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1. INTRODUCTION

David H Rowitch
Professor and Head of the Department of Paediatrics
University of Cambridge

It gives me great pleasure to introduce the Annual Report of the Division E Paediatric Research Governance and Strategy Working Group. In 2011 this small paediatric research group was established to document research activity across the Cambridge University Hospitals NHS Foundation Trust (known as CUH). Our group which reports to the CUH Research Board distributed reports documenting paediatric research activity in 2011 and 2012-2013. This annual report covers the time period 2014-2015 and presents the contributions, achievements and highlights of the remarkable people making up this group.

Paediatric illness has a collective impact on children, their families and society at large. Cutting-edge challenges are to identify individuals at risk and provide new therapies that can treat acute disease as well as adverse developmental effects that can have life-long consequences. The prevalence of rare/genetic disorders in Paediatrics argues for routine application of precision medicine to better understand the pathobiological sequence and tailor therapies to the individual patient. It is logical that such bespoke counselling should be provided at the beginning of the life course to have maximal impact as a preventive approach aimed to assuage or delay later onset of disease including chronic disease of adulthood (Figure 1). For example, early diagnosis of susceptibility to Type-1 Diabetes might prevent initial presentation with diabetic coma. Paediatrics has existing productive interactions within metabolic and cancer themes; we can expand these and develop new links with the Neuroscience and Women’s Health themes with a focus on neonatal brain disorders.

Figure: Developing new models of precision and preventative medicine. We gain insight into Paediatric disease through research to understand the precise impact of genes and the environment and injury on human development. By applying precision medicine approaches in Paediatrics we can maximize the impact of genomic information tailored to the individual. This model will determine how precision medicine can function to prevent or assuage onset of diseases of adulthood with implications for healthcare resource allocation over the life course.
**Vision for Clinical and Research Growth for the Next Quinquennium.** Paediatrics already has a strong clinical profile and outreach to the East of England. The recent Care Quality Commission (CQC) review of Children’s Services within the Addenbrooke’s Trust does credit to the outstanding contributions of clinicians. Demand for services greatly outweighs capacity and a new Children’s Hospital will be needed to address this gap, providing NHS and philanthropic funding can be secured.

The Department of Paediatrics will play roles in this process by providing a vision for research that will help maximize the potential of a new hospital, including innovative experimental medicine and clinical investigation, and new treatment options to children of the region. We have identified several areas for growth and development of Paediatric-relevant research that will embody this principle as part of a proposed virtual Children’s Health Research Institute. The mechanism of a virtual institute is to promote new research programmes through collaboration and integration with other units at Addenbrooke’s site, the Sanger Institute and other Cambridge University Departments (e.g. on Tennis Court Road) and Schools.

The publication of this report also highlights the next challenge which involves increasing engagement with Paediatrics across the campus and in particular interactions with the strong National Institute for Health Research Biomedical Research Centre (NIHR BRC) themes which underpin translational research development collaborations. We are preparing an application in the 2017 BRC renewal to establish a Women’s Health and Paediatric Research Theme, which will increase collaborative research involving paediatrics in the areas of neuroscience, oncology and diabetes and will also support new emerging areas such as inflammation. This will enhance our capabilities for early stage clinical research and experimental medicine. This new BRC theme will also enable greater academic interactions with colleagues from obstetrics and will in effect comprise a Division E research support scheme. The current 2014-2015 report provides the documentation to support this application.

The Department can serve to highlight research achievements relevant to Paediatrics at Addenbrooke’s campus in the form of a new website, away days and small seminars for trainees and students. These new meetings will augment Department-wide events put on the School of Paediatrics, the director of medical student teaching and symposia organized for regional professional development.

It has been an interesting few months since I have joined the faculty and I hope to meet with clinical and research staff to better understand common goals and what might be achieved at Cambridge in Paediatrics and in the East of England for children’s services.

Best wishes,

David H Rowitch, MD, PhD
2. DIVISION E PAEDIATRIC RESEARCH GOVERNANCE & STRATEGY GROUP

Remit:

The Division E Paediatric Research Governance & Strategy Group reports to the Cambridge University Hospitals (CUH) Research Board. Its responsibilities are to:

1. Co-ordinate paediatric research strategy, particularly with respect to clinical trials and observational studies.
   - Maximising potential for clinical research
   - Encouraging emerging themes
   - Regional network
   - Paediatric Bioresource

2. Oversee research governance issues in Paediatrics
   - Staff training
   - Research facilities
   - Study design and protocols

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

4. Develop a BRC Research Theme in Paediatrics
### Members:

<table>
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<tr>
<th>Name</th>
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<tr>
<td>David Dunger</td>
<td>Acad. Dept. Paediatrics</td>
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<td>Carlo Acerini</td>
<td>Acad. Dept. Paediatrics / CRN-Eastern</td>
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<td>Gordon Smith</td>
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<td>John Bradley</td>
<td>BRC and R&amp;D</td>
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<td>Robert Heuschkel</td>
<td>Director of Division E</td>
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<tr>
<td>Ian Wilkinson</td>
<td>Cambridge Clinical Trials Unit</td>
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<td>Sabine Klager</td>
<td>Cambridge Clinical Trials Unit</td>
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<td>Lucy Raymond</td>
<td>Clinical Genetics</td>
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<td>Amanda Cahn</td>
<td>Women's and Children's Services, the Rosie Hospital</td>
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<td>Stephen O'Rahilly</td>
<td>Metabolic Research</td>
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<td>Sandra Mulrennan</td>
<td>CRN-Eastern</td>
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<td>Denise Williams</td>
<td>Paediatric Oncology</td>
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<td>Peter Heinz</td>
<td>General Paediatrics</td>
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<td>Sadaf Farooqi</td>
<td>Institute of Metabolic Science</td>
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<td>Jag Ahluwalia</td>
<td>Medical Director</td>
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<td>Ken Ong</td>
<td>MRC Epidemiology</td>
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<td>Kathy Beardsall</td>
<td>Neonatology</td>
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<td>Topun Austin</td>
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<td>Rob Ross Russell</td>
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<td>Manali Chitre</td>
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<td>Matthias Zibauer</td>
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<td>Adil Aslam</td>
<td>Paediatric Surgery</td>
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<td>Nazima Pathan</td>
<td>Paediatric Intensive Care</td>
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<td>Caroline Saunders</td>
<td>Addenbrooke's Clinical Research Centre</td>
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<td>David Lomas</td>
<td>Radiology</td>
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<tr>
<td>Marijcke Veltman</td>
<td>NIHR Cambridge Biomedical Research Centre</td>
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<tr>
<td>Fiona Maxton</td>
<td>NIHR CRN-Eastern</td>
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</tbody>
</table>
Clinical Area Leads:

Medical Paediatrics  Rob Ross Russell
Paediatric Critical Care  Susan Broster
Paediatric Surgery  Stephen Farrell (deputy Adil Aslam)

Service Delivery Unit Leads:

Medical Paediatrics  (Rob Ross Russell)
Diabetes/Endocrinology  Carlo Acerini
Allergy  Andrew Clark
Respiratory  Donna McShane
Gastroenterology  Rob Heuschkel
Neurology  Manali Chitre
Haematology/Oncology  Boo Messahel
Rheumatology  Kate Armon
Cardiology  Wilf Kelsall

Paediatric Critical Care  (Susan Broster)
Neonatal Operational Delivery Network (ODN)  Sarah Rattigan
Paediatric Intensive Care Unit (PICU)  Sarah Morley
Acute Neonatal Transfer Unit (ANTS)  Sue Broster
Neonatal intensive Care Unit (NICU)  Angela D'Amore

Paediatric Surgery  (Stephen Farrell)

ENT  DIVISION D (not managed from Paediatrics)
Orthopaedics  Andreas Rehm – Kuldeep Stohr
Cleft  Hannah Rhead
Ophthalmology  Louise Allen
Paediatric Surgery  Stephen Farrell
3. SPECIAL FEATURES

In our special features section, we highlight two examples of Paediatric research themes that are building on existing achievements to establish future research resources.

3.1. The Cambridge Baby Growth Studies

The original Cambridge Baby Growth Study (CBGS) was a prospective, observational pregnancy and birth cohort, with initial infancy, and current continued childhood follow-up. The main aim was to investigate the antenatal and postnatal determinants of infancy growth, in addition to reproductive development, including the effect of environmental, genetic, hormonal and nutritional exposures. Across pregnancy and with multiple infancy visits until two years of age, we have collected extensive anthropometric, nutritional, demographic and biological data, including breast milk and blood or dried blood spot samples (Figures 1-5). This has therefore allowed detailed focus on the first 1000 days of life, at a time of emerging importance of the early origins of health and disease, such as obesity and type 2 diabetes.

On-going work includes the study of genetic factors, epigenetic changes and maternal endocrine disruptor exposure on infant growth and body composition. We have also been investigating infancy blood spot hormones, metabolites and the lipidome, and their associations with infant growth and nutrition. The Department of Paediatrics (Professor David Dunger, Dr Carlo Acerini, Dr Clive Petry, Dr Philippa Prentice) and Dr Ken Ong (MRC Epidemiology Unit) collaborate with other university research groups, including those led by Dr Miguel Constancia, Dr Sue Ozanne (Institute of Metabolic Science), Professor Nabeel Affara (Department of Pathology), Professor Eric Miska (Gurdon Institute) and the NIHR Core Biochemical Assay Laboratory. Lipidomic work with Dr Albert Koulman (MRC Human Nutrition Research Centre, Cambridge) has led to a recent BBSRC grant with the aim to further investigate metabolic efficacy of infancy nutrition.

Extension of the infancy cohort – the Cambridge Baby Growth Study II

Over the past three years we have been enriching the original infancy cohort with infants expected to be at high risk of adverse growth trajectories: small-for-gestational age infants and infants of mothers with diabetes. We are also currently finalising recruitment of further control infants. In addition to the detailed infancy data already collected, this will have increased focus on the very early infancy period (the first 3 months), which may be a critical time for later health and disease programming, and establishment of the gut microbiome, which may be related to differing infancy nutrition and growth patterns. This work is supported through an industry partner collaboration with Mead Johnson Nutrition.

By investigating the complex relationships between early nutrition, hormonal and physiological pathways and body composition changes, we aim to identify those infants at greatest risk, informing future interventional studies at this modifiable time of life, and impacting on long-term disease risk.
Figure 1: A CBGS participant undergoing an abdominal ultrasound test to measure subcutaneous and intra abdominal fat deposits to provide information on body composition changes after birth.

Figure 2: Head circumference measured for anthropometrical data in the CBGS.

Cambridge Baby Growth Outcome Study

Since late 2013 we have been conducting a follow-up assessment of the original CBGS birth cohort, now that they are 5-10 years old. Previous work has linked infancy growth trajectories to the timing of puberty, which in turn is robustly associated with long-term metabolic disease risks. CBGS allows a unique opportunity to link the wealth of early infancy exposures, including diet and nutritional biomarkers, to subsequent childhood outcomes, including detailed body composition and metabolism, assessed by oral glucose tolerance testing. We aim to continue to follow these children through puberty, to better characterise these outcomes, as well as the timing and magnitude of peripubertal sex hormone exposures.
Figure 3: A CBGS participant having sub-cutaneous fat assessed by using Holstein callipers to measure skinfolds of the thigh, arm, shoulder and flank.

Figure 4: DEXA scan being used to measure body composition and mineral bone density in a CBGS participant.
Figure 5: DNA sampling of cheek cells of CBGS participants and their parents to identify common genetic variants that will help explain the wide differences seen in growth patterns in infancy.

Infancy cohort collaborations

We have longstanding collaborations in both South Africa (“Birth to Twenty” cohort, with Professor Shane Norris) and The Gambia (with Professor Andrew Prentice). This allows us to explore the relevance of the CBGS findings to different populations. In the transitional setting of Soweto, South Africa, pregnancy and early life exposures may underlie the very rapid increases seen in gestational and type 2 diabetes. We have extended our collaborative work in South Africa, with the new Soweto First 1000 Days cohort, and have received support from the Cambridge-Africa Alborada research fund to investigate breast milk and infancy lipidomic profiles. Funded by the BBSRC, we will also further explore infancy lipidomic profiles and the metabolic efficacy of infancy nutrition in the Cambridge, South African and Gambian infancy cohorts.
3.2. **Research in Paediatric Gastroenterology**

Over the past 5 years, the clinical activity within the Department of Paediatric Gastroenterology, Hepatology and Nutrition has expanded very rapidly. As the largest regional referral centre within the East of England, we now see around 3000 children in outpatients, manage about 250 children with inflammatory bowel disease (IBD), and perform an average of 600 endoscopic procedures each year.

An integral aspect of the departmental development has been the establishment of an active research program, pursuing key clinical questions through clinical studies and translational laboratory research.

Led by Dr Matt Zilbauer, appointed as University Lecturer and Honorary Consultant in September 2013, the research group currently consists of a full time lab manager (Research Assistant), one PhD student, one full time post-doctoral fellow (Bioinformatician, joint appointment with the European Bioinformatics Institute – EBI), two international MD students, one clinical research fellow and a full time research nurse. We have part-funded the complete refurbishment of an outdated laboratory on Level 7 with Adult Gastroenterology, which is now the base for our research team.

The overall theme of the research group is focused on investigating the role of epigenetic mechanisms in regulating gene expression and cellular function of the human intestinal epithelium during health and disease. We are particularly interested in the potential impact of epigenetic alterations, perhaps driven by environmental change, on the disease pathogenesis of paediatric inflammatory bowel diseases (IBD). In addition to investigating fundamental biological aspects of epigenetic regulation, we are also exploring the use of cell type specific epigenetic and gene expression profiles as disease prognostic biomarkers in paediatric IBD (see below).

