication.
5. **GRANTS**

*Addenbrooke’s Hospital/University of Cambridge staff are highlighted*

A mouse model for neuroblastoma is being developed. 2010-2011. **Addenbrookes Charitable Trust, £19,995. Burke A, Turner, Hook L**

A Pharmacokinetic study of the combined use of Recombinant Human GH and IGF-1 in Children with Inflammatory Bowel (Crohn’s) Disease. 2011-2016. **Greater Glasgow Health Board £5,000. Ahmed SF (PI), Sanderson I, Dunger D.**


AdDIT (Adolescent Diabetes Intervention Trial) (drugs). 2008-2012. **Pfizer £109,100. Dunger D (PI).**


Assessment of Cerebral autoregulation in preterm infants. 2009-2012. **Evelyn Trust £40,000. Austin, T, Czoszynka M.**


Bt20 Plus: Intergenerational influences on health and wellbeing: Towards dynamic and multidimensional understanding of early development. 2012-2016. **Wellcome Trust. (£1,000,000). Norris S (PI), Stein A, Fall C, Dunger D.**

Clinical Application for Metabolic Profiling (EU-CLAMP; SME FP7- 262007). 2010-2012.

Closed-loop insulin delivery in the general ward - Towards achieving optimal glucose control in hospitalised patients with type 2 diabetes. 2013-2015. **MRC/University of Cambridge (Confidence in Concept). £60,000. Hovorka R (PI).**


Dexcom IV Medical Research Council and the UK Department for International Development. 2012-2013. £45,000. **Hovorka R (PI), Wilinska ME (Co-PI).**
Diabetes, Obesity, Metabolism, Endocrinology (DOME) and Bone Disorders Theme. 2012-2017. **BRC NIHR Biomedical Research Centre. £750,810. Dunger D (PI), Hovorka R.**


Food thresholds in the population ‘TEXTFALL’. 2012-2015. **Food Standards Agency £1,300,000. Clark A.**

Glucose in Very Preterm Infants. 2011-2013. **The Evelyn Trust. £73,000. Beardsall K (PI), Hovorka R, Dunger D.**


Improving glucose control in very preterm infants. 2011-2013. **Evelyn Trust.** £73,000. **Beardsall K** (PI), **Hovorka R** (CI), **Dunger D** (CI).

Improving the day to day management of diabetes during the pregnancy using innovative decision support. 2009-2013. **Diabetes UK.** £501,689. **Murphy H** (PI), **Hovorka R**, Simmons D, Rayman G, Speight J.

Infant manifestations of adult obesity susceptibility genotypes. 2010-2012. **European Society for Paediatric Endocrinology: Collaborative Research Grant.** 60,000 EUR. **Ong KK** (PI), Heude B, Ibanez L, **Dunger D**, Charles M, de Zegher F.

Investigation of Novel genetic markers for blood-based diagnosis and monitoring of common childhood cancers. 2012-2013 **SPARKS Innovation** £44,087. **Murray M**.

JDRF UK Centre for Diabetes Genes, Autoimmunity and Prevention (D-GAP). 2008-2013. **Juvenile Diabetes Research Foundation.** £750,000. **Dunger D** (PI), Peakman M, Wicker L, Todd J.

Metaplastic Paneth cells in disease pathogenesis of paediatric Inflammatory Bowel Disease (IBD). 2011-2013. **Children with Crohns and Colitis (CICRA)** £66,000. **Zilbauer M**, Heuschkel R.


Neonatal neuroprotection in the East of England. 2010-2012. **Health Foundation** £375,000. **Austin T**.

Neurovascular coupling during seizures. 2012-2014. (i): **Action Medical Research.** £130,000. **Austin, T**, Hebden J. (ii): **UCL (PhD Studentship).**

New approach to preventative treatment of the blinding disease Retinopathy of prematurity (ROP) **PREVENT-ROP.** 2013-2018. **FP7 HEALTH.2012.2.4.4-1**. Euros 425,928/£364,769 to Cambridge (total awarded Euros 2,696,648/£2,309,540). Coordinator Helstrom A, **Dunger D, Beardsall K**.

**NIHR Senior Investigator Award (Department of Health)** 2009-2013 £60,000. **Dunger D**.


Oral immunotherapy for severe food allergy ‘STOP’. 2010-2013. **National Institute for Health Research (NIHR) The Efficacy and Mechanism Evaluation (EME)**, £1,000,000. **Clark A**.

