2020

Paediatric Epilepsy Research Report

Young Epilepsy

Great Ormond Street Hospital for Children NHS Foundation Trust

UCL GREAT ORMOND STREET INSTITUTE OF CHILD HEALTH

Inside

youngepilepsy.org.uk

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Introduction

I am delighted to present our annual research report for the period July 2019 to June 2020 for the paediatric epilepsy research partnership across Young Epilepsy, UCL GOS - Institute of Child Health and Great Ormond Street Hospital for Children.

During this period, we have initiated 15 new research projects, adding to 30 active projects spanning the clinical, educational and social elements of paediatric epilepsy. We have published 62 peer-reviewed items of primary research, 28 reviews and a further 5 chapters in books.

We continue to share expertise with research and clinical colleagues and in January 2020 held our 10th International Paediatric Epilepsy Research Retreat for researchers and collaborators across the unit. This meeting was a wonderful celebration of the work of the unit over the past decade. We enjoyed record attendance as well as welcoming two eminent Research Moderators; Professor Alexis Arzimanoglou of University Hospitals of Lyon, and Professor Mathias Koepp of UCL Queen Square Institute of Neurology. The Retreat brings together early career and seasoned researchers to constructively share their research and forge collaborations.

Young Epilepsy have launched a new strategy which sets our research programme as one of our four key offers. As we further develop the programme under our core values of keeping young people at the centre of our work, working collaboratively and being courageous, we are thrilled to have successfully launched our first two joint funding initiatives with Epilepsy Research UK and Autistica. We have also initiated the first network of parents and young people with epilepsy who have volunteered to consult on, and steer, research. This network has been invaluable in the development of Young Epilepsy's Coronavirus and Epilepsy Experience survey, consultation on the methodology of a major randomised controlled trial and has recruited several members for project/governance steering boards. Through collaboration with other organisations and with the public, we look forward to a more courageous and representative voice for young people reflected in our research.

The successes of the year are thrown into sharp relief when the challenges are considered, such as the impact of Brexit on research funding and collaborations and,

even greater still, the changes to all lives and pursuits due to the COVID-19 pandemic. We are proud to have contributed to the strategies and advice for continuing epilepsy care and research during the pandemic, as well as supporting families during this difficult time.

We have also produced a short separate document, focusing solely on the impact of our research which I hope you will enjoy (see page 7).

Young Epilepsy exists to create a society where children and young people with epilepsy are enabled to thrive and fulfil their potential. A society in which their voices are respected and their ambitions realised. Our research programme exists to establish successively better outcomes by driving early diagnosis and intervention in every aspect of childhood epilepsy.

Professor Helen Cross OBE

The Prince of Wales's Chair of Childhood Epilepsy

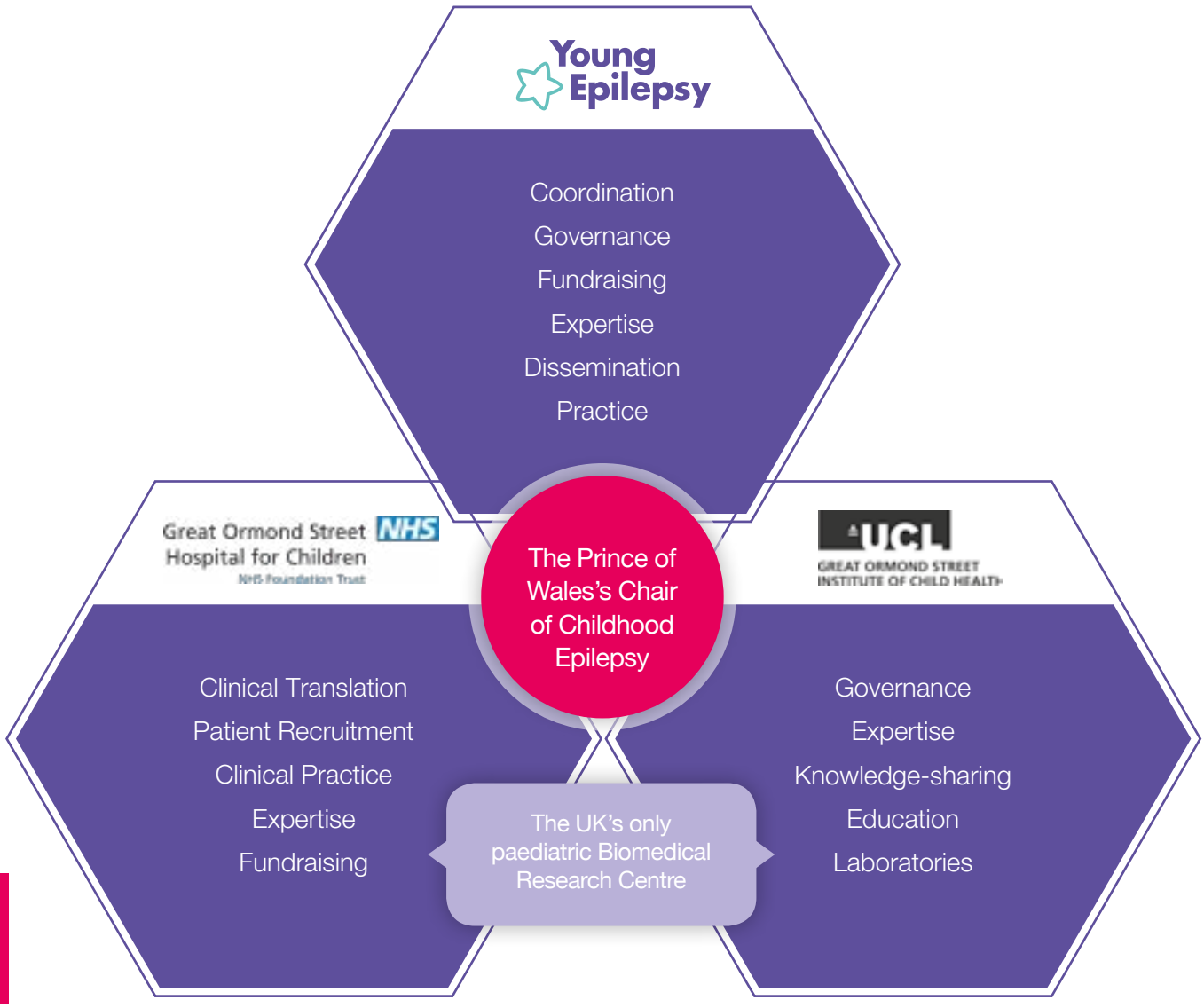
Who We Are

Research Partners

Led by the Prince of Wales's Chair of Childhood Epilepsy, Professor Helen Cross, our research programme is a collaborative scheme between Young Epilepsy, Great Ormond Street Hospital and UCL GOS - Institute of Child Health.