**The human mini-gut: a novel ex-vivo model to study epithelial function in GI health and disease:**

*Main collaborators:*

Dr Bon-Kyoung Koo (MRC Stem-Cell Institute, Cambridge)

Dr Trevor Lawley (Wellcome Trust Sanger Institute, Cambridge)

Dr Ludovic Vallier (MRC Stem-Cell Institute, Cambridge)

*Funding:* The Evelyn Trust (one year project grant, awarded June 2015)

Recent advances in the field of stem-cell biology have opened up the possibility of generating intestinal epithelial organoid cultures from induced pluripotent stem cells or crypt stem cells derived from mucosal biopsy material. The possibility to generate such organoids from human tissue provides researchers with unprecedented opportunities to study intestinal health and disease in a human, ex-vivo model. In collaboration with Dr Koo we have been able to establish this methodology in our laboratory, allowing us to use this human model to study the impact of epigenetic mechanisms (such as DNA methylation) in regulating cellular function in health and disease.
We have been generating human intestinal organoids (frequently referred to as “mini-guts”) from various gut segments obtained from children newly diagnosed with IBD and matched controls (Figure 6). We are currently in the process of validating this model and establishing how closely intestinal organoids resemble in-vivo intestinal epithelium, and identifying differences in the innate immune function (e.g. barrier) between children with IBD and controls. Ultimately, we are hoping that the results of these experiments will generate novel insights into disease pathogenesis and as such can lead to novel treatment approaches. To this end we are participating in a large collaborative initiative between the Wellcome Trust Sanger Institute (main collaborator Dr Trevor Lawley), the European Bioinformatics Institute (EBI) and GlaxoSmithKline (GSK), which aims to find novel treatment approaches for several common conditions including IBD (Centre for Therapeutic Target Validation, CTTV; http://www.targetvalidation.org).

![Image](image_url)

**Figure 6**: Left panel: Intestinal epithelial organoid cultures derived from mucosal samples obtained from 3 gut segments: Ascending Colon, Sigmoid Colon, Terminal Ileum. Images were taken at Day 1 and Day 6 post seeding of isolated intestinal crypts into matrigel. Right panel: Immunofluorescent staining of human intestinal organoid – blue: nuclear stain (Dapi), red: actin stain (Phalloidin)

**Development of disease prognostic biomarkers in paediatric IBD:**

**Main collaborators:**

Dr Paul Lyons, Prof Ken Smith and Dr Eoin McKinney (Cambridge Institute of Medical Research, CIMR)

Dr Oliver Stegle (European Bioinformatics Institute, EMBL-EBI)

The clinical disease course of children with IBD varies substantially. This can range from mild disease, which responds well to standard induction treatment and rarely requires additional escalation, to severe, treatment resistant disease. The latter presents with persistent, severe inflammation that despite the use of potent immunosuppressive therapy (e.g. biologics such as Infliximab), often requires surgical intervention. To date, despite extensive epidemiological and clinical studies, we are still unable to predict disease outcome early in the disease, and hence provide effective, personalised treatment to all patients.
As a major focus of our research activities, we are aiming to develop disease prognostic biomarkers, which will allow us to classify children with newly diagnosed with IBD according to outcome and adjust their treatment accordingly (i.e. individualised treatment protocols).

In collaboration with a research group based at the Cambridge Institute of Medical Research (Prof Ken Smith and Dr Paul Lyons), we are testing the use of CD8+ T-cells as disease prognostic biomarkers in children with IBD. A prognostic expression signature has already been shown to predict disease severity/outcome in adults suffering from lupus, vasculitis and IBD. Preliminary analyses in our patient cohort are promising and indicate the presence of a paediatric-specific expression signature, which seems to correlate with some of the outcome parameters (e.g. requirement for escalation to biologics – Figure 7).

In addition to using CD8+ gene expression profiles, we are also testing genome wide DNA methylation signatures in purified intestinal epithelium. These are obtained from children with newly diagnosed IBD to identify other potential biomarkers as well as possible predictors of response to treatment. We are fortunate to collaborate with Dr Oliver Stegle at the EBI, whose group are leaders in the field of bioinformatics, working on complex “omics” datasets in a translational clinical setting. Following a successful application to the recently introduced EBPOD-fellowship programme (collaboration between PIs at the EBI and Biomedical Research Campus (BRC)), we now have a full time bioinformatician (Dr Kate Howell) working on this project.

Figure 7: Preliminary data indicating the potential use of CD8+ T-cell gene expression profiles as disease prognostic biomarkers in paediatric IBD. A) Consensus clustering of CD8+ T-cell gene expression profiles obtained from children newly diagnosed with IBD highlighting clustering of patient subgroups. B) Kaplan Maier survival curve testing differences between the two main subgroups identified with regards to their requirement for treatment with biologics (i.e. anti-TNF-alpha antibody / Infliximab).
4. SUMMARY OF RESEARCH ACTIVITY

4.1. Paediatric Diabetes and Endocrinology

The paediatric diabetes/endocrinology unit has a longstanding track record of participation in laboratory and clinical research.

The research is primarily supported by clinical academic appointees (University of Cambridge and MRC) who hold honorary contracts with Cambridge University Hospitals NHS Trust.

The research output of the unit is internationally acclaimed and has supported a number of trainees and research fellows in completing higher degrees at MD or PhD level.

Recent and current topics of research are in the following areas:

- **Type 1 diabetes**
- **Glucose homeostasis and metabolism**
- **Postnatal growth and pubertal development**
- **Sex determination and reproductive tract development**
- **Endocrine disruption**

The major research themes in these topic areas include:

1. *The genetics and pathophysiology of Type 1 diabetes, its complications and treatment strategies during childhood and adolescence.*

Professor David Dunger’s group has been following the progress of over 12,500 young people with Type 1 diabetes (T1D) and their parents. This work has contributed to the discovery of many genes that predispose to T1D, as well as exploring the genetic and biochemical factors which predispose to diabetic complications in these young people. Ongoing studies include examination of the role of the growth hormone / insulin-like growth factor 1 axis in the development of insulin resistance and microalbuminuria, and the place of growth hormone inhibitors in preventing diabetic complications. The study of preventative treatment strategies includes work with Professor John Todd’s group in Cambridge where extensive genetic/phenotypic analysis has led to the development of early immune therapy interventions to prevent T1D. Since autumn 2015, Professor Dunger, together with Professor Chantal Mathieu (University of Leuven), are coordinating a large, EU (IMI funded) academia - industry collaboration establishing a comprehensive, interdisciplinary network of clinic and basic scientists tasked with recruiting, phenotyping and enrolling newly diagnosed patients with T1D into early intervention trials (*INNODIA project*).

In the area of diabetic complications, Professor Dunger and his team have also launched the first multi-national randomized controlled trial of ACE inhibitors and statins in adolescents with T1D (*AdDIT trial*), which will report its trial findings in 2016.
Professor Dunger and Dr Carlo Acerini (above left) are also involved in the clinical testing of closed loop insulin delivery (Artificial Pancreas Trials) in T1D using algorithms developed by Dr Roman Hovorka (above right) (Dept of Paediatrics/ Institute of Metabolic Science) which could reduce the risk of hypoglycaemia in patients undergoing intensive insulin therapy and thus improve long term outcomes.

2. The genetic and environmental determinants of size at birth, post-natal growth and risks for future adult cardio-metabolic disease.

Professor Dunger and Dr Ken Ong (left) (MRC Epidemiology) have long been involved in research into genetic/environmental determinants of birthweight and early postnatal weight gain which are both linked to lifetime risk for Type 2 diabetes. Studies are based around birth cohorts such as ALSPAC (University of Bristol) and the Cambridge Baby Growth Study, and are enhanced by studies of imprinted genes in the mother and fetus on maternal glucose metabolism during pregnancy and outcomes in the newborn.

The Cambridge Baby Growth Study (CBGS), (established 2001) is a unique cohort consisting of over 2000 infant / families recruited during pregnancy, with detailed postnatal/childhood follow-up. This study, under the direction of Dr Carlo Acerini, has provided a unique platform for studying the prenatal determinants of infant development and growth. This includes studying the effects of prenatal maternal glucose metabolism, exposures of growth restraint, as well as the influence of postnatal feeding practice on long term metabolic and neurodevelopmental outcomes. The remit of the CBGS study has been expanded with the recruitment of a new cohort focusing on infants born to mothers with diabetes during pregnancy and infants born small for gestational age (CBGS-II project). In addition, original CBGS participants, many of whom are approaching their 2nd decade of life, are being followed up in a study aimed at identifying the associations between early life biomarkers (including hormones, metabolites, lipids, and breast milk composition) and longer-term metabolic risk factors in mid-childhood (age 5 to 10 yrs) (CBGS-Outcome Study).

3. The effects of early infant feeding, changes in blood glucose and insulin levels and their impact on growth in the pre-term infant.

Data from large multi-national trials run from Cambridge, such as the NIRTURE study which explored early insulin therapy in preterm infants, have highlighted the need for new methods of controlling blood glucose levels in the newborn. Professor Dunger and Dr Katharine Beardsall (University Lecturer in Neonatology), are evaluating continuous glucose measurements and closed loop insulin delivery in vulnerable preterm infants as well as the assessment of novel therapies such as rhIGF-I (recombinant, human, Insulin-like Growth Factor-1) and long term outcomes of these neonatal interventions.
4. **Hormonal - gene - environment interactions and their impact on reproductive tract development, brain development and behaviour.**

The *Cambridge - Disorders of Sex Development (DSD) Database*, (established by Professor Ieuan Hughes [retired]), is a resource containing the detailed phenotypic and molecular genetic data on over 400 patients presenting with DSD. Dr Carlo Acerini supports studies establishing phenotype - genotype relationships in conditions such as the Androgen Insensitivity Syndrome (AIS) and other causes of DSD. The Cambridge DSD database contributes information to the international iDSD and iCAH database initiative. Dr Carlo Acerini, in collaboration with Professor Melissa Hines and Dr Vickie Pasterski (Department of Psychology), is evaluating the role of prenatal /postnatal hormonal environment on brain development and behaviour using AIS and congenital adrenal hyperplasia as contrasting models of androgen exposure.

These studies complement the work in the Cambridge Baby Growth Study on early gene - environmental interactions and their impact on male / female reproductive tract development, post-natal growth and metabolism. This includes epidemiological and laboratory studies (Dr Carlo Acerini) looking at metabolic and the epigenetic effects of prenatal exposure to putative *endocrine disrupting chemical* agents found in the environment (e.g. phthalates and phenols).
4.2. Paediatric Gastroenterology

Over the last 2 years, our department has made good progress towards the establishment of an active research program, pursuing key clinical questions through clinical studies and translational laboratory research.

Led by Dr Matt Zilbauer, who was appointed as University Lecturer and Honorary Consultant in September 2013, the research group currently consists of a full time lab manager (Research Assistant), one PhD student, one full time post-doctoral fellow (Bioinformatician, joint appointment with European Bioinformatics Institute – EBI), two international MD students, one clinical research fellow and a full time research nurse. We have part-funded the complete refurbishment of an outdated laboratory on Level 7 with Adult Gastroenterology, which is now the base for our research team.

One of the main research themes is focused on investigating the role of epigenetic mechanisms in regulating gene expression and cellular function of the human intestinal epithelium during health and disease. We are particularly interested in the potential impact of epigenetic alterations, perhaps driven by environmental change, on the disease pathogenesis of paediatric inflammatory bowel diseases (IBD).

The second major aspect of our research efforts is aimed at developing disease prognostic biomarkers in paediatric IBD using cell type specific epigenetic and gene expression profiles as. Key collaborators include Dr Oliver Stegle at the European Bioinformatic Institute (EBI) as well as Dr Paul Lyons and Prof Ken Smith at the Cambridge Institute of Medical Research (CIMR).

Lastly, an exciting recent development is based around a collaboration with Dr Bon-Kyoung Koo at the Cambridge Stem Cell institute, who is a world leader in the field of intestinal stem cell biology. In collaboration with his team we are in the process of establishing the human intestinal epithelial organoid culture model (frequently referred to as “human mini-gut”) in our lab. A recent grant awarded by The Evelyn Trust will allow us to set up this cutting edge methodology in our lab and enable us to use it in order to investigate the role of epigenetic mechanisms in IBD disease pathogenesis as well as explore their potential to test existing as well as novel therapeutic agents.

Current Studies:

Genomics and Epigenetics in Paediatric Gastrointestinal and Immune mediated Disease (GEPaedGI)

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.
Additional NIHR Portfolio approved studies:

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<td>Personalising Anti-TNF Therapy in Crohn’s Disease –</td>
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<td>Predicting Serious Drug Side Effects in Gastroenterology</td>
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<tr>
<td>Genetic, Environmental, Microbial Study</td>
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Other activities:

1. Establishment of an international working group on Epigenetics in Paediatric GI, Hepatology and Nutrition as part of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) under the lead of Cambridge (chair: Matt Zilbauer, Rob Heuschkel)

2. Joining an international healthcare network for children with IBD (ImproveCareNow) – funding obtained with patient recruitment to be commenced following introduction of the epic computer system

Key collaborators:

- Bon-Kyoung Koo (MRC, Wellcome Trust Stem Cell Institute, Cambridge)
- Oliver Stegle (EBI, Cambridge)
- Trevor Lawley (Sanger Institute, Cambridge)
- Ken Smith and Paul Lyons (CIMR, Cambridge)
- Arthur Kaser and Miles Parkes (Department of Medicine, Cambridge)
- Ludovic Vallier (Stem Cell Institute, Cambridge)
- Vardhaman Rakyan (Royal London, Blizzard Institute, London)
- Andreas Jenke and Jan Postberg (Witten Herdecke, Germany)
- Elke Cario (University of Bochum, Germany)
- Philip Rosenstiel (University of Kiel, Germany)
4.3. Neonatology

4.3.1. Neonatal Neuroscience

Dr Topun Austin runs a research group based in The Evelyn Perinatal Imaging Centre in the Rosie Maternity Hospital, which brings together scientists and clinicians across different specialties with a common interest in the developing brain.

The aims of this integrated clinical service and clinical research centre are to:

- Provide a high-quality clinical neurology service for high-risk mothers and newborn infants in the Rosie Hospital, Cambridge.
- Develop Cambridge University Hospitals NHS Foundation Trust as a regional centre for neonatal neurocritical care.
- Create a major programme of research into perinatal brain injury, imaging and repair.