Overnight hypoglycaemia prevention in adult subjects with type 1 diabetes: Closing the loop. 2008-2012. **Diabetes UK.** £ 700,525 **Hovorka R** (PI), **Evans ML**, Amiel S, Heller S, **Dunger D**.


PneumaScan development grant. *East of England Development Agency (Addenbrooke’s and PneumaCare)* £650,000. Iles R.


PREVENT –ROP 2012 -2017 Collaborative Project in the FP7 Cooperation Programme

Pump priming award for investigating gut barrier dysfunction in critical illness £5,000. Pathan, N.


SIOP CNS GCT II *James Nicholson* (UK Chief Investigator & International Co-chair) –*CRUK* grant £147,000 (University of Birmingham) - in set up

Study of T cells in Allergy and Resolution ‘STAR’. 2006-2011. *Food Standards Agency* £400,000. Clark, A.


The investigation of gene expression in GCTs, a national CCLG biological study. Medical Research Council, £230,961. Clinical Research Training Fellowship Murray M.

The investigation of LIN28/let-7 effects in malignant germ cell tumours. 2012-2013. Addenbrooke’s Charitable Trust Project, £56,517. Murray M.


The role of L-arginine in the survival of lymphoid cells as a potential target for therapeutic intervention. DATE. Leukaemia and Lymphoma Research Fund, £199 582. Metayer L.

Through the physicians eyes – non invasive home monitoring for COPD. Small Business Research Initiative (Addenbrooke’s and PneumaCare) £90,000. Iles R.

To undertake prospective multisource surveillance for all cases of progressive intellectual and neurological deterioration (PIND) occurring in children in the UK. 1997-2013. Department of Health £1,838,049. Verity C, Winstone AM, Stellitano L.


Using prebiotics to treat gut barrier dysfunction in severe malnutrition £35,000 Pathan, N
6. PUBLICATIONS


Austin T, Mitra S, Optical imaging of the neonatal brain European Paediatrics 2011;5:13-18

Austin T, O'Reilly H. Advances in imaging the neonatal brain Expert Opinion in Medical Diagnostics 2011; Feb 4

Austin T, Shanmugalingam S., Clarke P.. To cool or not to cool? Hypothermia treatment outside trial criteria. Archives of Diseases in Childhood. 2012;doi:10.1136/archdischild-2012-302069.


Branchio-Oto-Renal syndrome with obstructive sleep apnoea. Chavan A, Shastri A, Ross Russell RI. BMJ Case Reports; doi:10.1136/bcr.03.2009.1719 2012


Chitre M. Pitfalls in the diagnosis and misdiagnosis of epilepsy. Padiatrics and Child Health.2013 Jun;23(6)237-242


Maw, A; Gracey F; Holland AJ; Bateman, A. How should services for children with acquired brain injury be structured in order reduce morbidity, promote social participation and bring an enduring improvement in outcomes? An initial assessment of need. NIHR Collaborations for Leadership in Applied Health Research and Care (CLAHRC), Cambridgeshire. Fellowship research project 2011-2012


O’Donnell DR. A scoring model including procalcitonin, C-reactive protein, and urinalysis is superior to individual variables in detecting serious bacterial infection in children under three years old. J Pediatr. 2011 May; 158(5):862-3.


Ong KK, Kuh D, Pierce M, Franklyn JA. Childhood Weight Gain and Thyroid Autoimmunity at Age 60-64 Years: The 1946 British Birth Cohort Study. Journal Of Clinical Endocrinology & Metabolism 98(4):1435-1442 Apr 2013


Sarac I, Backhouse K, Shojaei-Moradie F, Stolinski M, Robertson MD, Bell JD, Thomas EL, Hovorka R, Wright J, Umpleby AM. Gender differences in VLDL1 and VLDL2 triglyceride kinetics and fatty acid kinetics in obese postmenopausal women


Shojaeef-Moradie F, Ma Y, Lou S, Hovorka R, Umpleby AM. Prandial Hypertriglyceridemia in Metabolic Syndrome is due to an Overproduction of both Chylomicron and VLDL Triacylglycerol.. Diabetes 29 Aug 2013


Thankamony A, Ong KK, Ahmed ML, Ness AR, Holly JM, Dunger DB. Higher levels of IGF-1 and Adrenal Androgens at Age 8 Years are Associated with Earlier Age at Menarche in Girls. J Clin Endocrinol Metab. 2012. 97(5):E786-90.