Collaboration and integrated working across the partner organisations puts us in a unique position to incorporate data which spans:

- the entire range of complexity and comorbidity in epilepsy
- all stages of diagnosis and care
- the full age range, from neonates to young adults
- multidisciplinary expertise to improve holistic understanding of epilepsy and service design.



Young Epilepsy exists to create a society where children and young people with epilepsy are enabled to thrive and fulfil their potential. A society in which their voices are respected and their ambitions realised.

Under our four key offers; information, health, learning and research, we aim to:

- equip young people with knowledge and promote public awareness
- drive improvements in healthcare and advocate for young people's right to the highest standards of health
- deliver innovative education services and advocate for young people with epilepsy's right to an education
- coordinate and fund research into the causes, treatments and impact of childhood epilepsy

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Great Ormond Street Hospital for Children (GOSH)

is an international centre of excellence in child healthcare, at the forefront of paediatric training in the UK. Together with UCL GOS - Institute of Child Health, GOSH forms the UK's only Biomedical Research Centre specialising in paediatrics. Most of the children we care for are referred from other hospitals throughout the UK and overseas. There are 63 different clinical specialties at GOSH; the UK's widest range of specialist health services for children on one site. 60% of the UK's epilepsy surgeries are carried out at GOSH.

University College London Great Ormond Street-Institute of Child Health (ICH)

together with its clinical partner Great Ormond Street Hospital for Children (GOSH), forms the largest concentration of children's health research in Europe.

The inspirational mission of the UCL Great Ormond Street Institute of Child Health is to "improve the health and well-being of children, and the adults they will become, through world-class research, education and public engagement".

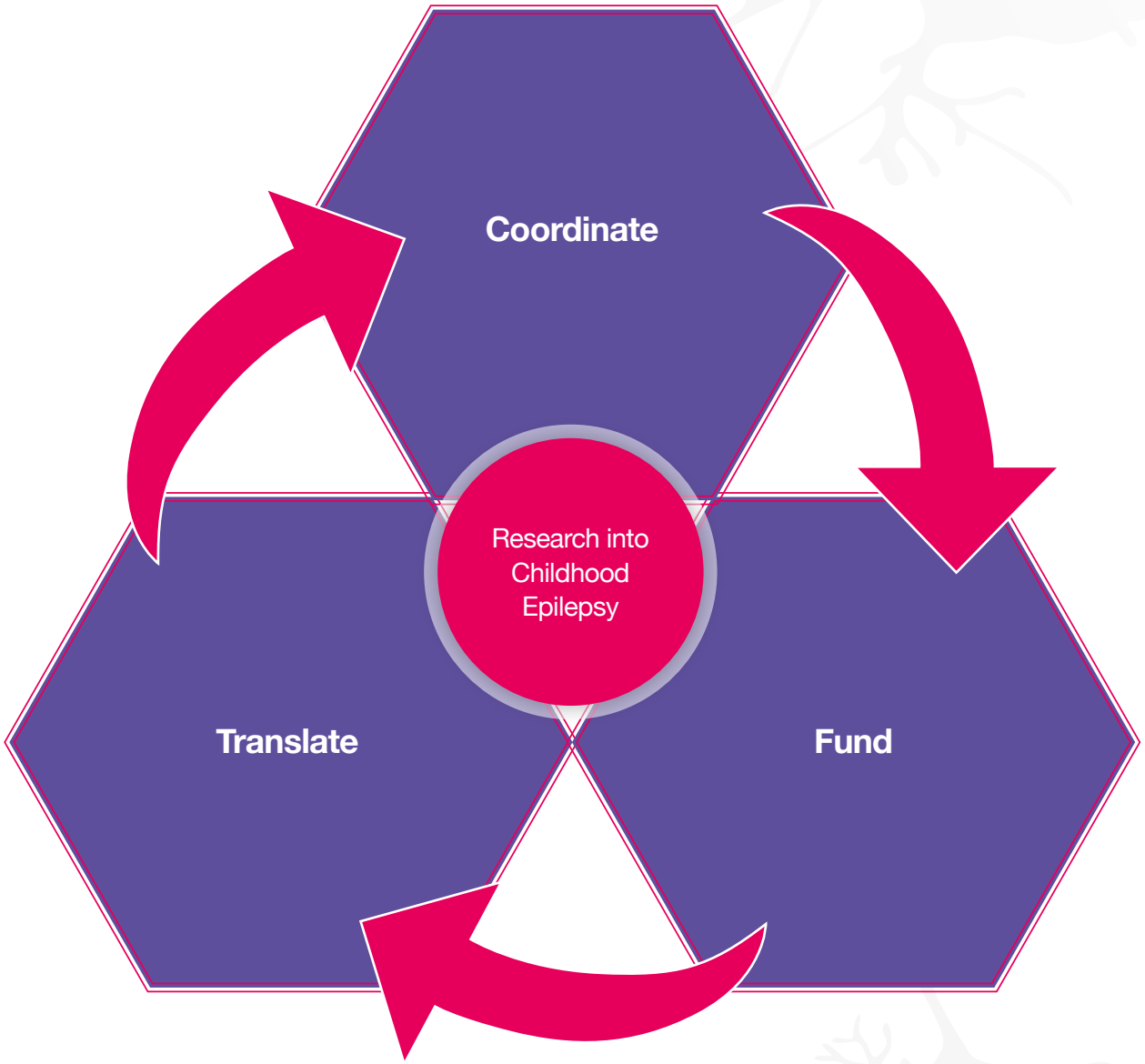
The academic strategy of GOS ICH is focused on five scientific research and teaching departments:

- Developmental Biology and Cancer
- Developmental Neurosciences
- Genetics and Genomic Medicine
- Infection, Inflammation and Immunology
- Population Policy and Practice

What We Do

Research Strategy

Our research programme exists to ensure the best outcome for every child by optimising diagnosis, treatment, and support for all aspects of childhood epilepsy. The programme operates under six strategic goals, organised in three workstreams.