There are currently three main research themes of the group:

1) Understanding cerebrovascular control in sick and preterm infants in the immediate days after birth.
2) Developing tools to relate the development of neural networks in newborn infants with patterns of behaviour.
3) Translating best research into clinical practice through the development of a neonatal neurocritical care network.

To date the centre has received over £3M of research grants and capital funding; the key achievements have been:

- Establishment of an award winning regional service for neonatal neuroprotection across the East of England.
- Development of a neonatal neurocritical care service at the Rosie Hospital, including a major equipment grant and funding of a specialist nurse secondment in neonatal neurocritical care.
- Opening of a unique functional brain imaging research facility in the heart of the Rosie Hospital.
- Installation of an MRI scanner within the imaging centre, providing state-of-the-art imaging facilities for mothers and babies.
- Formation of neoLAB, a collaboration with University College London, to develop new technologies to study the developing brain (www.neoLABresearch.com).
- Creation of collaborative networks within Cambridge (Clinical Neuroscience - Professor Marek Czosnyka, Dr Peter Smielewski; Psychology - Dr Vicky Leong; Psychiatry - Professor Simon Baron-Cohen, Professor John Suckling; Radiology - Professor David Lomas), the UK (Birkbeck, University of London - Professor Mark Johnson; University College London - Professor Jem Hebden, Professor Clare Elwell; University of Edinburgh – Dr James Boardman) and Europe (Copenhagen - Professor Gorm Greisen; Rotterdam - Dr Jeroen Dudnick).
The centre currently employs a clinical nurse specialist (Kelly Spike), clinical research nurse (Andrea Edwards), computer scientist research associate (Gordon Stevenson), and 3 medically-trained PhD students, (Drs Cristine Costa, Chuen Wai Lee and Maria Chalia). An MPhil Student (Peppar Cyr) and 2 research associates (Nathan Hayes and Liana Amunts) joined the group in September 2015. There are currently 6 ongoing studies and 4 due to start in 2015.

As well as developing clinical practice and research, the Cambridge Centre for Perinatal Neuroscience is also active in providing education and training in neonatal neurology, including:

- Development of an online educational resource on neonatal neurology and neuroprotection: ([www.bebop.nhs.uk](http://www.bebop.nhs.uk)).
- Running courses on neonatal cranial ultrasound as part of the Cambridge Perinatal Group ([www.cambridgeperinatalgroup.org](http://www.cambridgeperinatalgroup.org)).
- Participation in the BPNA neonatal neurology courses ([www.bpna.org.uk/neonate](http://www.bpna.org.uk/neonate)).

**Achievements in 2014/2015:**

- Installation of an MRI scanner in the Evelyn Perinatal Imaging Centre. Operated by clinical radiology, the scanner will provide a valuable service for neonates as well as being an important research resource in the coming years (Figure 8).
- Transfer of MONSTIR2 – a unique time-of-flight 3D optical tomography system – from University College London to the Evelyn Perinatal Imaging Centre (Figure 8).
- Obtaining a further £664k of grant income, bringing the total capital and research funding obtained since 2009 to £3.2M. Grants include an MRC clinical training fellowship (Dr Chuen Wai Lee), £700k award in collaboration with UCL and Birkbeck College, from the Bill and Melinda Gates foundation to study functional brain activation in the newborn, and 2 of the 4 Addenbrooke’s Charitable Trust – Biomedical Research Centre new nursing research scholarships (Andrea Edwards and Emily Johnson).
- Invitation to speak at national and international meetings, including presentation at the CUHFT annual members meeting and one of four researchers invited to showcase research at 10 Downing Street at an event organised by Action Medical Research.

**Public engagement in Science:**

- Public lecture on ‘Shining Light in the Newborn’ as part of the 2015 Cambridge Science Festival.
- Opening of the Evelyn Perinatal Imaging Centre to the public as part of the 2015 Cambridge Science Festival.
- The film ‘The Golden Window’, a collaboration with Anglia Ruskin University, shortlisted for the British Universities Film & Video Council Learning on Screen awards 2015.
- Presentation at the SET for Britain exhibition 2014 at the Houses of Parliament, (Dr Chuen Wai Lee).
- Presentation at 10 Downing Street, as one of four clinical scientists, on behalf of Action Medical Research.
Figure 8: Clockwise from top: optical images of changes in blood volume associated with neonatal seizures, infant being studied in the Evelyn Perinatal Imaging Centre, SAMBA study on NICU, MONSTIR II with research fellow Laura Dempsey, research group in EPIC, MRI scanner installed in EPIC.

Current Studies:

1) **Study of Autoregulatory Monitoring in BAbies (SAMBA)** Prospective cohort study investigating cardiac function and cerebral autoregulation in preterm infants (Figure 8). Funding: COT/CAPES (CC PhD), SPARKS (2013-2015)

2) **SAFEguarding the Brain Of Our Smallest Children (SafeBoosC)** European multicenter phase 2 RCT comparing cerebral oxygen targeted therapy vs conventional therapy in preterm infants in the first 48 hours of life. Funding: Danish Medical Research Council

3) **Optical-EEG** Prospective cohort study investigating neurovascular coupling in the newborn brain. Funding: Action Medical Research (2012-2014)/Evelyn Trust Fellowship (2014-2016)

4) **Fast Optical Tomography On Neonates (FOTON)** Prospective cohort study investigating functional activation, resting state cortical networks and neurovascular coupling in infants with acquired brain injury using fast optical tomography. Funding: Engineering and Physical Sciences Research Council (EPSRC)

5) **Behaviour and Resting state Activation In Newborns (BRAIN)** Prospective cohort study investigating newborn behaviour and development of resting state cortical networks in healthy infants and infants at risk of brain injury. Funding: Evelyn Trust Fellowship/Medical Research Council
6) Study Of auditory response and Newborn Development (SOUND) A pilot prospective cohort study investigating the acoustic environment on the NICU, whether it adversely impacts on newborn cerebral function and if an educational programme of noxious sound awareness on staff can improve the acoustic environment. Funding: ACT Nursing AHP Research Training Fellowship

Studies due to start recruiting in 2015 (funding and R&D/REC approval in place):

7) Brain Imaging in Global Health (BRIGHT) A prospective longitudinal study to establish standard curves of brain function for age and to use these to identify early biomarkers of disrupted neurocognitive development. Funding: Bill & Melinda Gates Foundation

8) Cambridge Human Imaging & Longitudinal Development study (CHILD) Prospective pilot cohort study investigating the different effects of prenatal and postnatal hormones on brain development and behaviour in typically developing children and siblings of children with a diagnosis of autism. Funding: Wellcome Trust

9) Neuro-genetic biomarkers of dyslexia (SPELL) Prospective pilot cohort study investigating neurooscillatory and genetic markers of dyslexia in the newborn infant. Funding: Rosetrees Trust

10) Social touch as means to modulate attention and facilitate learning infants (TOUCH) Prospective cohort study investigating social touch as a means to modulate attention and facilitate learning in the newborn infant. Funding: British Academy

4.3.2. Neonatal metabolism and glucose control

Dr Kathryn Beardsall leads a research group in neonatal metabolism. Since 2011 this has attracted over £1.5M of research funding. The themes of the research group are:

- Early regulators and management of glucose control in the newborn
- Impact of early growth on metabolic programming for later life

Active collaborations include those with the Cambridge Institute of Metabolic Science, University of Cambridge Department of Chemical Engineering as well as University of Warwick, University of Gottenberg and Karolinska Sweden, University Hospital Sant Joan de Deu Barcelona, VU University Amsterdam.

Current studies:

**REACT** We have recently completed the feasibility study for the REACT Trial which involved the use of real time CGMs in neonatal intensive care and are preparing to start recruitment to the REACT multicenter trial. This multicentre randomized controlled Trial of Real Time Continuous glucose monitoring in neonatal intensive care aims to assess the potential role of real time CGMs to optimize glucose control in preterm infants (Figure 9). It will recruit 200 babies over the next 2 years and is funded by NIHR EME.
**PREVENT-ROP** This is an international multicentre trial with the aim to develop a novel preventative intervention for the blinding disease retinopathy of prematurity (ROP) as well as the other complications of prematurity. This work is based on the concept that replacement of critical growth factors, normally provided in utero and reduced due to the disruption of the maternal/foetal interaction, to the infant being born prematurely will help prevent the complications of premature birth. The project is funded through FP7 consortium.

**CONCEPTT Neonatal Study: Continuous Glucose Monitoring in Women with Type 1 Diabetes in Pregnancy Trial** This study uses 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 I diabetes. It aims to provide detailed information regarding the early patterns of glucose control in a cohort of women with variable glucose control in pregnancy.

**POCKET Point of Care Ketone Measurement** This study aims to validate the accuracy of point of care measurement of ketones at the cot side in infants at risk from hypoglycaemia. Hypoglycaemia is common affecting 30% of newborn babies and management often leads to increasing medical interventions and babies and mothers being separated. Although hypoglycaemia may be physiological it can lead to neurological impairment and determining who is most at risk is challenging. Development of this technology would help to identify those at significant risk who require urgent intervention whilst avoiding medical interventions and separation of mothers and babies in others.

**NIRTURE Childhood Study: (Neonatal Insulin Therapy in Europe)** we are following up at 8-10 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 determine the impact of hyperglycemia and hypoglycemia on neurological and metabolic outcomes in childhood.
**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.

### 4.3.3. Neonatal Haematology

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 2014-2015 Probiotics** in Premature Infants (PIPS) – PI Kathryn Beardsall; Down Syndrome Haematology Study – PI V Venkatesh.

### 4.3.4. 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
4.4. Paediatric 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. We are involved in a wide range of research projects at local, national and international level and aim to actively collaborate with colleagues wherever possible. We are recruiting as site PI’s to a number of research projects, particularly in the area of neurogenetics, epilepsy, acquired brain injury and neurometabolic disorders.

We are also co-applicants on a number of national projects.

All our consultants are NHS clinicians. One consultant has 1 PA (based on a consultant’s full-time work commitment of 10 programmed activities (PAs) per week) of research time.

We are looking forward to the arrival of our first clinical research fellow later this year.

**Current Research Activity within the department**

**Individual Research Projects:**

**Dr Alasdair Parker**

- SPEED/GEL studies – exome sequencing in children’s neurological disorders
  - Co-applicant, PI: Dr Lucy Raymond.

- Gene therapy in GM2 Gangliosidosis - Co-applicant, PI: Prof Tim Cox

- NIHR study on everolimus in childhood tuberose sclerosis (TS) – AP, Principal investigator

- NIHR study on metformin in childhood tuberose sclerosis (TS) - AP, Principal investigator
  - Chief Investigator: Dr F O’Callaghan, Bristol

- International collaborative Infantile spasms study – collaborator

- Identification of the genetic and clinical abnormalities in PEHO syndrome, implications for the treatment of childhood epilepsies and sleep disorders - Co-supervisors: Dr M Chitre, Dr A Parker, Prof G Woods

**Dr Anna Maw**

- NIHR Programme Grant: The Futures Project - How should the NHS deliver rehabilitation services for children after acquired brain injury? Co-applicant and site PI. Lead Investigator – Dr Rob Forsyth, University of Newcastle

- ADAPT Approaches and Decisions for Acute Pediatric TBI. University of Pittsburgh, Pennsylvania, USA. Co-investigator

- NIHR Brain Injury Healthcare Technology Co-operative (HTC) – collaboration with recent successful application for funding for HTC for paediatric brain injury. Project lead: Dr Topun Austin

Cognitive Behaviour Therapy Skills in Children who have sustained an Acquired Brain Injury - Site PI – CUH, Project lead: Anna Adlam/Jessica Ingham UEA

Cognitive outcomes in children with mild TBI. - Principle Investigator and project lead. Research assistant: Francine Kieta

Nocturnal epilepsy and cognitive outcomes – joint project with MRC-CBU in development.

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 work stream 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)

Dr Gautam Ambegaonkar

NIHR study: FOR-DMD Study. Finding optimal regime of steroids in DMD. Site PI (CUH); CI : Dr Robert Griggs, Rochester USA

SANAD II - RCT comparison of Standard and New Antiepileptic Drugs (SANAD II). – Co applicant (Paediatrics CUH)

Application of Next Generation Sequencing technologies to patients affected by unexplained limb-girdle muscular weakness: the MYO-SEQ project. Site PI; CI – Prof Volker Straub, Newcastle upon Tyne, UK

Impact of hypermobility in children with Charcot Marie Tooth disease: an observational study. Chief Investigator. CUH (proposed; not yet accepted)

Dr Deepa Krishnakumar

ENCEPH UK study – UK intervention RCT – Development and evaluation of an intervention based around the national guidelines on the management of suspected encephalitis, and its evaluation through a cost effectiveness analysis - Site Principle Investigator
USCOM- UK multicentre study of children with opsoclonus myoclonus study- awaiting local R & D approval- Site PI

National Paediatric IVIG Survey – Currently awaiting registration with Audit department

Mitochondrial Disease patient cohort- national history study and patient registry – Awaiting local PI approval

SANAD II- co- investigator with Dr Chitre
4.5. **Paediatric 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, Dr Amos Burke (above left) Consultant Paediatric Oncologist, Addenbrooke’s Hospital, is developing collaborative research in the field of lymphoid malignancies with Prof Guy Brown (above middle) (University department of Biochemistry) and Dr Suzanne Turner (above right) (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.

Working with Dr Anthony Bench (Haematology and Oncology diagnostic Service), Amos Burke is investigating the detection of residual disease in childhood B-NHL. This is a biological study attached to the Inter-B-NHL Ritux 2010 clinical trial (Amos Burke UK Lead Investigator). With Dr Suzanne Turner the correlation of MDD/MRD in B-NHL with tumour propagating cells is also being investigated.

**Germ Cell Tumours (GCTs)**

Dr James Nicholson (above left), a consultant paediatric oncologist and Dr Matthew Murray (above middle), an academic consultant paediatric oncologist, 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) (above right).