Vance GHS; Roberts GC; Goldring S; Cox H; Warner JO; Hughes S; Clark A; Luyt D; Gillies D; Proudfoot C; North J; Gardner J; Sihra B; Fox AT. A national audit of paediatric pollen immunotherapy practice in the UK: patient selection and programme safety. Clin Exp Allergy2011 ;41: 1313-23.


Verity C, Winstone AM, Stellitano L, Krishnakumar D, Will R, McFarland R. The clinical presentation of mitochondrial diseases in children with progressive intellectual and


Wilinska ME, Hovorka R. Closed-Loop In Icu: Preclinical In Silico Studies To Assess System Level Hazards. Diabetes Technology & Therapeutics 15:A83-A83 Feb 2013

Williams DM Neonatal malignancy Chapter in: Textbook of Neonatology 2012
Editors: Rennie and Robertson


### 7. LIST OF RESEARCH STAFF

#### University of Cambridge Department of Paediatrics Academic Staff

<table>
<thead>
<tr>
<th>Name</th>
<th>Position and Department Details</th>
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<tbody>
<tr>
<td>Professor David Dunger</td>
<td>Acting Head of Department (2011- ); Professor of Paediatrics; NHS Honorary Consultant</td>
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<tr>
<td>Professor Ieuan Hughes</td>
<td>Professor of Paediatrics/Foundation Chair of Paediatrics; NHS Honorary Consultant</td>
</tr>
<tr>
<td>Dr Carlo Acerini</td>
<td>Senior University Lecturer; NHS Honorary Consultant</td>
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<tr>
<td>Dr Nazima Pathan</td>
<td>University Lecturer; NHS Honorary Consultant</td>
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<tr>
<td>Dr Kathryn Beardsall</td>
<td>University Lecturer; NHS Honorary Consultant</td>
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<tr>
<td>Dr Matthias Zilbauer</td>
<td>University Lecturer</td>
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<tr>
<td>Dr Rachel Williams</td>
<td>Clinical Lecturer</td>
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<td>Dr Ruben Willemsen</td>
<td>Clinical Lecturer</td>
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<tr>
<td>Dr Ajay Thankamony</td>
<td>Clinical Lecturer</td>
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<tr>
<td>Dr Clive Petry</td>
<td>Senior Research Associate</td>
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<tr>
<td>Dr Roman Hovorka</td>
<td>Director of Research</td>
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#### Academic Associated/Affiliated Lecturers

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<tr>
<th>Name</th>
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<tbody>
<tr>
<td>Dr Alisdair Parker</td>
<td>Consultant Paediatric Neurologist</td>
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<tr>
<td>Dr Amos Burke</td>
<td>Consultant Paediatric Oncologist</td>
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<tr>
<td>Dr Andrew Clark</td>
<td>Consultant in Paediatric Allergy</td>
</tr>
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<td>Dr Robert Ross Russell</td>
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<td>Dr Richard Iles</td>
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<td>Dr Pat Set</td>
<td>Consultant Radiologist</td>
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<td>Dr Roddy O’Donnell</td>
<td>Consultant Paediatrician (Respiratory Medicine and Intensive Care)</td>
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<td>Dr Sarah Morley</td>
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<tr>
<td>Dr Wilf Kelsall</td>
<td>Consultant Neonatologist/Paediatric Cardiologist</td>
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<tr>
<td>Dr Peter Heinz</td>
<td>Consultant Paediatric Accident &amp; Emergency</td>
</tr>
<tr>
<td>Mr David Conlan</td>
<td>Paediatric Surgeon (not in Children’s Services)</td>
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<tr>
<td>Dr Rachel Williams</td>
<td>Consultant Paediatric Endocrinologist</td>
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<tr>
<td>Dr Ken Ong</td>
<td>MRC Group Leader &amp; Consultant Paediatric Endocrinologist</td>
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#### Research Support Staff