Workstream 1: Understanding Childhood Epilepsies

Around half of people diagnosed with epilepsy never learn the cause of it. This is concerning from both the personal and clinician perspective. The more we know about what causes epilepsy and how the underlying cause is affecting the individual patient, the better clinicians can manage, treat and support the patient to better understand themselves.

GOAL 01

Gain a better understanding of the medical causes of epilepsy

22% projects currently contribute to this goal

The majority of epilepsy treatment is symptomatic. The more we know about the underlying causes of the epilepsies, the more chance there is of developing curative, targeted treatments.

- ✓ Cohort studies to evaluate prevalence, natural history and outcome of comorbidities
- ✓ Experimental animal model studies to examine the effects of epileptiform discharges on development
- ✓ Studies to determine the molecular or genetic basis to the epilepsies
- ✓ Correlative neurophysiology and neuropsychology studies
- ✓ Collaborative outcome studies

GOAL 02

Gain a better understanding of how epilepsy affects development and behaviour

23% projects currently contribute to this goal

Epilepsy is associated with myriad comorbidities. Evidence suggests that the effects of these comorbidities have a greater impact than seizures over the course of someone's life. This work will help us to understand how to treat epilepsy holistically.

- ✓ Cohort epidemiological studies to determine incidence, prevalence and outcome
- ✓ Population and family studies to gain further insights into new treatments
- ✓ Enhanced structural studies using neuroimaging to increase detection of structural correlates
- ✓ Correlative studies in neurophysiology to enhance detection of origin
- ✓ Pathological examination of tissue from surgical specimens to enhance our understanding of structural correlates and related epileptogenesis

Workstream 2: Outstanding Treatment

Epilepsy treatments have not changed very much over time and the process of finding the right combination of treatments for each patient can take a long time. This is very hard on patients, and their families. Continued advancement of imaging, surgery, dietetics, genomics, targeted treatment, and new medicines is therefore crucial in the quest to effectively treat and one day perhaps cure every epilepsy.

GOAL 03

Improving diagnosis and treatment to determine the benefits of early interventions in improving long-term outcomes

28% projects currently contribute to this goal

The longer one has epilepsy, the longer its underlying cause is able to threaten or cause damage. Effective diagnostic processes, optimal treatments and early intervention are vital in slowing or halting any damage.

- ✓ Short and long-term evaluation of outcome following early epilepsy surgery
- ✓ Evaluation of new medical treatments
- ✓ Evaluation of educational intervention
- ✓ Novel diagnostic and imaging methods

Workstream 3: Outstanding Support

This workstream is set to tackle the wider challenges associated with growing up with epilepsy and in treating childhood epilepsies. It is important to know what epilepsy is and how to treat it but if the right systems and supports are not in place to act on this knowledge then patients cannot benefit.

GOAL 04

Gain a better understanding of barriers to learning and determine the benefits of educational interventions.

5% current projects contribute to this goal

We know that epilepsy can affect the way people learn and therefore may significantly affect someone's academic achievement if not properly understood. We want to know exactly what the challenges are and how best to support children with epilepsy in education.

- ✓ Evaluation of measures of progress in children with severe impairments
- ✓ Evaluation and development of targeted educational interventions across all educational settings
- ✓ Evaluating and enhancing the understanding of professionals working with children with epilepsy

GOAL 05

Make life better for children and families and make support systems more effective

18% projects currently contribute to this goal

Childhood epilepsy can affect the whole family and treatment must involve multiple disciplines and agencies. Support for families must be evidenced and treatment pathways must be made more efficient and the family voice should be reflected in research. Evidencing these needs allows service providers to plan more effective services.

- ✓ Patient and public inclusion and representation in research design and management
- ✓ Interventional behaviour programmes
- ✓ Rehabilitation and follow-up studies
- ✓ Assessment of service provision
- ✓ Evaluation of the impact of epilepsy on family life
- ✓ Evaluation of the economic costs involved in epilepsy care

GOAL 06

Develop a network of multidisciplinary professionals to strengthen our research and shape the education of future practitioners

5% projects currently contribute to this goal

To ensure the continuation of excellent research in paediatric epilepsy by nurturing future talent and continually improving knowledge.

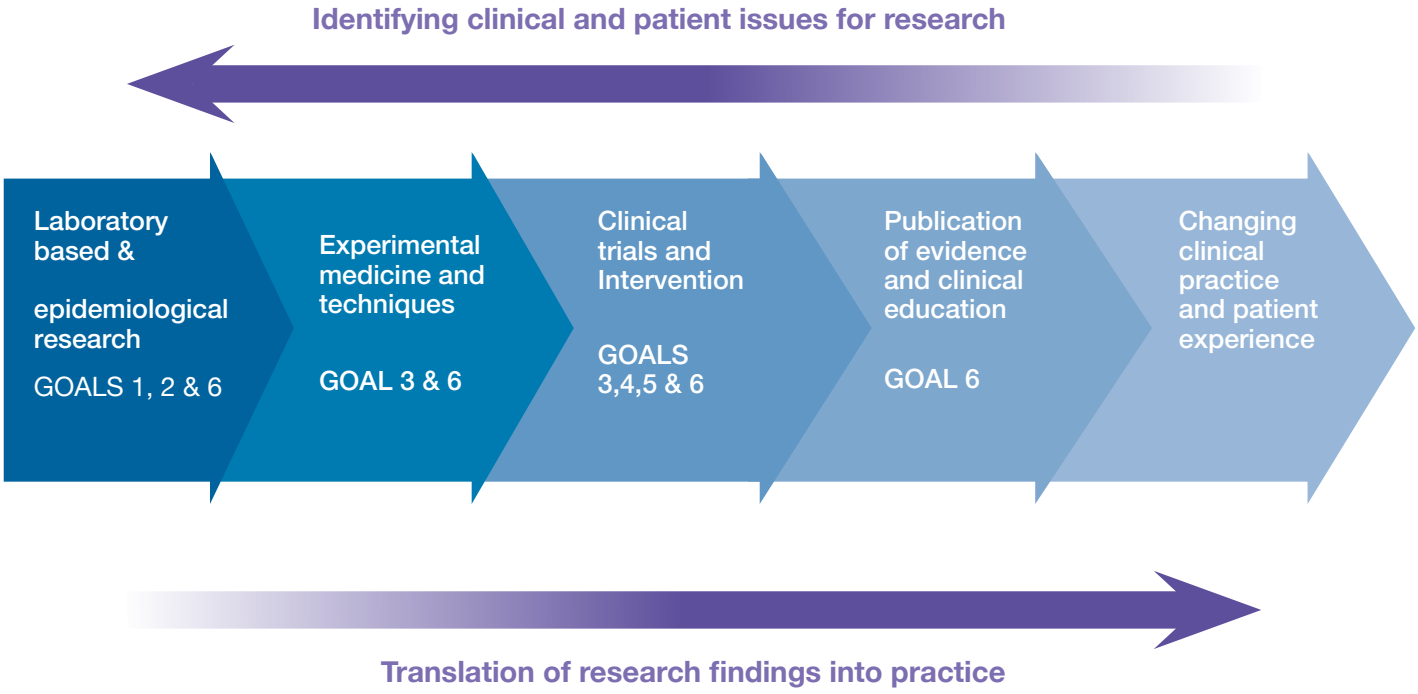
- ✓ Development of training fellowships
- ✓ Projects working towards higher degrees with encouragement for independent working thereafter
- ✓ Joint working between ICH, GOSH and Young Epilepsy
- ✓ Enhancing research and interoperability across all areas of expertise
- ✓ Providing specialist education events and networking opportunities