Collaboration with US and UK colleagues in extracranial GCT data pooling (Matthew Murray and James Nicholson)

- refining risk group stratification; published in JCO in 2015
- The AGCT1531 international trial has received Children’s Oncology Group (COG) approval, incorporating young adults as well as children, participants from at least 2
continents, include biological as well as clinical questions (much of biological work to take place in Cambridge).

- The AGCT1531 trial, including biological endpoints and the establishment of a publicly accessible integrated clinico-pathological-molecular database, has been underpinned by a five year $2.3 million grant from St. Baldrick’s, on which Matthew Murray (co-Principal Investigator) led the UK effort. This grant includes funding for a post-doctoral scientist, technician and consumables.

Collaboration with international colleagues in identifying consensus in intracranial GCT management (Matthew Murray and James Nicholson)

- The results of the International Delphi consensus process were presented in Japan in 2015 at the Fourth International Symposium and will be published in Lancet Oncology later in 2015

CCLG 2002 BS 03 (collaboration with Prof Nick Coleman of Dept of Pathology, and Dr Matthew Murray). The lab team now comprises:

- Dr Emma Bell, a post-doctoral scientist, funded through a formal collaboration with Astra Zeneca (2014-2016 minimum), establishing serum microRNAs as a clinical test for GCTs

- Dr Shivani Bailey, a paediatric oncology trainee undertaking a PhD studying over-expressed microRNAs in GCTs. She has been awarded a three year Fellowship from Action Medical Research (2015-2018) following a one year Cambridge NIHR BRC Fellowship (2014-2015)

- Ms Marta Ferraresso, a PhD student investigating the replenishment of under-expressed microRNAs in GCTs, funded by a four year Department of Pathology Fellowship (2014-2018)

- Ms Katie Raby, laboratory technician, with particular remit for serum microRNA studies in solid tumours of childhood, funded by Children with Cancer UK, and a study of gene expression in GCTs from teenage and young adult (TYA) patients.

Outputs have included:

- completed and published work on CGH, mRNA and microRNA profiles
- comparison of genomic changes and gene expression in different histological subtypes
- diagnostic implications of measurement of serum miRNA
• incorporation into international trials
• early progress towards targeted therapy based on miRNA expression

Detection of genetic abnormalities in solid tumours of childhood, Principle Investigator for this study of serum microRNA, which started to recruit in 2010, with Matthew Murray as lead co-investigator. This has led to novel ‘blood-based fingerprints’ for common childhood tumours, in particular segregating high-risk from low-risk neuroblastoma cases.

Other solid tumours

Dr Boo Messahel, a consultant paediatric oncologist, 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 improved risk stratification for patients following definitive surgery for the primary disease.

Non Malignant Haematology

Dr Mike Gattens, consultant paediatric haematologist, is involved in the following studies:

BRIDGE - genetic analysis of inherited platelet disorders
ITP National Registry.

We are one of a small number of paediatric haemophilia centres in the UK which have recruited patients into international portfolio adopted commercial studies for the following:

PUPS B LONG study (998HB303) – PI Mike Gattens
KIDS A LONG study (8HA62PED) – PI Mike Gattens
GENA-05 (Human Cl rFVIII) PUPS study – PI Mike Gattens

Additionally, Dr Mike Gattens is the co-investigator for additional commercial studies primarily under adult haemophilia team.

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 Clinical Research Network: Cancer as a model for the development of shared care governance across England.

Chief investigators or co-investigators on national and international trials

AGCT1531 International Trial of Extracranial GCTs. Matthew Murray (UK Biology Lead and Co-Principal Investigator) St.Baldrick’s grant $2.3 million.
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) – CRUK grant £162,490.

Trial Associated research project Determination of the prognostic significance of MDD and MRD in paediatric Burkitt lymphoma/leukaemia. Amos Burke (Chief Investigator) LLR Grant £128,600

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

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)

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

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

Additional research responsibilities and positions

Dr Amos Burke was reappointed in 2015 as National Institute for Health Research Clinical Research Network: Cancer (NIHR CRN:Cancer) Specialty National Lead for Children and Young People and also NIHR CRN: Eastern LCRN subspecialty lead for Children and Young people. He is a member of NCRI CCL CSG (National Cancer Research Institute Children’s Cancer and Leukaemia Clinical Studies Group) and active on the Novel Agents subgroup. He is also a member of the NCRI Lymphoma CSG (National Cancer Research Institute Lymphoma Clinical Studies Group) and chairs the Paediatric NHL subgroup and is also a member of the European Intergroup Collaboration for Childhood Non-Hodgkin Lymphoma (EICNHL) as UK lead for B-NHL (Figure 10).

Figure 10: Dr Amos Burke (Consultant Paediatric Oncologist, Addenbrooke’s Hospital and Chief Investigator for Inter-B-NHL Ritux 2010 clinical trial) with Dr Suzanne Turner (Senior Lecturer, Department of Pathology, University of Cambridge) and Ms Sorcha Forde (PhD student, Department of Pathology, University of Cambridge) discussing the flow cytometric profile of a Burkitt lymphoma taken from a child enrolled in the trial.
Dr James Nicholson is:

- NCRI CCL CSG, member NCRI CCL CSG Germ Cell Tumour Subgroup, Member and Ex-Chair
- SIOP-Europe Brain Tumour Group, member
- Member International Society of Paediatric Oncology (SIOP) Scientific Programme Advisory Committee
- Teenage Cancer Trust Advisory panel
- CCLG, Chair
- CCLG Guidelines Development Group, Member (exec sponsor)

Dr Denise Williams chairs the European Intergroup Collaboration for Childhood Non-Hodgkin Lymphoma (EICNHL).

Dr Matthew Murray is:

- NCRI Testis Cancer CSG - Member and Biology Lead
- NCRI Teenage and Young Adult (TYA) CSG Biology Subgroup, Member
- NCRI CCL CSG Germ Cell Tumour Subgroup, Member
- SIOP-Europe Brain Tumour Group, Member

Figure 11: Dr Matthew Murray (Academic Consultant Paediatric Oncologist) receiving the donation of funds raised by former patient Max Williamson, his family and friends to support paediatric germ cell research at the University of Cambridge and Addenbrooke’s Hospital.
Current Studies in Paediatric Oncology and Haematology:

1. A trial of rituximab with chemotherapy for children and teenagers who have B cell lymphoma or leukaemia
2. Learning form the experts: a research study looking at children's experiences of being diagnosed with cancer
3. British Childhood Cancer Survivor Study (BCCSS) - A case control studies into risks of adverse health outcomes in survivors of childhood cancer
4. Improving population outcomes for renal tumours of childhood IMPORT
5. High Risk Neuroblastoma Study 1 of SIOP Europe
6. A protocol for non-metastatic rhabdomyosarcoma
7. A protocol for non-rhabdomyosarcoma soft tissue sarcomas
8. Pilot study to investigate the early prediction of toxicity following induction chemotherapy in Ewing's sarcoma by blood-borne biomarkers and correlation with age-dependent pharmacokinetic variation (PK 2013 01)
9. International Randomised Controlled Trial for the Treatment of Newly Diagnosed Ewing's Sarcoma Family of Tumours
10. Phase 1-2 Safety and Efficacy Study of DACOGEN (decitabine) in Sequential Administration With Cytarabine in Children With Relapsed or Refractory Acute Myeloid Leukemia
11. CYP3A5 Genotype as a potential risk factor for the development of Ifosfamide Nephrotoxicity in Children
12. Factors associated with childhood tumours
13. Prospective Trial for the diagnosis and treatment of children, adolescents and young adults with Intracranial Germ Cell Tumours
14. Paediatric Tumour Study - Detection of Genetic abnormalities in Solid Tumours of Childhood
15. International collaborative treatment protocol for infants under one year with acute lymphoblastic or biphenotypic leukaemia
16. UK National Randomised Trial for Children and Young Adults with ALL and Lymphoma 2011
17. Evaluating the costs and benefits of the CLIC Sargent ‘More than my Illness’ service model Project proposal
18. A Phase 2 Multi-Center, Historically-Controlled Study of Dasatinib Added to Standard Chemotherapy in Pediatric Patients with Newly Diagnosed Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia (closed 29-May-14)
19. Pilot study to investigate the feasibility of 13-cis-retinoic acid pharmacokinetic monitoring in high-risk neuroblastoma patients (PK 2008 03) (closed 13-May-15)
20. A pilot study to investigate the experiences of families participating in paediatric pharmacology cancer trials (closed 30-Apr-15)
21. Investigating the clinical use of 13-valent pneumococcal conjugate vaccine (Prevenar 13) in childhood acute lymphoblastic leukaemia (closed 31-Jul-14)
22. A phase II open-label, randomized, Multi-centre comparative study of Bevacizumab-based therapy in Paediatric patients with newly Diagnosed supratentorial, Infratentorial cerebellar, or Peduncular high-grade glioma (closed 26-Jan-15)
Future Studies:

1. Phase 1b/2 Study of Carfilzomib in Combination with Dexamethasone, Mitoxantrone, PEG-asparaginase, and Vincristine (UK R3 Induction Backbone) in Children with Relapsed or Refractory Acute Lymphoblastic Leukemia
2. International Study for treatment of Standard Risk Childhood Relapsed ALL 2010
3. An international clinical program for the diagnosis and treatment of children, adolescents and young adults with ependymoma
4. International Randomised Controlled Trial of Chemotherapy for the Treatment of Recurrent and Primary Refractory Ewing Sarcoma
5. A phase I/II, multicenter, open-label, Dose-escalation study of the safety and Pharmacokinetics of cobimetinib in Pediatric and young adult patients with previously treated solid tumors
6. An early-phase, multicenter, open-label Study of the safety and Pharmacokinetics of anti-pd-I antibody (mpdl3280a) in pediatric and young adult Patients with previously treated solid tumors
7. LCH IV
8. PNET 5
9. MyeChild AML 01
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.

Statement of research:

Dr Nazima Pathan, University lecturer and Honorary Consultant in Paediatric Critical Care, has an established track record as a clinical academic within the field of Paediatric Critical Care. She has obtained personal and project grant funding to support her research, leading to publication in high impact journals and personal awards from a range of societies including the Royal College of Paediatrics and Child health (2004), the Paediatric Cardiac Intensive Care Society (2006) and the European Society of Intensive Care Medicine (2013).

After completing her clinical training she was awarded a HEFCE clinical senior lecturer award at Imperial College London/Royal Brompton Hospital. During this time she was the lead for research in Paediatric Critical Care and managed a research team including post-doctoral scientists, preclinical medical students, research nurses and 2 PhD students.

She was appointed as a University Lecturer in Paediatric Intensive Care in January 2013. She has established several research studies within the PICU, continuing on her interest in the pathophysiology of organ failure in critical illness, and complex data analysis to investigate biomarkers of adverse outcome.

Current and planned research programmes:

Nutrition & gut homeostasis in severe and critically ill children-

Dr Pathan has an interest in the gut microbiome and the host in severe disease and has studies in several areas. These include severely malnourished children (in collaboration with the Wellcome Trust, Kilifi), in children with congenital heart disease and in children with critical illness. She is examining the potential for gut protective interventions to improve gut barrier function, restore the microbiome and improve recovery from illness in severe illness. Having completed pilot work she is planning a Wellcome Trust Tropical Medicine grant to take the malnutrition work further, and an application to the British Heart Foundation and the MRC to examine the biomarker potential of metabolic profiling in congenital heart disease and paediatric critical illness. She is particularly interested in intestinal ischemia reperfusion injury and the role of the gut as a driver of systemic inflammation and metabolic dysregulation in critical illness.

In the critically ill population, Dr Pathan is currently undertaking work to examine the changes in gut microbiome in paediatric critical illness, the potential for dietary interventions to restore gut homeostasis and reduce gut barrier dysfunction, which she has
previously demonstrated to be a contributor to organ failure and disease severity in this patient population.

Dr Pathan is particularly interested in host beneficial gut metabolites such as short chain fatty acids which are likely to be extremely depleted in critical illness. Future work will evaluate the therapeutic potential of enterally administered short chain fatty acids to restore intestinal homeostasis in the critically ill child.

Collaborators – Prof Kath Maitland (Cambridge), Prof Elaine Holmes (Imperial), Prof Gary Frost (Imperial), Prof Robert Glen (Cambridge), Dr Estee Torok (Cambridge), Dr Julian Parkhill (Cambridge).

Use of metadata for patient stratification & the identification of disease predictive biomarkers

Dr Pathan has an established interest in undertaking complex data analysis in critically ill children. Her research group has undertaken transcriptomic and metabolic profiling and the identification of biomarkers to predict disease severity and outcome.

This includes identification of myocardial depressant pathways in septic shock, metabolic biomarkers of poor outcome in paediatric critical illness, regional oxygen saturation as a marker of adverse outcome following congenital heart surgery.

This work closely links with her work in nutrition and gut homeostasis outlined above.

Collaborators: Prof Elaine Holmes (Imperial), Prof Jeremy Nicholson (Imperial), Prof G Frost, Dr J Marchesi (Imperial), Dr P Ramnarayan (UCL).

Inflammation & metabolism in the pathophysiology of organ failure in critical illness

Dr Pathan has used in vitro models of myocardial function as well as in vivo assessments of patient cardiac contractility to investigate the pathophysiology of myocardial dysfunction in septic shock, identifying Interleukin 6, acting via p38 Mitogen activating protein kinase and PI3 kinase is a major pathway, which could be a focus for future interventions to support cardiac function in children with septic shock.

Other work has focused on metabolic and inflammatory mediators or energy failure and organ dysfunction in the critically ill child.

Collaborators: Prof Elaine Holmes (Imperial), Prof Jeremy Nicholson (Imperial), Prof Mark Peters (UCL), Dr P Ramnarayan (UCL).

Dr Shruti Agrawal has research interests in Trauma and Head injury. She is the local PI for a multicenter study on outcomes from traumatic brain injury (ADAPT study). Her other ongoing project is a prospective trial studying micro dialysis and brain tissue oxygen monitoring in paediatric head injury with the Division of Academic Neurosurgery at Cambridge. Dr Agrawal is also a part of ongoing observational study looking at cerebral auto-regulation in Paediatric head injury in collaboration with the Cambridge University Neurosciences Department.
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 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.
4.7. Respiratory, Allergy and General Paediatrics

4.7.1. Respiratory Paediatrics

Respiratory paediatric research at the University of Cambridge is led by Dr Richard Illes and Dr Robert Ross Russell.