#### Research Nurses

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<tr>
<th>Specialty</th>
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<tr>
<td>Diabetes and Endocrinology</td>
<td>Suzanne Smith</td>
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<td>Jennifer Ashford</td>
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<td>Karen Forbes</td>
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<td>Samantha Gorman</td>
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<td>Neonatal Metabolism</td>
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<td>Jenna Ridout</td>
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<td>Neonatal Neuroscience</td>
<td>Andrea Edwards</td>
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<td>Claire O’Mara</td>
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<td>Jane Tunnacliffe</td>
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<td>Yvonne King</td>
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<td>Anne Marie Winstone</td>
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<td>CLRN Research Nurses</td>
<td>Claire Jonas, Jo Bytham, Jacqui Tahari</td>
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<td>Dr Jenny Conlan</td>
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<td>Karen Whitehead, Catherine Guy, Katrin Mooslehner-Allen, Komal Nayak, Rieko Tadakoro-Cuccaro, Max Wong, Vickie Estes</td>
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**CLRN Research Facilitator: Diabetes and Endocrinology**

Vicky Cambridge  CLRN Research Facilitator
### 8. APPENDICES

#### 8.1 APPENDIX 1

NIHR PORTFOLIO STUDIES

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<td>BAPS-CASS: Congenital Diaphragmatic Hernia v1</td>
<td>Dr Jenny Kurinczuk</td>
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<td>Biologics for Children with Rheumatic Diseases - The Extended Biologics Study</td>
<td>Dr Kimme Hyrich</td>
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<td>BSPAR ECS</td>
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<td>Cambridge Baby Growth Outcome Study</td>
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<td>CCRN 951 (LAL Deficiency)</td>
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<td>30/04/2013</td>
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<td>Closing the loop in adolescents during non-compliance behaviours</td>
<td>Dr Roman Hovorka</td>
<td>01/07/2011</td>
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<td>Closing the loop in young children with type 1 diabetes</td>
<td>Dr Roman Hovorka</td>
<td>01/09/2012</td>
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<td>Closing the loop in youth in type 1 diabetes in the home setting</td>
<td>Dr Roman Hovorka</td>
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<td>COG study</td>
<td>Prof Nazneen Rahman</td>
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<td>Combination rhGH + rhIGF-1 in childhood/adolescent Crohn’s</td>
<td>Prof Faisal Ahmed</td>
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<td>DETEMIR GLARGINE</td>
<td>Prof David Dunger</td>
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<td>DRN 068 Adolescent Type 1 Diabetes Intervention Trial (AdDIT)</td>
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<td>DRN 309 The Cambridge Baby Growth Study</td>
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<td>DRN 438 (TrialNet Oral Insulin Study)</td>
<td>Prof Polly Bingley</td>
<td>02/05/2011</td>
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<td>DRN 450 (DGAP - Unaffected Siblings: Phase 2)</td>
<td>Prof David Dunger</td>
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<td>DRN 494 (Antithyroid drug treatment in paediatric Graves' disease)</td>
<td>Dr Tim Cheetham</td>
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<td>DRN 552 (Incident and high risk type 1 diabetes cohort – ADDRESS-2)</td>
<td>Prof D. Johnston</td>
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<td>DRN085 Nephropathy Family Study (NFS)</td>
<td>Prof David Dunger</td>
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<td>DRN100 (TrialNet)</td>
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<td>DRN486</td>
<td>Dr Suki Balendra</td>
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<td>EUCLIDS</td>
<td>Prof Michael Levin</td>
<td>01/03/2013</td>
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<td>Genetics of Human Epilepsy</td>
<td>Prof Deb Pal</td>
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<td>Genetics of Obesity</td>
<td>Prof I S Farooqi</td>
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<td>Home testing of 24/7 closed-loop in young people with type 1 diabetes</td>
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<td>Prof P. Brocklehurst</td>
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<td>ICISS</td>
<td>Dr Finbar O'Callaghan</td>
<td>03/03/2009</td>
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<td>JUMP Joining together to Understand diabetes mellitus type 2 Progression in children.</td>
<td>Prof Tim Barrett</td>
<td>29/06/2009</td>
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<td>'MARBLE'</td>
<td>Dr Sudhin Thayyil</td>
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<td>Prof Peter Clayton</td>
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<td>Dr Raina Liesner</td>
<td>10/08/2012</td>
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<td>MCRN180 (AHEAD)</td>
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<td>Measuring clinical severity in infants with bronchiolitis (1)</td>
<td>Dr Paul McNamara</td>
<td>30/11/2011</td>
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<td>Metformin in Tuberous Sclerosis Complex (MTS)</td>
<td>Dr finbar O’Callaghan</td>
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<td>NESGAS</td>
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<td>PCV13 in ALL</td>
<td>Dr Juliet Gray</td>
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<td>Platelets for Neonatal Transfusion Study</td>
<td>Dr Simon Stanworth</td>
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<td>Predicting serious drug side effects in gastroenterology</td>
<td>Dr Tariq Ahmad</td>
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<td>Prednisolone in Nephrotic Syndrome: The PREDNOS Study</td>
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<td>Structural Brain Abnormalities and Learning Disability</td>
<td>Dr Usha Kini</td>
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<td>Study of haematology in newborns with Down syndrome</td>
<td>Prof Irene Roberts</td>
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<td>Study of Tolerance to Oral Peanut</td>
<td>Dr Andrew Clark</td>
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<td>Surveillance to identify any children in the UK with variant CJD</td>
<td>Dr Christopher Verity</td>
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<td>The Cleft Collective Cohort Studies</td>
<td>Prof Jonathan Sandy</td>
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<td>The Impact of Delayed Puberty on Adolescent Brain Development</td>
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<td>Wheeze and Intermittent Treatment: WAIT</td>
<td>Prof Jonathan Grigg</td>
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8.2 APPENDIX 2