Research Impact

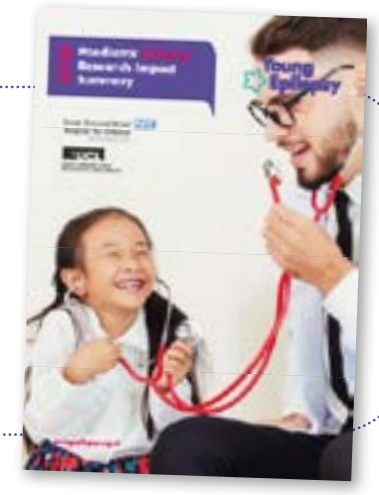
The process

Our research originates from the identification of clinical problems and feedback from patients. Ideas are then developed into project plans for which funding is sought and an expert team assembled. The end result is to publish results as original research which has stood up to the review and critique of independent experts – a process known as peer review. This ensures robust evidence on which we can implement changes and/or conduct further research.

The diagram below illustrates the cyclical relationship between, identifying the clinical and patient issues for research, and then translating the research findings in practice.



This year we have published a stand alone Research Impact Report which covers the impact of research across the partnership in greater detail. This is available online and in print from Young Epilepsy.



Past Impact

Some of the key achievements of the research partnership to date

2001

Appeal to fund Europe's first Chair in Childhood Epilepsy Launched by Young Epilepsy, UCL GOS – ICH and GOSH with support from HRH The Prince of Wales

2004

Professor Brian Neville appointed of first incumbent of The Prince of Wales's Chair of Childhood Epilepsy

Overseen research in **NEW NEUROIMAGING TECHNIQUES** which has resulted in an increase in the number of children considered for epilepsy surgery

Identified significant **SLEEP DIFFICULTY**, and risk levels for **STRESS, ANXIETY AND DEPRESSION IN MOTHERS** of children with epilepsy

LAUNCH OF YOUNG EPILEPSY'S EDUCATION RESEARCH PROGRAMME to highlight the impact of epilepsy on learning and the urgent need to develop new strategies and interventions

Overseen several studies determining outcomes from epilepsy surgery and promoted surgery as an intervention both nationally and internationally

Hosted a **DARZI FELLOWSHIP**, jointly with UCL-ICH, UCL Partners and Whittington Hospital NHS Trust. **IDENTIFIED CRITICAL GAPS IN CARE PATHWAYS** and developed national recommendations for future provision of epilepsy services

Established a **SUCCESSFUL EUROPEAN REFERENCE NETWORK,** a network of centres specialising in care of individuals with rare and complex epilepsies across Europe

Established the first evidence base for the use of the **KETOGENIC DIET** (a high fat, low carbohydrate diet) and widened its use in children and infants with drug resistant epilepsy

Contribution to the **DEVELOPMENT, AND HOSTING OF, THE WORLD'S FIRST WEARABLE MAGNETOENCEPHALOGRAPHY (MEG) SYSTEM FOR CHILDREN,** in collaboration with UCL Institute of Neurology, Magnetic Shields Ltd and the University of Nottingham

Pilot work in the health economics of epilepsy strongly illustrated the need to explore further the real cost of childhood epilepsy in order to aid service provision and commissioning

Research into how **SLEEP** and **DEVELOPMENT** contribute to a better understanding of the causes of cognitive impairment in epilepsy

Professor Helen Cross OBE appointed The Prince of Wales's Chair of Childhood Epilepsy

2008

Contribution to the **EPILEPSY12 NATIONAL AUDIT**

Ground-breaking research evidencing the extent of **EDUCATIONAL DIFFICULTIES** and the high rate of cognitive and behavioural problems in school age children with epilepsy

2009

Opening of award-winning Neville Childhood Epilepsy Centre in Lingfield, which hosts our rehabilitation, diagnostic, and assessment services

Epidemiological studies into the **INCIDENCE, CAUSES, TREATMENTS AND IMPACT OF EPILEPSY IN INFANCY**

Participated in the national commissioning of the **CHILDREN'S EPILEPSY SURGERY SERVICE (CESS)**

Contributed to the **DEVELOPMENT** of **BUCCAL MIDAZOLAM** (one of the most widely used emergency epilepsy medications) and implemented training on its administration

First annual Young Epilepsy Paediatric Epilepsy Research Retreat held to foster national research collaboration

2011

Established vital genetic collaborations through gene discovery and contribution to cohort studies

Professor Helen Cross becomes the first woman elected, in its 100+ year history, to President (2021-2025) of the International League Against Epilepsy

Demonstrated that **REAL IMPROVEMENTS** can be seen with long-term follow-up, in relation to **SEIZURE FREEDOM AND WEANING FROM MEDICATION** following epilepsy surgery

Continued **DISCOVERY OF NEW GENETIC CAUSES** of epilepsy in collaboration with UCL Institute of Neurology

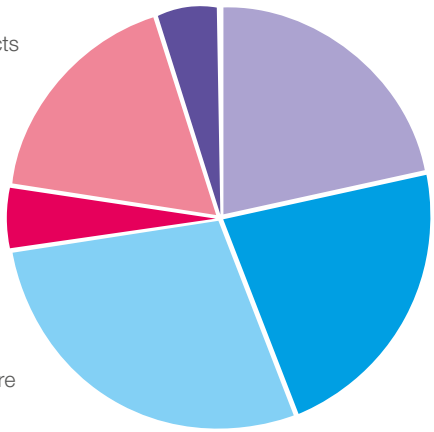
2019

Current Impact

Key outputs of the partnership between July 2019 and June 2020:

45 live research projects

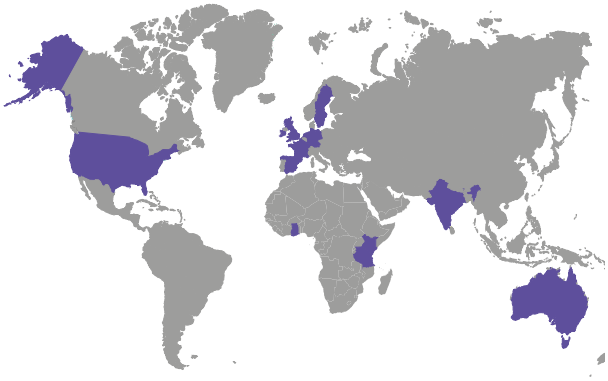
- 22% of projects contributed to the medical causes of epilepsy
- 23% of projects contributed to understanding how epilepsy affects development and behaviour
- 28% of projects contributed to improving diagnosis, treatment and early intervention
- 5% of projects contributed to a better understanding of barriers to learning and the benefits of educational interventions
- 18% of projects contributed to making life better for children and families and support systems more effective
- 5% of projects contributed to developing a network of multidisciplinary professionals to strengthen our research and shape the education of future practitioners



34 Principal Investigators
(senior leaders of research)

19 PhD students

37 international active Research Collaborators

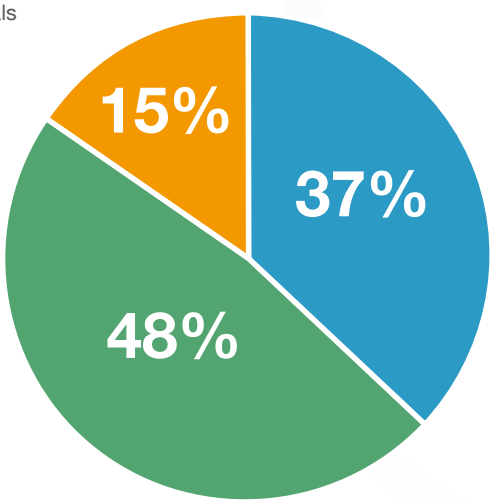


Geographic reach of Principal Investigators and Active Collaborators

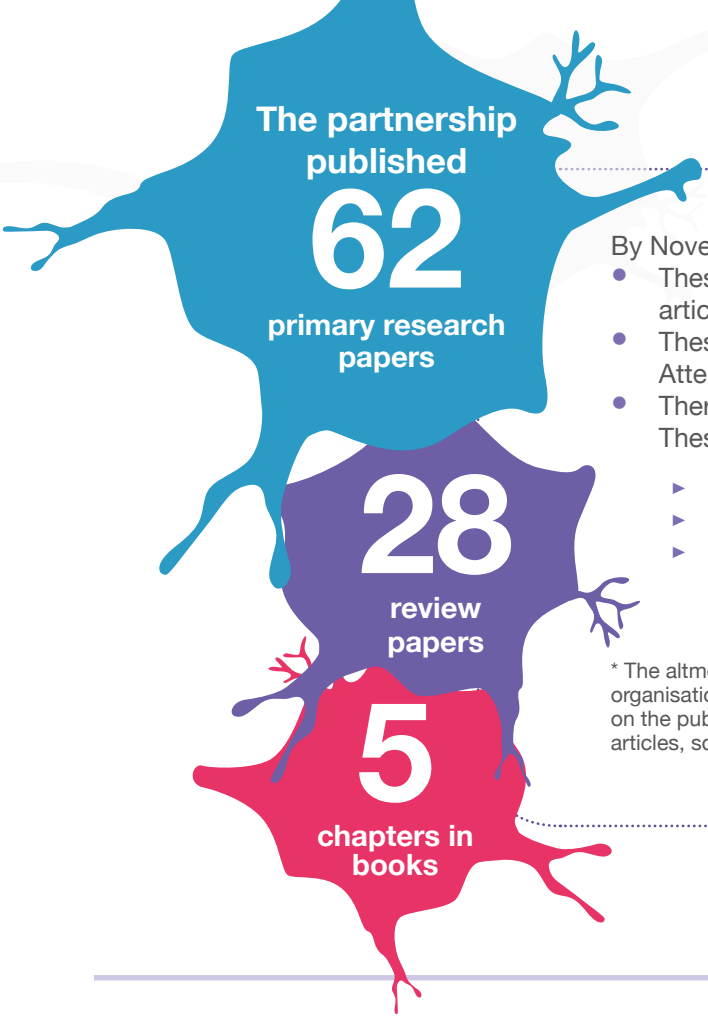
Percentage number of projects contributing to each workstream

(weighted by number of goals per workstream)

- Workstream 1: Understanding Childhood Epilepsies
- Workstream 2: Outstanding Treatment
- Workstream 3: Outstanding Support



Over
£24million
secured in funding across the partnership



By November 2020

- These papers had been cited by a further 989 research articles
- These research papers had achieved the highest Altmetric Attention score* of any year of work produced by the team
- There were nine high impact papers underlying this success. These papers:
  - are cited in a further 847 research publications
  - were referenced in 5 international policy documents
  - mentioned by 455 international news outlets, 167 blogs, 4214 Tweets, 35 Facebook pages, across more than 70 countries

* The altmetric attention score is produced by an independent bibliographic data organisation, Dimensions (**https://app.dimensions.ai/**), and is calculated based on the public attention that an individual publication has received across news articles, social platforms, and policy documents.

Young Epilepsy was delighted to announce our first joint funding initiatives for epilepsy research:

EPILEPSY RESEARCH UK & YOUNG EPILEPSY FELLOWSHIP AWARD

£300,000 Fellowship Award for research into childhood epilepsy to be awarded in 2021 by Epilepsy Research UK and Young Epilepsy

Young Epilepsy AUTISTICA Epilepsy Research UK

epilepsy and autism joint award

£30,000 to create a dossier of evidence to better understand autism Awarded in 2020 by Autistica, Young Epilepsy and Epilepsy Research UK

Held the 10th and largest Annual Paediatric Epilepsy Research Retreat to date – with 106 researchers coming together to share knowledge and discuss 34 projects

Established the UK's first patient involvement network for childhood epilepsy research with nearly...