Dr Richard Illes studies Structured Light Plethysmography (SLP) in conjunction with the Department of Signal Processing, Cambridge University, UK and clinical sites worldwide that include: Cambridge, Stoke on Trent, Oxford, Southampton, Birmingham Heartlands, Birmingham Queen Elizabeth, Paris, Genoa, Dublin, Copenhagen and Beijing.

Dr Ross Russell has developed algorithms to assess arterial oxygenation in adult and paediatric patients without the need for invasive arterial blood gas measurements. This allows pulmonary shift and shunt to be calculated from the relationship between ambient oxygen and arterial oxygen saturation measured from a standard pulse oximeter. For this research he collaborates with the University of Cambridge’s Division of Anaesthesia and Department of Engineering. 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. He also chairs the European Academy of Paediatrics (EAP) Tertiary Care Council that determines specialty training accreditation within all paediatric subspecialties in Europe.

Current Studies:

Our involvement in NIHR studies (TORPEDO and ESPE) continues although some of the studies (WAIT, TIDES) are now complete. A joint study with the MRC Human Nutrition Unit looking at bone density in children with cystic fibrosis (CF) is also nearing completion. This study utilised the PQ CT scanner, which analyses bone mineral content in great detail. Dr Ross Russell has a study looking at ventilation mismatch in neonates with chronic lung disease. Smaller studies on CF related diabetes (Dr McShane) and CF nutrition and lung disease (Dr Ross Russell) have also taken place.

Work on the non-invasive assessment of VQ and shunt continues. Several studies are currently underway in Cambridge and abroad. Locally it is being used in the quantitative evaluation of chronic lung disease in infants with BPD. Smaller studies in scoliosis, adults with liver disease and bronchiolitis are also active.

CF related diabetes

Donna McShane is working on the early assessment of glucose dysfunction in CF. Data analysed in Cambridge has shown evidence of early markers of developing dysglycaemia that may be valuable in detecting early disease.

Future Studies:

We have been awarded a grant from Fisher & Paykel to investigate ventilation parameters in infants with bronchiolitis over this winter (beginning at the end of 2015).
4.7.2. Paediatric Allergy

Dr Andrew Clark leads research on children’s allergy at Cambridge University Hospital (CUH). 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. Final reports have been submitted and published (Lancet 2014). 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 in 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.

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:
Dr 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 has been Chief Investigator in a study correlating spinal canal depth with body weight in children which has been presented at a national conference of the Royal college of Paediatrics and Child Health and published in the Archives of Disease in Paediatrics. She has worked on the use of simulation in paediatric training which was presented at the 7th International Paediatric Simulation Conference in Vancouver in May 2015.
5. Grants
Grants active and awarded during 2014/15

Diabetes and Endocrinology

01/10/2015-30/09/2022 PI 10%
IMI2 H2020-JTI-IM 12-2014-01-01 Euros 17,630,000 (Cambridge Portion- Euros 2,900,000)
Translational approaches to disease modifying therapy of type 1 diabetes mellitus (T1DM).
The INNODIA project

01/01/2016 - 31/12/2018
Grant for Growth Innovation (Merck) Euros 200,000
David Dunger (PI), Ajay Thankamony, Anders Juul, Rikke Beck Jensen, Ken Ong

1/5/2015 - 1/5/2019
BBSRC/DRINC (Diet and Health Research Industry Club - Full Proposals) £549,226
BB/M027252/1. The validation of biomarkers of metabolic efficacy in infant nutrition.
Koulman A (PI), Dunger D (Co-I), Moore S, Norris S, Griffin J, Gibson G, Ong K, Smith J

01/01/2015 - 31/12/2018
DUK £1,068,514.00 BDA 15/0005233
T1D UK Immunotherapy Consortium: Clinical Engagement and Training (CET) Core.
Colin Dayan (PI), David Leslie, David Dunger (Co-Applicant), Frank Waldron-Lynch, John Todd

01/01/2015 - 31/12/2018
DUK £1,138,460 Cambridge £125,703.50 BDA 15/0005230
Examining immunological effects of proinsulin peptide administration in children with, or at-risk of type 1 diabetes (T1D).
Mark Peakman, Polly Bingley, David Dunger (Co-Applicant), Anette Ziegler, Ezio Bonifacio, Toby Provost

01/04/2014 - 31/3/2018
NIHR Senior Investigator Award £45,000. (reference NF-SI-0513-10012)
Dunger, D

01/03/2013 - 28/02/2018
FP7 HEALTH.2012.2.4.4-1. PREVENT-ROP. £391,058 (Cambridge) (Total awarded Euros 2,696,648/£2,309,540).
New approach to preventative treatment of the blinding disease retinopathy of prematurity (ROP).
Ann Helstrom, David Dunger (Co-I), K Beardsall
01/06/2015 - 01/06/2017
**Mead Johnson** £193,264
Cambridge Baby Growth Studies (there is also a separate donation account held by Addenbrooke’s circa £160,548)
David Dunger (PI), Philippa Prentice

27/04/2008 - 26/03/2017 (extended)
**British Heart Foundation.** £1,268,755 Ref SP/071002/23394
The Adolescent Type 1 Diabetes Cardio Renal Protection Study (AdDIT).
Deanfield J(PI), Daneman D, Dunger D (Co-I), Jones T.

01/02/2015 - 31/01/2017
**The Helmsley Charitable Trust (HCT) Prevention Alliance for Type 1 Diabetes (HPAT)**
European Platform
Cambridge US$940,139 (Germany US$763,612)
Gina Agiostratidou, John Todd, Anette Ziegler, Frank Waldron-Lynch, David Dunger (Co-I) (PI time: 5.0), Chris Wallace, Neil Walker, Adrian Mander Peter Achenbach, Andreas Beyerlain, Thomas Danne, Dorit Ludwig

01/01/2013 - 31/12/2016
**Bill & Melinda Gates Foundation.** Cambridge £409,698
Identification of nutritionally modifiable hormonal and epigenetic drivers of positive and negative growth deviance in rural African fetuses and infants.
Bernstein, RM, Moore, SE, Prentice, AM, Affara NA, Darboe MK, Dunger DB (Co-I) (PI time 5%), Fulford, AJC, Hennig, BJ, Nabwera, HM, Ong, KK.

01/11/2014 - 30/09/2016
**Juvenile Diabetes Research Foundation (JDRF)** $1,995,784 (Cambridge $178,070 /£110,814)
JDRF Grant key: 2-SRA-2014-277-M-R
Validation of Novel and Candidate Biomarkers for Diabetic Kidney Disease in Large Cohorts of people with Type 1 Diabetes
Helen Colhoun (PI), David Dunger (Co-I), Per-Henrik Groop, Carol Forsblom, Neil Dalton , Colin Palmer, Paul McKeigue.

01/10/2013 - 30/09/2016
**NIHR EME.** £677,000. Ref: 11/133/07
Real Time Continuous glucose monitoring in neonatal intensive care.
Beardsall KB, Dunger D (Co-PI), Hovorka R

01/09/2007 - 31/08/2016 (extended)
**Juvenile Diabetes Research Foundation (JDRF)** £3,081,150 ($4,995,843.66)
Adolescent Type 1 Diabetes Cardio Renal Protection Study (AdDIT). Ref 08-2007-902
Dunger D (PI), Dalton N, Deanfield J, Neil A, Prevost T.

01/09/2014-31/08/2016
**Juvenile Diabetes Research Foundation (JDRF)** Total: $1,187,530.59 (year 1)
JDRF Grant Key: 2-SRA-2014-256-M-R
Project Title: Overnight closed loop in sub-optimally controlled type 1 diabetes under free living conditions (APCam11)
Roman Hovorka, Dunger D, (Co-I) (PI time 3.0)
Juvenile Diabetes Research Foundation International (JDRF). £5,012,303.79 (£2,942,331.96)
Closing the Loop in Children and Adolescents (#22-2011-668)
Hovorka R (PI), Dunger DB (Co-I), Acerini C (Co-I)

Diabetes UK £1,260,132 Ref: PO NO 2177 BDA:RD06/003341
The Adolescent Type 1 Diabetes Cardio Renal Protection Study (AdDIT).
Dunger D (PI), Dalton N, Deanfield J, Neil A, Prevost T.

Health and wellbeing of female adolescents and young adults: transgenerational risk of metabolic disease in South Africa.
Dunger D (PI), Norris S.

The Influence of Paternally-Expressed Foetal Imprinted Genes on Maternal Blood Pressure During Pregnancy.
Dunger DB (PI), Petry C

The European Federation of Pharmaceutical Industries and Associations (EFPIA). Euros 235,000. (£206,139)
SUMMIT (Surrogate markers for Micro and Macrovascular hard endpoints for Innovative diabetes Tools).
Leif Groop, Jacqueline Postma, Dunger D (Co-I), Dalton N.

Medical Research Council. £193,037.00
Development of evaluation of biomarkers of infant nutrition growth and body composition.
Training Fellowship
P Prentice, D Dunger

Children’s Kidney Research Fund. £78,000
The Cambridge Surgical Outcomes Study of Disorders of Sex Development
Acerini C, Pasterski V

Newlife Foundation. £15,000
Exploring the causal relationships between maternal endocrine disrupting chemical exposures and male reproductive disorders in infant offspring.
Acerini, C

National Institutes of Health (US). $ 2,347,840.00
Brains and behaviour in individuals with disorders of sex development
Hines M, Acerini C (Co-PI), Lueders E

Paediatric Gastroenterology

01/2015 – 01/2016  The Evelyn Trust, Project Grant, Development of the human “mini-gut” model to study IBD pathogenesis (Value: £45K)

02/2015 – 03/2018  EBPOD Fellowship (Candidate: Dr Kate Howell, in Collaboration with Dr Stegle, EBI), Developing disease prognostic biomarkers in paediatric IBD (Approximate value: £150K)

06/2015 – 06/2016  Addenbrooke’s Charitable Trust (ACT), Project Grant, Epigenetics in Paediatric IBD – Investigating DNA methylation in the intestinal epithelium (Value: £20K)

06/2015 – 06/2016  Crohn’s and Colitis in Childhood (3Cs Charity), Support for Research into Paediatric IBD (non-peer reviewed - Value: £50K)

01/2014 – 01/2016  Isaac Newton Trust / Wellcome Trust ISSF / University of Cambridge Joint Research Grants Scheme; CD8+ T-cell gene expression and DNA methylation signatures as disease prognostic biomarker in Paediatric IBD (Value: £80K)

02/2014 – 02/2016  Crohn’s in Childhood Research Association (CICRA), Project Grant, CD8+ T-cell gene expression signature as disease prognostic biomarker in Paediatric IBD (Value: £100K)

02/2013 – 02/2016  Crohn’s in Childhood Research Association (CICRA), PhD studentship, Epigenetics in Paediatric IBD (Value:~£70K)

03/2012 – 03/2014  The Evelyn Trust, Project Grant, Epigenetics in Paediatric IBD (Value: £64K)

Neonatology

Improving glucose control in very preterm infants. 2011-2014. Evelyn Trust. £73,000. Beardsall K (PI), Hovorka R (CI), Dunger D (CI).


Real Time continuous glucose monitoring in preterm infants National Institute of Health Research Efficacy and Mechanism Evaluation program. Program £725,000 2013- 2015 Beardsall K Dunger DB and Hovorka RM


CONCEPTT Neonatal Study 01/03/2014 -31/02/2015 Diabetes and Wellness Foundation £19,700
POCKET Validation of the use of point of care technology to measure ketone and lactate levels in the new born at risk from hypoglycaemia due to impaired perinatal counter regulation
01/01/2014-31/12/2014 Addenbrookes Charitable Trust £6650

MRC Fellowship, 2014-2016: BRAIN - Behaviour and Resting state Activation In Newborns. £130k

Nick Haan Neonatal neurocritical care nurse secondment, 2015. £20k

British Academy/Leverhulme (with Birkbeck BabyLab, University of London), 2015-2016: TOUCH - Understanding the role social touch plays in cognitive development. £9.6k

Rosetrees Trust (with Vicky Leong, Psychology), 2015-2016: Identifying neuro-genetic oscillatory biomarkers of dyslexia risk in neonates. £11k

Bill & Melinda Gates Foundation (with UCL-BORL, Birkbeck BabyLab, University of London), 2015-2017: BRIGHT - Brain Imaging and Global Health. $700k

Addenbrooke’s Charitable Trust/Biomedical Research Centre Nurses, Midwives & Allied Healthcare Professional Research Training Fellowships, 2015-2016. £44k

Paediatric Neurology

No direct grants. Projects are funded from other departments.

Oncology and Haematology

Dr Amos Burke:

Lead applicant, Dr Burke is the UK Chief Investigator:

1. 2011-2021 Cancer Research UK £162,490
   Intergroup trial for children or adolescents with B-cell NHL or B-AL: evaluation of rituximab efficacy in high risk patients (Inter-B-NHL ritux 2010).

2. 2014-2019 Leukaemia and Lymphoma Research (TARP) £128,600
   Determination of the prognostic significance of MDD and MRD in paediatric Burkitt lymphoma/leukaemia.