CLINICAL PRACTICE TRAINING SIGNPOSTS

Trial Training for Clinical Trials Staff

- Trial-specific training guidance document specifically for trial teams CCTU GD010 PDF
- Trial-specific training record specifically for trial teams, CCTU FRM051 PDF
- Good Clinical Practice (GCP) training procedure for clinical trial staff, for all staff working on CTIMPs at the trust, R&D SOP006 PDF
- Staff Training Records, the guidance is specifically for CCTU staff but can be used as an example of what MHRA would like to see, CCTU SOP017 PDF
- Staff training records should include as a minimum:
  - CV
  - evidence of continuing professional development
  - evidence of GCP training
  - evidence of specific training for role
  - job description

In addition it is also good practice to have:
- Record of training on relevant standard operating procedures (SOP)
- Any other relevant training, e.g. attendance at meetings

To find these documents:
Cambridge University Hospitals SOPs

Cambridge University Hospitals Document Library

If you can’t find what you are looking for then contact Anna Diaz at Paediatrics on as336@medschl.cam.ac.uk for copies of SOP’s, guidance documents and forms or if this is not possible Carolyn Sexton CCTU Manager on Carolyn.sexton@addenbrookes.nhs.uk

Sample Handling Training and Guidance documents from Addenbrooke’s Clinical Research Centre (ACRC)

- ACRC Sample Handling Room Hand Book, ACRC INF014
- ACRC/FRM086 Use of Gilson Pipettes Training and Competency
- ACRC/FRM097 Use of Centrifuges Training and Competency
- ACRC/FRM098 Safe Use of Dry Ice Teaching and Competency
- Recording ACRC Staff Training Records ACRC/SOP0078
- Using the NRES CV Template, ACRC/TPL005
If you would like copies of any of these documents please contact Carolyn Sexton, Addenbrooke’s Clinical Research Centre QA Manager on:

Carolyn.sexton@addenbrookes.nhs.uk

**External Training, useful links and email alerts**

- Valid Informed Consent training is advertised on the Comprehensive Clinical Research Network website [http://www.crncc.nihr.ac.uk/about_us/ccrn](http://www.crncc.nihr.ac.uk/about_us/ccrn) and through the Network 15 emails and Connect.

- Local Trust links: Network 15 trust circulation email for research staff on site, Network, R&D, CRF

- National Institute for Health research training and development site page and NIHR portal to the network and CRFs sites

- [http://www.crncc.nihr.ac.uk/workforce_development/workforce_development](http://www.crncc.nihr.ac.uk/workforce_development/workforce_development)

- Research Nurse Competency Framework for Clinical Research Nurses
  

- Non clinical staff competency framework

## TRAINING MATRIX

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<td>All staff working clinically with children</td>
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<td>Annual</td>
<td>Nurses working in a clinical role</td>
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### Training resources

- GCP and IRAS  
  [http://www.crncc.nihr.ac.uk/about_us/ccrn/west_anglia/news/training](http://www.crncc.nihr.ac.uk/about_us/ccrn/west_anglia/news/training)
- Informed consent  
- Various Addenbrooke’s Clinical Research Centre – contact  
  [caroline.saunders@addenbrookes.nhs.uk](mailto:caroline.saunders@addenbrookes.nhs.uk)
- Various Cambridge Clinical Trials Unit – contact  
  [Carolyn.sexton@addenbrookes.nhs.uk](mailto:Carolyn.sexton@addenbrookes.nhs.uk)