140 members

Conducted important research into the experiences of people with epilepsy during the COVID-19 restrictions in the UK

Translation of research outcomes into the development of the **Young Epilepsy Online Guide for Schools** **youngepilepsy.org.uk/guide-for-schools/**

Researcher and research supported content published on **The Channel**, Young Epilepsy's online information resource for young people with epilepsy **thechannel.org.uk**

What's Next?

Looking to the future of childhood epilepsy research three key themes emerge which are strongly aligned to our Workstreams:

Genetic Revolution

Advances in genetics over the past decade have brought us closer than ever to understanding the causes of almost every epilepsy. 40% of people with epilepsy never know what causes their epilepsy and this can mean identifying the right treatment is a challenge. This number is even higher in early-onset and childhood epilepsies. Almost all the unknown causes of epilepsies are likely to be genetic in origin. The better we understand the origin, the better we can positively impact the pace and effectiveness of treatment. It is important to understand that a genetic cause of epilepsy very rarely means that it was inherited from a parent. The great majority of genetic epilepsies are caused by changes in a person's genetic make-up which happened within that individual and was not inherited.

Targeted Treatment

Apart from surgery and ketogenic diet therapies, all epilepsy treatment is symptomatic. This means it does not treat the cause or alter the condition, it relieves symptoms such as seizures. With the recent advances in imaging and genomics we have started to develop treatments which target the cause of the epilepsy such as more advanced surgery and gene therapy.

Expertise Without Borders

As the understanding and treatment for epilepsy advances, so must the support networks to deliver new learning to patients. Not all hospitals, regions and countries have the same opportunities to support the epilepsies, and so borderless collaboration is vital to maximise the outcomes for all children, and young people with epilepsy. The European Reference Network for Rare Epilepsies - EpiCARE, initially led in the UK by Professor Cross and now by Professor Arzimanoglou in Lyon, brings together experts from 43 highly specialised health centres across 24 European countries and they can each contribute to the care of individual cases.

Research Projects

This section outlines the new, ongoing, and competed projects between July 2019 and June 2020.

The projects are presented under the workstream they most contribute to. They have coloured, numbered ‘neurons’ in the top right corner which illustrate all of the goals to which they contribute. Each project also features a ‘What this means?’ box which gives a summary of the work and intended impact. You can look up more details about each project team in the Researchers section.

New Projects

Workstream 1- Understanding Childhood Epilepsies

Functional effects of *SCN1A* mutations – New insights from biophysics and computational modelling

Project Aim: Linking functional properties of SCN1A miss-sense mutations with their resultant phenotypes

Investigators: Richard Rosch, Elaine Hughes, Kathleen Gorman, Colin Peters, Peter Ruben

Summary: Changes to the gene *SCN1A* is one of the most thoroughly investigated genetic causes of epilepsy. This gene controls sodium channel functionality – a critical component of cell structure. Yet even within the well-known *SCN1A*-related epilepsies, new phenotypes are still emerging, and the complexities of genotype-phenotype relationships remain only partially understood. We combine biophysical measurements of the functional properties of the sodium channel variants found in patients with epilepsy, with computational modelling of neuronal function to understand better how different miss-sense mutation in the same gene – *SCN1A* – result in a wide range of phenotypes.

What this means: Even when patients have apparently the same genetic mutation, there are still differences within the individual. This is because whilst we may have identified the cause of a particular epilepsy – such as a genetic mutation – we still might not understand exactly how it works or how each part of the mechanism of that gene/mutation results in the particular epilepsy syndrome of each patient.
By investigating in detail, the effects of specific mutations in a single gene, we hope to improve our understanding of the effects of genetic mutations in individual patients, and ultimately improve our treatments for each patient individually.

Shining a light on the genetic basis of Sunflower Syndrome

Project Aim: Investigate the genetic basis of this rare photosensitive epilepsy

Investigators: Amy McTague, Manju Kurian

Summary: Sunflower Syndrome is a rare, photosensitive epilepsy, named for sun-seeking behaviour or stereotyped reflex seizures in bright light. Affected patients have many hand-waving episodes per day (the patient waves their hand in front of their own eyes and this stimulates a seizure). Hand-waving episodes are resistant to treatment and significantly impair quality of life. Children with Sunflower Syndrome also experience other seizure types including absences, eyelid and other myoclonias and generalised tonic clonic seizures. Sunflower Syndrome is often associated with significant neurodisability; many patients have co-morbid learning difficulties, autistic spectrum disorder, attention deficit hyperactivity disorder, anxiety and depression.
There remain a number of unanswered questions including whether the hand-waving episodes represent a reflex seizure or compulsive self-induction of seizures. We have established an international cohort of patients including families with significant family history and will undertake trio whole genome sequencing which will be analysed using Ingenuity and Alamut software, initially for known disease-causing genes followed by analysis for copy number variants and novel genes using differing inheritance models. Putative variants will be validated by Sanger sequencing and functional validation of likely disease-causing variants will be undertaken.

What this means: Sunflower Syndrome is a rare photosensitive epilepsy characterised by self-induction of seizures in children. We don't yet know what causes Sunflower Syndrome but we believe it has a genetic basis and we will be looking at an international cohort of patients and sequencing their entire genome alongside their biological parents. We will cross reference this with known epilepsy causing genes, against variations of these and will look for previously unknow epilepsy causing genes. Short-term findings of this study will immediately improve the current genetic screening for epilepsy. We hope the long-term findings will reveal causal genes - giving a strong basis on which to develop targeted treatment for this condition.

Modelling childhood genetic epilepsies in zebrafish larvae

Project Aim: Identifying whole-brain network dysfunction at single neuron resolution in larval zebrafish models of genetic epilepsies

Investigators: Richard Rosch, Dominic Burrows, Jade Lau, Martin Meyer

Summary: There are many limitations to what we can understand about epilepsy from measuring its effects in humans, or the commonly used rodent models with the available recording methods. Zebrafish larvae offer a unique perspective in that they are transparent and small enough in size so that they allow whole-brain calcium imaging at single cell resolution during epileptic seizures. Zebrafish are a novel experimental model for the investigation of some of the most severe epilepsy syndromes of childhood, with the future potential to guide and trial novel therapeutic approaches for translation into human patients.
In this research project we identify and characterise whole-brain abnormalities in genetic models of childhood epilepsies at single cell resolutions, in order to identify novel treatment strategies for some of the most complex epilepsy syndromes.