3. NIHR CRN support funding for InterB-NHL ritux 2010 trial ~£8000

Named/Co-Investigator on the following Research Grant:

4. 2011-2015 Leukaemia and Lymphoma Research Fund £248,288
   Dependence of Lymphoma and Leukaemia cell proliferation and survival on L-arginine

Dr James Nicholson:

Lead applicant, Dr Nicholson is the UK Chief Investigator:

5. 2010-2017 Cancer Research UK £148,000
Prospective trial for the diagnosis and treatment of children, adolescents and young adults with Intracranial Germ Cell Tumours (SIOP CNS GCT II)

Named/Co-Investigator on the following Research Grant (Dr Murray is also a Co-Investigator on this grant):

6. 2012-2014 Children with Cancer UK and Great Ormond Street Hospital Children's Charity (CwCUK/GOSHCC) Grant £99,840  
Novel genetic markers for blood-based monitoring of treatment response in common childhood cancers

Dr Matthew Murray:

Co-Principal Investigator on the following Research Grant:

7. 2015-2020 St. Baldrick’s Grant $2.3 million  
Improving outcomes for children, teenagers and young adults with extracranial germ cell tumours

Principal Investigator on the following Research Grant:

8. 2015-2018 Children with Cancer UK £148,428  
Targeting oncogenic microRNA clusters in malignant germ cell tumours using tiny locked nucleic acids

Named/Co-Investigator on the following Research Grants:

9. 2014-2016 Astra Zeneca/University of Cambridge collaboration ~£180,000  
Investigating the clinical role of serum microRNAs for cancer diagnosis and prognosis

10. 2015-2018 Action Medical Research PhD Training Fellowship £197,895  
Targeting oncogenic microRNA clusters in malignant germ cell tumours using tiny locked nucleic acids

11. 2014-2018 BBSRC Departmental PhD Fellowship ~£60,000  
Investigating the role of tumour suppressor microRNAs in malignant germ cell tumours

Targeting oncogenic microRNA clusters in malignant germ cell tumours using tiny locked nucleic acids

Consultancies with Pharmaceutical Companies:

13. 2014-2016 AstraZeneca/University of Cambridge collaboration/consultancy ~£180,000  
Investigating the clinical role of serum microRNAs for cancer diagnosis and prognosis

Paediatric Intensive Care Unit (PICU)

2015: King Faisal PhD Scholarship to fund a research dietitian undertaking a doctoral research programme.
2014: Great Ormond Street for Children Charity. £43000 (Co-I) ‘Quality of life and functional outcomes 12 months after emergency admission to paediatric intensive care’

2014: Research Grant from Evelyn Trust; £57,000 (PI) to support research on Gut health in Critical Illness

**Respiratory, Allergy and General Paediatrics**

2015: Fisher & Paykel. Project grant 2015 (£60,000): To investigate ventilation parameters in infants with bronchiolitis over this winter (end of 2015).

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

Diabetes and Endocrinology


Ruan Y, Elleri D, Allen JM, Tauschmann M, Wilinska ME, **Dunger DB**, Hovorka R. Pharmacokinetics of diluted (U20) insulin aspart compared with standard (U100) in children aged 3-6 years with type 1 diabetes during closed-loop insulin delivery: a randomised clinical trial. **Diabetologia.** 2015.58(4);687-90. PMID:25537835.


Increased Cross-Gender Identification Independent of Gender Role Behavior in Girls with Congenital Adrenal Hyperplasia: Results from a Standardized Assessment of 4- to 11-Year-Old Children. Arch Sex Behav. 2015 Jul;44(5):1363-75. doi: 10.1007/s10508-014-0385-0. Epub 2014 Sep 20. PMID: 25239661


Invited peer reviews:


Marcovcechio ML, Dunger D. Can increased albumin excretion provide evidence of early renal and cardiovascular disease in adolescents with type 1 diabetes? Diabetes Management. 2014; Review


Gastroenterology


Neonatology


Neurology


Recent posters and oral presentations


Seizure Cessation in a breast fed infant whose mother was following a Modified Atkins Style Ketogenic Diet. Champion H, Dowd Z, Maw A, Ambegaonkar G. International Conference on Dietary Treatment of Neurological Disorders, 2014


Adrenoleukodystrophy and Avoidable and Treatable Illness. Parsons A, Carr D, Parker APJ. BPNA Annual Conference 2015.


Oncology and Haematology

Sara Stoneham, Juliet P Hale, Carlos Rodriguez-Galindo, Ha Dang, Thomas Olson, MD, Matthew Murray, James Amatruda, Claire Thornton, G. Suren Arul, Deborah Billmire, Mark Krailo, Dan Stark, Al Covens, Jean Hurteau, Sally Stenning, James C Nicholson, David Gershenson, A. Lindsay Frazier, MD3. Adolescents and Young Adults with a “Rare” Cancer: Getting Past Semantics to Optimal Care for Patients With Germ Cell Tumors. Oncologist 2014;19:1–4


A Lindsay Frazier, Juliet P Hale, Carlos Rodriguez-Galindo, Ha Dang, Thomas Olson, Matthew Murray, James F. Amatruda, Claire Thornton, G. Suren Arul, Deborah Billmire, Furqan Shaikh, Farzana Pashankar, Sara Stoneham, Mark Krailo, James C Nicholson. Revised Risk Classification for Pediatric Extracranial Germ Cell Tumors Based on 25 Years of Clinical Trial Data from the United Kingdom and United States. J Clin Oncol. 2015, Jan 10;33(2):195-201 (epub 2014, 10.1200/JCO.2014.58.3369)


**Paediatric Intensive Care Unit (PICU)**


**Respiratory, Allergy and General Paediatrics**


Wilson R, Khalid A and Iles R. Use of SLP to identify disordered thoraco-abdominal breathing patterns in COPD Mr Willem de Boer. Respiratory Paediatrics, 2014. Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK, CB20QQ 2R&D, PneumaCare Ltd, Cambridge, Cambridgeshire, United Kingdom, CB40WS.


Ventilation strategies in the PICU. Mini-symposium – R Ross Russell Section Editor. Paediatric respiratory reviews (In Press)


Anagnostou K, Clark A. Peanut immunotherapy. Clin Transl Allergy 2014;4:30


# 7. LIST OF RESEARCH STAFF

<table>
<thead>
<tr>
<th>University of Cambridge Department of Paediatrics Academic Staff</th>
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<tbody>
<tr>
<td>Professor David Rowitch</td>
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<td>Professor David Dunger</td>
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<td>Dr Carlo Acerini</td>
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<td>Dr Kathryn Beardsall</td>
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<td>Dr Matthias Zilbauer</td>
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<td>Dr Nazima Pathan</td>
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<td>Dr Roman Hovorka</td>
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<td>Dr Ken Ong</td>
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<td>Dr Ruben Willemsen</td>
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<td>Dr Daniela Elleri</td>
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<td>Dr Ajay Thankamony</td>
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<td>Dr Clive Petry</td>
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<tr>
<th>Academic Associated/Affiliated Lecturers</th>
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<tbody>
<tr>
<td>Dr Amos Burke</td>
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<td>Dr Andrew Clark</td>
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<td>Mr David Conlan</td>
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<td>Dr Peter Heinz</td>
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<td>Dr Richard Iles</td>
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<td>Dr Wilf Kelsall</td>
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<td>Dr Sarah Morley</td>
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<td>Dr Roddy O'Donnell</td>
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<td>Dr Alasdair Parker</td>
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<td>Dr Robert Ross Russell</td>
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<td>Dr Pat Set</td>
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<td>Dr Rachel Williams</td>
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<th>Research Nurses</th>
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<tr>
<td>Diabetes and Endocrinology</td>
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<tr>
<td>Dr</td>
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<tr>
<td>Catherine Fullah</td>
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<td>Dr</td>
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<td>Dr</td>
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<td>Dr</td>
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<td>Neonatal Metabolism</td>
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<td>PICU</td>
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## Research Nurses

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<tr>
<th>Speciality</th>
<th>Nurse Name</th>
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<tbody>
<tr>
<td>Neonatal Neuroscience</td>
<td>Andrea Edwards</td>
<td>Research Nurse (Clinical)</td>
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<td></td>
<td>Claire O'Mara</td>
<td>Lead Nurse</td>
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<tr>
<td>Oncology</td>
<td>Jane Tunnacliffe</td>
<td>Research Nurse</td>
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<tr>
<td>Paediatric Allergy</td>
<td>Yvonne King</td>
<td>Research Nurse</td>
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<tr>
<td>Neurology</td>
<td>Jacqui Tahari</td>
<td>Research Nurse</td>
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<tr>
<td>Gastroenterology</td>
<td>Claire Lee</td>
<td>Research Nurse</td>
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## CRN Research Nurses

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<thead>
<tr>
<th>Category</th>
<th>Nurse Name</th>
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<tbody>
<tr>
<td>CRN Research Nurses</td>
<td>Jo Bytham</td>
<td>Research Nurses</td>
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<tr>
<td>CRN Generic Nurses</td>
<td>Jacqui Tahari</td>
<td>Working across sub specialities and regional locations dependant on study needs</td>
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<td>Petra Tucker</td>
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## Clinical Research Fellows

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<tr>
<th>Speciality</th>
<th>Research Fellow</th>
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<tr>
<td>Diabetes and Endocrinology</td>
<td>Dr Kate Howell</td>
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<tr>
<td>Neonatal Neuroscience</td>
<td>Dr Cristine Costa</td>
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<td>Dr Cheun Wai Lee</td>
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<td>Dr Laura Dempsey</td>
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<td>Dr Robert Cooper</td>
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<td>Respirator and Cystic Fibrosis</td>
<td>Dr Jenny Conlan</td>
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<tr>
<td>Allergy</td>
<td>Dr Sabita Islam</td>
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<tr>
<td>General Paediatrics</td>
<td>Dr Birgit Ulbrich</td>
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## Research Manager (BRC)

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<thead>
<tr>
<th>Research Manager (BRC)</th>
<th>BRC Paediatric Research Theme</th>
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<td>Dr Suchismita Roy</td>
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## Research Laboratory Staff: Diabetes and Endocrinology

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<tr>
<th>Speciality</th>
<th>Person Name</th>
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<tbody>
<tr>
<td>Diabetes and Endocrinology</td>
<td>Karen Whitehead</td>
<td>Chief Research Technician</td>
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<td></td>
<td>Radka Platte</td>
<td>Assistant to Chief Research Technician</td>
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<td></td>
<td>Komal Nayak</td>
<td>Lab Manager</td>
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<td></td>
<td>Sarah Thurston</td>
<td>Research Assistant</td>
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<tr>
<td>Allergy</td>
<td>Dr Loraine Foley</td>
<td>Research Technician</td>
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## Study and Trial Managers

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<th>Study and Trial Managers</th>
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<tbody>
<tr>
<td>Dianne Picton</td>
<td>Clinical Trials Monitor</td>
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<tr>
<td>Stella Silvester</td>
<td>Reno Protection Trial Coordinator</td>
</tr>
<tr>
<td>Catherine Guy</td>
<td>Study Manager</td>
</tr>
</tbody>
</table>
**Study and Trial Managers**

<table>
<thead>
<tr>
<th>Name</th>
<th>Position</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tracy Stevens</td>
<td>Clinical Trials Administrator</td>
</tr>
<tr>
<td>Susan Chapman</td>
<td>Research Administrative Assistant</td>
</tr>
<tr>
<td>Anna Diaz</td>
<td>BPSED Administrative Assistant</td>
</tr>
</tbody>
</table>

**CLRN Research Facilitator: Diabetes and Endocrinology**

<table>
<thead>
<tr>
<th>Name</th>
<th>Position</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maxine Glover-Bennett</td>
<td>CRN-Eastern Research Facilitator</td>
</tr>
</tbody>
</table>

**Visiting Research Fellows**

<table>
<thead>
<tr>
<th>Name</th>
<th>Supervisor</th>
<th>Co-supervisor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr Philippa Prentice</td>
<td>Burak Salgin</td>
<td>Maike Markstein</td>
</tr>
<tr>
<td>Vickie Estes</td>
<td>Beatrice Reghi</td>
<td>Esther Leenen</td>
</tr>
<tr>
<td>Dr Ajay Thankamony</td>
<td>Kwang Yang Lee</td>
<td>Margarida Vieira</td>
</tr>
<tr>
<td>Noemi Fuentes</td>
<td>Catarina Mendes</td>
<td>Theresa Maier</td>
</tr>
<tr>
<td>Violeta Delgado-Carballar</td>
<td>Saduf Chaudhry</td>
<td>Adrian Rad</td>
</tr>
<tr>
<td>Max Wong</td>
<td>Connie Hui</td>
<td>Yasmine Ouarezki</td>
</tr>
<tr>
<td>Anna Prats-Puig</td>
<td>Gianluca Tornese</td>
<td></td>
</tr>
</tbody>
</table>

### 8. LIST OF ACADEMIC CLINICAL FELLOWS

<table>
<thead>
<tr>
<th>Fellow</th>
<th>Supervisor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ben Fisher</td>
<td>Carlo Acerini</td>
</tr>
<tr>
<td>Sanchita Pal</td>
<td>Robert Ross-Russell</td>
</tr>
<tr>
<td>Katrina Crawford</td>
<td>Kathryn Beardsall</td>
</tr>
<tr>
<td>Rebecca Tibbot</td>
<td>Andrew Clark</td>
</tr>
<tr>
<td>Alexander Ross</td>
<td>Matthias Zilbauer</td>
</tr>
<tr>
<td>Jake Mann</td>
<td>David Savage</td>
</tr>
<tr>
<td>Elizabeth Radford</td>
<td>Matthias Zilbauer</td>
</tr>
</tbody>
</table>

### 9. LIST OF PhD STUDENTS

<table>
<thead>
<tr>
<th>Student</th>
<th>PhD Supervisor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Judith Kraiczy</td>
<td>Matt Zilbauer</td>
</tr>
<tr>
<td>Yue Ruan</td>
<td>Roman Hovorka</td>
</tr>
<tr>
<td>Martin Tauschmann</td>
<td>Roman Hovorka</td>
</tr>
<tr>
<td>Antigoni Eleftheriou</td>
<td>David Dunger</td>
</tr>
<tr>
<td>Sara Zaher</td>
<td>Nazima Pathan</td>
</tr>
</tbody>
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# 10. Appendices

**APPENDIX 1**

**NIHR PORTFOLIO STUDIES**

Studies in which the University of Cambridge or Cambridge University Hospitals Investigator is the Lead Investigator:

<table>
<thead>
<tr>
<th>Short study title</th>
<th>Study Description</th>
<th>University of Cambridge/ Cambridge University Hospitals Investigator</th>
<th>Study Start date (where available)</th>
<th>Study Completion Date or Proposed Completion Date (where available)</th>
<th>Activity Status (Jan 2016)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Automated closed-loop in children and adolescents with T1D</td>
<td>An open-label, single-centre, randomised, 2-period cross-over study to assess the efficacy and safety of a novel automated overnight closed-loop glucose control system on day 1 of continuous glucose monitoring sensor insertion in comparison to day 3 to 4 after sensor insertion in children and adolescents with type 1 diabetes (APCam09)</td>
<td>Dr Roman Hovorka</td>
<td>09/05/2014</td>
<td>07/03/2015</td>
<td>Closed (in follow-up)</td>
</tr>
<tr>
<td>BRAIN: Behaviour and Resting state Activity In Newborns</td>
<td>Investigating newborn brain function and behaviour associated with prematurity and brain injury.</td>
<td>Dr Topun Austin</td>
<td>01/07/2014</td>
<td>01/10/2016</td>
<td>Open</td>
</tr>
<tr>
<td>Cambridge Baby Growth Outcome Study</td>
<td>Nutritionally related biomarkers of changes in body composition and metabolic risk in children: The Cambridge Baby Growth Outcome Study</td>
<td>Professor David Dunger</td>
<td>31/10/2013</td>
<td>31/12/2017</td>
<td>Open</td>
</tr>
<tr>
<td>CHILD Study</td>
<td>The Cambridge Human Imaging and Longitudinal Development (CHILD) Study: Prenatal, neonatal and postnatal hormonal effects on infant health and brain development</td>
<td>Professor Simon Baron-Cohen</td>
<td>01/07/2015</td>
<td>01/04/2016</td>
<td>Open (in set-up)</td>
</tr>
<tr>
<td>CONCEPTT Newborn Study</td>
<td>Glucose Control and metabolic adaptation in offspring of women with Type 1 Diabetes recruited to the CONCEPTT Study. Open</td>
<td>Dr Kathryn Beardsall</td>
<td>15/05/2014</td>
<td>31/12/2016</td>
<td>Open</td>
</tr>
<tr>
<td>C-pepT1D Study</td>
<td>Evaluation of novel method that measures beta-cell function by dried blood spots in children and adolescents with a recent diagnosis of type 1 diabetes (C-pepT1D)</td>
<td>Professor David Dunger</td>
<td>20/10/2014</td>
<td>02/09/2016</td>
<td>Open</td>
</tr>
<tr>
<td>Short study title</td>
<td>Study Description</td>
<td>University of Cambridge/ Cambridge University Hospitals Investigator</td>
<td>Study Start date (where available)</td>
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<td>Activity Status (Jan 2016)</td>
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<tr>
<td>DETEMIR GLARGINE</td>
<td>A comparison of the effects of insulin Detemir with insulin Glargine on weight gain in female adolescents and young adults with type 1 Diabetes on basal bolus regime</td>
<td>Professor David Dunger</td>
<td>01/04/2008</td>
<td>31/12/2015</td>
<td>Open</td>
</tr>
<tr>
<td>DRN 491 (Phenotypes and Obesity)</td>
<td>Phenotypic characterisation of subjects with genetic defects associated with severe childhood obesity</td>
<td>Dr I Sadaf Farooqi</td>
<td>01/01/1998</td>
<td>31/12/2017</td>
<td>Open</td>
</tr>
<tr>
<td>DRN 492 (Diabetes and complications associated with obesity)</td>
<td>Metabolic &amp; Endocrine characterisation of subjects with severe obesity</td>
<td>Dr I Sadaf Farooqi</td>
<td>01/01/1998</td>
<td>31/12/2017</td>
<td>Open</td>
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<tr>
<td>DRN 779 (The EstID Study)</td>
<td>Hepatic Growth Hormone in young women with type 1 diabetes: comparison with controls and effects or oral and transdermal estrogen administration</td>
<td>Professor David Dunger</td>
<td>27/09/2011</td>
<td>30/06/2015</td>
<td>Open</td>
</tr>
<tr>
<td>DRN085 Nephropathy Family Study (NFS)</td>
<td>NFS- Genetic analysis of risk factors for the development of diabetic complications.</td>
<td>Professor David Dunger</td>
<td>05/03/2001</td>
<td>31/03/2014</td>
<td>Closed (in follow-up)</td>
</tr>
<tr>
<td>Gaucherite- A study to classify Gaucher disease</td>
<td>Predictive measures to stratify clinical outcomes in children and adults with Gaucher disease and responses to specific therapies</td>
<td>Prof Timothy M Cox</td>
<td>01/03/2015</td>
<td>27/09/2019</td>
<td>Open</td>
</tr>
<tr>
<td>Home testing of 24/7 closed-loop in young people with type 1 diabetes</td>
<td>An open-label, single-centre, randomised, two-period crossover study to assess the efficacy, safety and utility of automated closed-loop glucose control, day and night over 7 days in comparison with continuous subcutaneous insulin infusion combined with continuous glucose monitoring in the home setting in children and adolescents with type 1 diabetes</td>
<td>Dr Roman Hovorka</td>
<td>28/08/2014</td>
<td>31/07/2015</td>
<td>Closed - follow-up complete</td>
</tr>
<tr>
<td>INSIGNIA: Exploring mutational signatures in humans</td>
<td>Exploring the biological processes underlying mutational signatures identified in cancer</td>
<td>Dr Serena Nik-Zainal</td>
<td>18/03/2014</td>
<td>31/01/2018</td>
<td>Open</td>
</tr>
<tr>
<td>Short study title</td>
<td>Study Description</td>
<td>University of Cambridge/Cambridge University Hospitals Investigator</td>
<td>Study Start date (where available)</td>
<td>Study Completion Date or Proposed Completion Date (where available)</td>
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</tr>
<tr>
<td>ISO (Investigation of Segmental Overgrowth)</td>
<td>Investigation of segmental overgrowth disorders</td>
<td>Dr Robert K Semple</td>
<td>15/03/2013</td>
<td>21/03/2018</td>
<td>Open</td>
</tr>
<tr>
<td>NIRTURE Follow-up</td>
<td>Do neonatal IGF1 levels predict the long-term outcome of preterm infants?</td>
<td>Professor David Dunger</td>
<td>26/11/2014</td>
<td>01/09/2016</td>
<td>Open</td>
</tr>
<tr>
<td>REACT</td>
<td>Real Time continuous glucose monitoring in the newborn (REACT)</td>
<td>Dr Kathryn Beardsall</td>
<td>01/06/2015</td>
<td>04/08/2017</td>
<td>Open</td>
</tr>
<tr>
<td>Real Time continuous glucose monitoring in the newborn</td>
<td>Real Time continuous glucose monitoring in the newborn (feasibility)</td>
<td>Dr Kathryn Beardsall</td>
<td>13/06/2014</td>
<td>11/07/2015</td>
<td>Closed</td>
</tr>
<tr>
<td>SAMBA 1</td>
<td>Prospective cohort study investigating cardiac function and cerebral autoregulation in preterm infants. Circulatory function and cerebrovascular control of blood flow and oxygen delivery to the brain in newborn infants undergoing intensive care</td>
<td>Dr Topun Austin</td>
<td>02/05/2013</td>
<td>30/03/2016</td>
<td>Open</td>
</tr>
<tr>
<td>Small at birth study</td>
<td>Retrospective follow up of children born small for gestational age: impact of catch up growth on body composition and insulin resistance in childhood</td>
<td>Professor David Dunger</td>
<td>22/06/2011</td>
<td>01/10/2016</td>
<td>Open</td>
</tr>
<tr>
<td>Surveillance to identify any children in the UK with variant CJD</td>
<td>To undertake prospective multisource surveillance for all cases of progressive intellectual and neurological deterioration occurring in children in the UK</td>
<td>Dr Christopher Verity</td>
<td>01/01/1997</td>
<td>31/03/2017</td>
<td>Open</td>
</tr>
<tr>
<td>The Cambridge Baby Growth Study II</td>
<td>Study of antenatal, nutritional and genetic factors on infant weight gain, body composition and fat distribution in infants born Small-for-Gestational Age and Infants of Diabetic Mothers: The Cambridge Baby Growth Study II</td>
<td>Dr Carlo Acerini</td>
<td>28/04/2011</td>
<td>31/03/2017</td>
<td>Open</td>
</tr>
</tbody>
</table>
# Studies in which the University of Cambridge or Cambridge University Hospitals Investigator is a participant:

<table>
<thead>
<tr>
<th>Short study title</th>
<th>Study Description</th>
<th>Cambridge Investigator</th>
<th>Study Start date (where available)</th>
<th>Study Completion Date or Proposed Completion Date (where available)</th>
<th>Activity Status (Jan 2016)</th>
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<tbody>
<tr>
<td>ADAPT</td>
<td>Approaches and Decisions for Acute Pediatric Traumatic brain injury (TBI)</td>
<td>Dr Shruti Agrawal</td>
<td>17/02/2014</td>
<td>31/01/2016</td>
<td>Open</td>
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<tr>
<td>ADDRESS-2</td>
<td>An incident and high risk type 1 diabetes research cohort - after diabetes diagnosis research support system-2 (ADDRESS-2)</td>
<td>Professor David Dunger</td>
<td>01/08/2012</td>
<td>31/12/2017</td>
<td>Open</td>
</tr>
<tr>
<td>Biomarkers of Acute Serious Illness in Children (BASIC)</td>
<td>Understanding the genetic basis and biological pathways underlying critical illness and how they influence outcome in children requiring emergency intensive care</td>
<td>Dr Nazima Pathan</td>
<td>01/04/2014</td>
<td>31/03/2016</td>
<td>Open</td>
</tr>
<tr>
<td>Dasatinib (CA180-372)</td>
<td>A Phase 2 Multi-Center, Historically-Controlled Study of Dasatinib Added to Standard Chemotherapy in Pediatric Patients with Newly Diagnosed Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia</td>
<td>Dr Mike Gattens</td>
<td>19/12/2012</td>
<td>29/05/2014</td>
<td>Closed (in follow-up)</td>
</tr>
<tr>
<td>ECHO</td>
<td>Experiences of Children with Copy Number Variants</td>
<td>Mr Per N Hall</td>
<td>01/01/2010</td>
<td>30/06/2017</td>
<td>Open</td>
</tr>
<tr>
<td>EU-AIMS Accelerated Longitudinal Study</td>
<td>Accelerated Longitudinal European Autism Project to establish Biomarkers of the Autism Phenotype</td>
<td>Professor Simon Baron-Cohen</td>
<td>01/04/2012</td>
<td>31/03/2017</td>
<td>Open</td>
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<tr>
<td>EUCLIDS</td>
<td>The European Union Childhood Life-threatening Infectious Diseases Study</td>
<td>Dr Nazima Pathan</td>
<td>24/04/2012</td>
<td>01/12/2016</td>
<td>Open</td>
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<tr>
<td>Euro Ewing 2012</td>
<td>International Randomised Controlled Trial for the Treatment of Newly Diagnosed Ewing's Sarcoma Family of Tumours</td>
<td>Dr Denise Williams</td>
<td>19/05/2015</td>
<td>30/04/2018</td>
<td>Open</td>
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<tr>
<td>Fact Study</td>
<td>Factors associated with childhood tumours</td>
<td>Dr Amos Burke</td>
<td>21/03/2005</td>
<td>31/12/2020</td>
<td>Open</td>
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<tr>
<td>Short study title</td>
<td>Study Description</td>
<td>Cambridge Investigator</td>
<td>Study Start date (where available)</td>
<td>Study Completion Date or Proposed Completion Date (where available)</td>
<td>Activity Status (Jan 2016)</td>
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<tr>
<td>Fast Optical Tomography On Neonates (FOTON)</td>
<td>Development of three-dimensional fast optical tomography to study the brain of healthy infants and newborn infants at high risk of brain injury</td>
<td>Dr Topun Austin</td>
<td>01/10/2014</td>
<td>01/01/2018</td>
<td>Open</td>
</tr>
<tr>
<td>GEM</td>
<td>GEM Project. A Multidisciplinary Human Study on the Genetic, Environmental and Microbial Interactions that Cause Inflammatory Bowel Disease</td>
<td>Dr Matthias Zilbauer</td>
<td>_</td>
<td>09/01/2020</td>
<td>Open</td>
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<tr>
<td>GWAS in children with DDH</td>
<td>Genome-wide association of common alleles with developmental dysplasia of the hip</td>
<td>Mr Andreas Rehm</td>
<td>01/01/2012</td>
<td>21/10/2016</td>
<td>Open</td>
</tr>
<tr>
<td>Herby</td>
<td>A phase II open-label, randomized, multi-centre comparative study of bevacizumab-based therapy in paediatric patients with newly diagnosed supratentorial, infratentorial cerebellar, or peduncular high-grade glioma</td>
<td>Dr James Nicholson</td>
<td>01/04/2012</td>
<td>26/01/2015</td>
<td>Closed (in follow-up)</td>
</tr>
<tr>
<td>I2S2</td>
<td>A randomised controlled trial of iodide supplementation in preterm infants with follow-up at 2 years</td>
<td>Dr Kathryn Beardsall</td>
<td>08/03/2010</td>
<td>22/04/2015</td>
<td>Closed (in follow-up)</td>
</tr>
<tr>
<td>IMPORT</td>
<td>Improving population outcomes for renal tumours of childhood (IMPORT)</td>
<td>Dr Boo Messahel</td>
<td>20/03/2013</td>
<td>06/03/2017</td>
<td>Open</td>
</tr>
<tr>
<td>Inter-B-NHL Ritux 2010 - Version 1.0</td>
<td>A trial of rituximab with chemotherapy for children and teenagers who have B cell lymphoma or leukaemia (InterB-NHL Ritux 2010 Version 1.0)</td>
<td>Dr Amos Burke</td>
<td>27/03/2014</td>
<td>31/12/2018</td>
<td>Open</td>
</tr>
<tr>
<td>Interfant 06</td>
<td>International collaborative treatment protocol for infants under one year with acute lymphoblastic or biphenotypic leukaemia</td>
<td>Dr Mike Gattens</td>
<td>12/06/2008</td>
<td>30/04/2016</td>
<td>Open</td>
</tr>
<tr>
<td>JUMP Joining together to Understand diabetes mellitus type 2 Progression in children.</td>
<td>Type 2 Diabetes in Childhood: Building a platform for interventions to prevent the progression to cardiovascular disease</td>
<td>Professor David Dunger</td>
<td>11/11/2009</td>
<td>31/03/2017</td>
<td>Open</td>
</tr>
<tr>
<td>Short study title</td>
<td>Study Description</td>
<td>Cambridge Investigator</td>
<td>Study Start date (where available)</td>
<td>Study Completion Date or Proposed Completion Date (where available)</td>
<td>Activity Status (Jan 2016)</td>
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<tr>
<td>MCRN180 (AHEAD)</td>
<td>Advocate haemophilia outcome database (ahead)</td>
<td>Dr David Perry</td>
<td>27/07/2012</td>
<td>31/12/2015</td>
<td>Open</td>
</tr>
<tr>
<td>MCRN2368 (SPO969)</td>
<td>A multi-centre, double-blind, randomized, placebo-controlled, parallel-group study to investigate the efficacy and safety of Lacosamide as adjunctive therapy in subjects with epilepsy ≥4 years to &lt; 17 years of age with partial-onset seizures</td>
<td>Dr Manali Chitre</td>
<td>21/10/2015</td>
<td>01/05/2017</td>
<td>Open</td>
</tr>
<tr>
<td>MCRN2732 (ROPP-2008-01)</td>
<td>Determination of the rhIGF-1/rhIGFBP-3 Dose, Administered as a Continuous Infusion, Required to Establish and Maintain Longitudinal Serum IGF-1 Levels Within Physiological Levels in Premature Infants, to Prevent Retinopathy of Prematurity. A Phase 2, Randomized Controlled, Assessor-blind, Dose-confirming, Pharmacokinetic, Safety and Efficacy, Multicenter Study</td>
<td>Dr Kathryn Beardsall</td>
<td>27/10/2014</td>
<td>31/05/2015</td>
<td>Closed (in follow-up)</td>
</tr>
<tr>
<td>NB 2002 06 (High Risk Neuroblastoma)</td>
<td>High Risk Neuroblastoma Study 1 of SIOP Europe</td>
<td>Dr Boo Messahel</td>
<td>10/02/2003</td>
<td>28/02/2018</td>
<td>Open</td>
</tr>
<tr>
<td>NCRN - 2382 - DACOGEN in Sequential Administration with Cytarabine in Children</td>
<td>Phase 1-2 Safety and Efficacy Study of DACOGEN (decitabine) in Sequential Administration With Cytarabine in Children With Relapsed or Refractory Acute Myeloid Leukemia</td>
<td>Dr Amos Burke</td>
<td>05/02/2014</td>
<td>15/08/2016</td>
<td>Open</td>
</tr>
<tr>
<td>NRSTS 2005</td>
<td>A protocol for non-rhabdomyosarcoma soft tissue sarcomas</td>
<td>Dr Denise Williams</td>
<td>26/06/2007</td>
<td>01/03/2017</td>
<td>Open</td>
</tr>
<tr>
<td>PCV13</td>
<td>Investigating the clinical use of 13-valent pneumococcal conjugate vaccine (Prevenar 13) in childhood acute lymphoblastic leukaemia</td>
<td>Dr Mike Gattens</td>
<td>22/10/2013</td>
<td>31/07/2014</td>
<td>Closed (in follow-up)</td>
</tr>
<tr>
<td>Pharmacokinetic variation and toxicity in Ewing’s sarcoma (Ewings PK Study)</td>
<td>Pilot study to investigate the early prediction of toxicity following induction chemotherapy in Ewing’s sarcoma by blood-borne biomarkers and correlation with age-dependent pharmacokinetic variation</td>
<td>Dr Denise Williams</td>
<td>25/06/2014</td>
<td>31/03/2019</td>
<td>Open</td>
</tr>
<tr>
<td>Short study title</td>
<td>Study Description</td>
<td>Cambridge Investigator</td>
<td>Study Start date (where available)</td>
<td>Study Completion Date or Proposed Completion Date (where available)</td>
<td>Activity Status (Jan 2016)</td>
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</tr>
<tr>
<td>PK 2007 02 (CYP3A5 ifosfamide nephrotoxicity)</td>
<td>CYP3A5 Genotype as a potential risk factor for the development of Ifosfamide Nephrotoxicity in Children</td>
<td>Dr Amos Burke</td>
<td>15/06/2009</td>
<td>31/07/2016</td>
<td>Open</td>
</tr>
<tr>
<td>PK 2008 03 (13-cis-retinoic acid monitoring study)</td>
<td>Pilot study to investigate the feasibility of 13-cis-retinoic acid pharmacokinetic monitoring in high-risk neuroblastoma patients (PK 2008 03)</td>
<td>Dr Amos Burke</td>
<td>18/09/2009</td>
<td>13/05/2015</td>
<td>Open</td>
</tr>
<tr>
<td>Prednisolone in Nephrotic Syndrome: The PREDNOS Study</td>
<td>Long-term tapering versus standard prednisolone (steroid) therapy for the treatment of the initial episode of childhood nephrotic syndrome: national multicentre randomised double blind trial</td>
<td>Dr Peter Heinz</td>
<td>04/07/2011</td>
<td>07/10/2014</td>
<td>Closed (in follow-up)</td>
</tr>
<tr>
<td>PREDNOS 2</td>
<td>Short course daily prednisolone therapy at the time of upper respiratory tract infection in children with relapsing steroid sensitive nephrotic syndrome; the PREDNOS 2 study</td>
<td>Dr Peter Heinz</td>
<td>28/02/2013</td>
<td>01/10/2016</td>
<td>Open</td>
</tr>
<tr>
<td>Prospective Coeliac Disease Diagnostic Evaluation (ProCeDE)</td>
<td>Prospective Coeliac Disease Diagnostic Evaluation (ProCeDE)</td>
<td>Dr Adrian Thomas</td>
<td>02/08/2012</td>
<td>30/04/2014</td>
<td>Closed (in follow-up)</td>
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<tr>
<td>Rare diseases of the bone, joint and vessels Study (RUDY)</td>
<td>Rare diseases of the bone, joint and vessels study (RUDY)</td>
<td>Dr Kenneth Poole</td>
<td>–</td>
<td>31/04/2016</td>
<td>Open</td>
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<tr>
<td>rEEcur</td>
<td>International Randomised Controlled Trial of Chemotherapy for the Treatment of Recurrent and Primary Refractory Ewing Sarcoma</td>
<td>Dr Denise Williams</td>
<td>29/08/2014</td>
<td>30/09/2019</td>
<td>Open</td>
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<td>RMS 2005 (ESSG1)</td>
<td>A protocol for non-metastatic rhabdomyosarcoma</td>
<td>Dr Denise Williams</td>
<td>28/03/2007</td>
<td>31/12/2018</td>
<td>Open</td>
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<td>SIOP CNS GCT II</td>
<td>Prospective Trial for the diagnosis and treatment of children, adolescents and young adults with Intracranial Germ Cell Tumours</td>
<td>Dr James Nicholson</td>
<td>23/10/2012</td>
<td>14/03/2017</td>
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<td>Short study title</td>
<td>Study Description</td>
<td>Cambridge Investigator</td>
<td>Study Start date (where available)</td>
<td>Study Completion Date or Proposed Completion Date (where available)</td>
<td>Activity Status (Jan 2016)</td>
</tr>
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<td>---------------------------</td>
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<tr>
<td>SIOP Ependymoma II</td>
<td>An international clinical program for the diagnosis and treatment of children, adolescents and young adults with ependymoma</td>
<td>Dr James Nicholson</td>
<td>30/04/2015</td>
<td>31/03/2020</td>
<td>In set-up</td>
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<td>The Children’s INterval Appendicectomy (CHINA) Study</td>
<td>A Prospective Randomised Evaluation of Interval Appendicectomy versus Conservative Follow-Up Following Successful Non-Operative Treatment of Appendix Mass in Children</td>
<td>Mr Stephen Farrell</td>
<td>01/06/2011</td>
<td>31/12/2014</td>
<td>Closed (in follow-up)</td>
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<tr>
<td>The I-DSD Registry</td>
<td>The International Disorder of Sex Development Registry</td>
<td>Dr Carlo Acerini</td>
<td>01/03/2015</td>
<td>26/06/2017</td>
<td>Open</td>
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<tr>
<td>The Metabolic Effects of DNA Epimutations in Growth Disorders</td>
<td>The Metabolic Effects of DNA Epimutations in Growth Disorders</td>
<td>Professor David Dunger</td>
<td>24/06/2014</td>
<td>08/01/2016</td>
<td>Open</td>
</tr>
<tr>
<td>TORPEDO-CF</td>
<td>Trial of Optimal Therapy for Pseudomonas Eradication in Cystic Fibrosis</td>
<td>Dr Robert Ross-Russell</td>
<td>01/06/2010</td>
<td>30/09/2016</td>
<td>Open</td>
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<td>TrialNet</td>
<td>Trial net: Natural History study of the development of T1D (US study)</td>
<td>Professor David Dunger</td>
<td>01/11/2011</td>
<td>01/01/2019</td>
<td>Open</td>
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<td>UKALL 2011</td>
<td>UK National Randomised Trial for Children and Young Adults with ALL and Lymphoma 2011</td>
<td>Dr Mike Gattens</td>
<td>12/06/2012</td>
<td>30/04/2019</td>
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</tbody>
</table>
Training and training tools available for research staff undertaking paediatric clinical research studies in CUH include the following:

1. **Research induction training**

   **Introduction for Clinical Research Staff** – a one day training day commissioned by the CUH/BCR R&D department for non-medical staff new to working in a clinical research post on the Cambridge Biomedical Research campus. This training takes place three times a year.

   Course content: Understanding and applying key concepts relevant to clinical research ethics, including NRES approval, consenting and recruiting participants, the law and clinical research, Research Governance, data management & information governance in clinical research, setting up participant study visits, safety reporting. The course is mandatory for honorary research contract holder with the CUH R&D. Advertised via CUH e-mail distribution Network 15.

   Contact: Kornelia Hathaway, Education & Training Manager, Addenbrooke’s Clinical Research Centre (ACRC), email:kornelia.hathaway@addenbrookes.nhs.uk

2. **External Training**

   Accessible via the NIHR CRN Learn webpages [http://learn.nihr.ac.uk/](http://learn.nihr.ac.uk/) requires online registration with NIHR CRN Learn. There is a choice of eLearning and face to face courses

   2.1. Good Clinical Practice training – eLearning course or face to face

   2.2. Informed Consent in Paediatric Research – eLearning

   2.3. Valid Informed Consent Training – face to face

3. **Useful national guidance documents for clinical research staff training**

   Developed in collaboration with staff from the ACRC and utilised by the research staff on the ACRC


   Contact: Kornelia Hathaway, see above


   Contact: Anne Elmer, Senior Clinical Research Sister, ACRC
e-mail:anne.elmer@addenbrookes.nhs.uk

   3.3. **Competency Assessment Template** – Version 1 – July 2014

   Designed to assist staff who have to create competency assessments on specific skills, such as use of a high risk device. Available online: [http://cambridge.crf.nihr.ac.uk/wp-content/uploads/2015/04/Competency-Assessment-Template-no-photo_Vers-1-July-2014.pdf](http://cambridge.crf.nihr.ac.uk/wp-content/uploads/2015/04/Competency-Assessment-Template-no-photo_Vers-1-July-2014.pdf)


   [https://www.rcn.org.uk/development/research_and_innovation/rs/historical-research-society-initiatives/competencies](https://www.rcn.org.uk/development/research_and_innovation/rs/historical-research-society-initiatives/competencies)
4. **Cambridge Clinical Trials Unit (CCTU) Standard Operating Procedures**


These include documents on:

4.1 The early stage of a trial before it can start: planning, protocol development, set-up phase
4.2 Trial documentation
4.3 Pharmacovigilance
4.4 Data management and statistics
4.5 Sampling
4.6 Conduct of a trial
4.7 Closing down a trial – post-study procedures and archiving

Contact: Carolyn Sexton, Quality Assurance Manager, Addenbrooke’s Clinical Research Centre (ACRC), email: Carolyn.Sexton@addenbrookes.nhs.uk

5. **Research and Development Standard Operating Procedures**


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

These documents are specific to the ACRC but could be used as guide to write local procedures:

- ACRC/SOP075 Equipment Management
- ACRC/SOP060 Use of Bench Top Centrifuges
- ACRC/SOP061 Maintenance of Bench Top centrifuges
- ACRC/SOP071 Use of Automatic Pipettes
- ACRC/SOP074 Use of Dry Ice
- ACRC/SOP088 Preparation of Blood Films
- ACRC/SOP069 Transport of Biological Samples
- ACRC/SOP072 Use of the Sartorius Balance
- ACRC/SOP081 Transport and use of Liquid Nitrogen
- ACRC/SOP086 Use of the Biohazard Spill Kit
- ACRC/SOP079 Use of the Class II Safety Cabinet
- ACRC/SOP043 Temperature Monitoring Fridges and Freezers
- ACRC/SOP055 Response in the Event of a Fridge or Freezer breakdown

ACRC documents are available from ACRC staff via Q-Pulse (an online document management system). If copies are required of any of these documents please contact Carolyn Sexton, QA Manager, Addenbrooke’s Clinical Research Centre at: carolyn.sexton@addenbrookes.nhs.uk

7. **Training for clinical research nurses trained in adult care who are employed to undertake paediatric research studies**

Paediatric competency training for clinical research nurses in the ACRC. Face to face training provided by the ACRC paediatric research sister for ACRC staff equipping staff new to working in clinical research studies involving children. Contact: Anne Elmer, Senior Clinical Research Sister, ACRC, tel 01223 596048; email:anne.elmer@addenbrookes.nhs.uk


A guide for adult-trained nurses who facilitate paediatric clinical research studies. Not currently online. Available on request from Anne Elmer, see above.