What this means: We are using Zebrafish larvae instead of mouse models to better understand some of the most severe genetic epilepsies of childhood. Zebrafish larvae are transparent, and this means we can see how each brain cell is functioning. This level of resolution will allow a much greater understanding of the brain networks involved in these complex epilepsies and lead to new, targeted, treatments.

Epilepsy Dossier: Autism and epilepsy: laying out the evidence

Investigators: Colin Reilly, Sophie Bennett, Roz Shafran, Amy McTague, Emma Dalrymple, David Skuse, Neha Batru, Eleni Zarakoviti

Project Aim: Undertake a systematic review of factors associated with the occurrence of epilepsy in individuals with autism

Summary: Epilepsy is a common co-occurring condition in people with autism. We will systematically review quantitative and qualitative studies which have focused on the health economic aspects of living with both autism and epilepsy. We will focus on the lived experience of individuals which allows us to consider the social, educational, human and economic costs of having both conditions. Data from the systematic reviews will be combined with data from PPI groups to create a dossier. The Dossier will be a written report and consist of insights from PPI groups, synthesis of data/evidence from the systematic reviews and synthesis of economic data. The Dossier will identify the key issues with respect to the management of epilepsy in autistic individuals, highlight key studies and identify the main gaps in the current research literature. The needed next steps/milestones in research/practice will be outlined creating a baseline from which future research and practice innovations can be evaluated.

What this means: We will review current evidence surrounding the impact of having both epilepsy and autism and will combine this evidence with data from patient focus groups to present a dossier of what we know so far about having both conditions. This will then be used to identify gaps in the knowledge and provide direction for future research.

Autism spectrum disorder (ASD) and epilepsy

Project Aim: The assessment of autism for children with complex epilepsy poses many challenges; from fluctuating profiles to diagnostic overshadowing and atypical presentations. This project reviews the issues involved by drawing on more than 20 years' experience of neurodevelopmental assessment of children with complex epilepsy at GOSH.

Investigators: Harriet Holmes, Francesca Sawer, Maria Clark

Summary: Lots of the behavioural and communication weaknesses of autism are also commonly present in children with epilepsy. However, the trajectory of these difficulties over time and fluctuating nature of the developmental profile, is often very different to "typical" ASD and in our experiences, can often mirror the fluctuations of epilepsy, leading us to question its formal classification.

The uniqueness and rarity of the presentations we see, means that making a child's difficulties understandable and accessible/treatable often means using mainstream diagnoses such as autism which may not be the best fit. We aim to explore issues around assessment, confounding comorbidities and high-risk groups as well as exploring challenges faced by families. We aim to publish the findings as a practice paper.

What this means: We will review the challenges in diagnosing autism in children with epilepsy experienced over 20 years at GOSH to try to learn whether there is a more effective model to support children with epilepsy who present also with symptoms of autism.

Neuro-LinK: Determining long-term outcomes in children with chronic neurological conditions (ICH Data science initiative)

Aim: Determine the long-term health outcomes of children treated at GOSH in three well-defined cohorts via data linkage with The Hospital Episode Statistics (HES) database

Investigators: Jessica Pickles, Deborah Ridout, Torsten Baldeweg, Darren Hargrave, Thomas Jacques, Katie Harron, Vandana Ayyar Gupta, Francesco Muntoni

Summary: We are interested in obtaining long-term outcome data, including hospital admissions and education outcome, for children with neurological conditions such as brain tumours, Duchenne Muscular Dystrophy and epilepsy surgery candidates. In particular, we are interested in those patients with neurological chronic disease who manage their condition over extensive periods, often require multiple interventions and may receive several forms of treatment. We will engage with PPI groups to discuss our project aims. Their feedback and advice will be instrumental in developing our application to seek approval.

There is a clear absence of long-term clinical outcomes associated with large paediatric cohorts, hindering the translation of research findings to our patients' life course and their expected clinical progression of disease. The project is aiming to access health outcomes for specific patient groups to appreciate the extent of the burden of disease for patients both during and after receiving their primary care at GOSH.

What this means: There is not enough information of the long-term outcome trajectory of children with chronic neurological conditions. We want to truly understand the burden of such conditions on patients so that we can better understand how to manage and treat them within the NHS.

Workstream 2- Outstanding Treatments

Children's Epilepsy Surgery Service (CESS) network stereoelectroencephalography (SEEG) outcomes

Aim: Assess the outcomes of children undergoing SEEG across the UK

Investigators: Aswin Chari, Rachel Thornton, Martin Tisdall & the entire CESS SEEG team

Summary: SEEG involves inserting between 5-20 carefully planned electrodes as part of the pre-surgical evaluation in children with difficult-to-localise epilepsy. We have conducted a national study across the CESS networks to identify outcomes and predictors of outcome in these children. Across 6 centres, we analysed 125 SEEG implantations in 121 children, identifying factors that were associated with identifying a seizure onset zone and subsequent good outcome following surgery. It is hoped that such work will better inform our selection, SEEG planning and interpretation to improve outcomes in these children.

What this means: The purpose of pre-surgical planning in epilepsy is to identify the epilepsy causing part of the brain (epileptogenic area) and understanding how this part of the brain impacts on the rest of the brain. SEEG is one of the procedures used in pre-surgical evaluation to find the epileptogenic area. We will look at past data to determine the most successful factors for SEEG electrode placement and improve practice.

MELD (Multi-centre Epilepsy Lesion Detection) as an Adjunct for SEEG Trajectories (MAST) trial

Aim: Assess the utility of a novel machine learning algorithm in helping to plan electrode trajectories in children undergoing stereoelectroencephalography (SEEG)

Investigators: Sophie Adler, Konrad Wagstyl, Aswin Chari, Zubair Tahir, Martin Tisdall

Summary: This clinical trial is a pilot study aimed at assessing the utility of a locally developed machine-learning lesion detection algorithm in planning SEEG electrode trajectories. It is a rare prospective study of novel artificial intelligence technology and aims to recruit 20 patients over the next 2 years.

Prior to setting up the trial, we assessed whether the algorithm may have been useful in previous SEEG cases and found that many of the lesions identified corresponded to where the seizures arose from. Interestingly, in 3/34 cases, a seizure onset zone was not found on SEEG and the algorithm identified lesions that were not being targeted.

What this means: We hope to show how useful a novel artificial intelligence software (that we developed at ICH) is at improving the detection of abnormalities associated with epilepsy. We are starting with a first stage 'pilot' study to get a better idea of how we can use it and ensure it is safe before deciding on whether or not we should conduct a larger study. At the time of writing, we have already recruited 4 patients to the study!

Early surgery for radiologically evident focal cortical dysplasia

Aim: Assess the proportion of children with a radiologically evident focal cortical dysplasia that become medication resistant and subsequently undergo surgery

Investigators: Ido Ben Zvi, Noelle Enright, Aswin Chari, Christin Eltze, Martin Tisdall, Helen Cross

Summary: Surgical treatment for children with drug-resistant epilepsy due to a focal cortical dysplasia is an established treatment. There is evidence that the duration of epilepsy can influence outcomes and therefore, earlier treatment may be beneficial. We sought to assess the natural history of focal cortical dysplasia, including the proportion of patients that become drug-resistant, those that go on to have surgery, their outcomes and safety of treatment.

What this means: We want to establish whether having surgery earlier in the disease, i.e. before drug resistance is established, is safe and has further benefit than later surgery (post- drug resistance).

Wearable magnetoencephalography (MEG) at Young Epilepsy

There are three new projects under this programme.

MEG Project 1: The Young Epilepsy Diagnostic Suite

Investigators: Rosemarie Pardington Gareth Barnes, Helen Cross, David Woolger, Richard Bowtell, Matthew Brookes, Tim Tierney, Torsten Baldeweg, Konrad Wagstyl, Richard Rosch

Summary: Our flagship project which brings the Neville Childhood Epilepsy Centre at Young Epilepsy and research programme together in a world-leading clinical innovation for children and young people with epilepsy.

The new Diagnostic Suite will offer upgraded electroencephalogram (EEG), sleep telemetry and home telemetry services alongside the world's first wearable Optically Pumped (OP) magnetoencephalography (MEG) unit within a lightweight magnetically shielded room (Mu-Room). The overarching goal of the Young Epilepsy Diagnostic Suite is to offer world leading clinical neuroimaging technology in a comfortable and seamless environment for patients and their families.

Currently MEG is a neuroimaging tool which is of very limited availability to children and young people with epilepsy, due to the equipment expense, weight, maintenance cost, fixed sensor location, intimidating aesthetic and the need to be perfectly still during the investigation. The OP-MEG and lightweight Mu-Room system overcomes each of these barriers to clinical use – chiefly the need to stay still. For the first time, MEG is now a clinically feasible tool in the diagnosis and surgical evaluation of children and young people with epilepsy – particularly those with complex needs who cannot tolerate other forms of neuroimaging such as EEG or magnetic resonance imaging (MRI).

MEG measures minute changes in the magnetic fields within the brain to create detailed images of brain function, and for the first time, during movement. In children, OP-MEG is more than 10 times more sensitive than current MEG systems and offers an entirely new avenue of clinical neuroimaging and brain function research. This increase in sensitivity is largely due to the sensor's placement in a wearable helmet next to the scalp, rather than in a fixed, adult sized hood, allowing freedom of movement within the shielded room.

The lightweight magnetically shielded Mu-Room is a novel design with the aim to make this technology feasibly affordable for healthcare facilities. The first lightweight Mu-Room is currently being installed in the Neville Childhood Epilepsy Centre at Young Epilepsy.

The team will pioneer the use of this technology in paediatric epilepsy as well as a central laboratory for initiatives exploring applications beyond epilepsy.

The primary outcome of this project is to provide clinicians with a novel technology which informs earlier and more accurate interventions for children with epilepsy. Epilepsy has enormous impact on a person's life and is usually present with additional developmental needs. The longer a child has uncontrolled seizures, the more likely there will be an impact in the longer term. Early, accurate intervention is critical to improving patient outcomes and quality of life in childhood epilepsy. As the hosts of the first wearable OP-MEG and lightweight Mu-Room system, the Young Epilepsy Diagnostic Suite will become the centre from which best practice is developed, demonstrated and disseminated to visiting clinicians, practitioners, commissioners and the public, with the needs and voices of children and young people with complex needs at its centre.

As well as the obvious benefits to clinical practice, Young Epilepsy are planning to schedule time for the new facility to be available for future research projects into the wider use of this innovative technology.

MEG Project 2: Moving functional brain imaging into the real world

Aim: Work with children with epilepsy, their parents, carers and teachers, to co-produce child-friendly appealing and engaging brain scanning technology and procedures for the new OP-MEG scanners

Investigators: Gareth Barnes, Cassandra Hugill, Mark Lim, Tim Tierney, Stephanie Mellor, George O'Neill, Hefin Jones, Amy Muggeridge, Rosemarie Pardington

Summary: We will work with children with epilepsy, their parents, carers, and teachers; researchers, and clinicians to coproduce, design and implement child-friendly wearable scanners, interactive games/tasks within the room. We are developing this for the new OP-MEG system at Young Epilepsy and for future services to draw upon this learning.

We are working alongside an artist and designer, to run several diverse focus groups, workshops and interactive sessions for different cohorts of children and their families/carers. We will use the feedback from these sessions to design and build prototype room designs, interactive tasks and scanner helmets to be used in a clinical setting.

We hope to demonstrate that, through engagement, this project increases our ability to effectively scan very young children within a stimulating environment. Our success will be measured through compliance rate and typical scan duration achievable for the child patients in the new OP-MEG system at Young Epilepsy.

What this means: We hope to codevelop the right activities and aesthetics and protocols to ensure that the scanning experience is engaging, tolerable and successful for children.

Project 3: Development of a lifespan compliant magnetoencephalography system

Aim: Build an OP-MEG system for children aged 0-15years, that will offer direct clinical applicability, increased practicality, better data, and lower cost compared to current systems.

Investigators: Matthew Brookes, Richard Bowtell Gareth Barnes, Helen Cross, Rosemarie Pardington

Summary: Conventional MEG systems use sensors that are cryogenically cooled and fixed in a one-size-fits-all helmet. Performance is limited by a gap between the head and sensors, which is larger for infants, greatly reducing sensitivity. Further, movement relative to the sensors causes dramatic reductions in data quality (even 5mm movements render data unusable). For these reasons, conventional MEG is inadequate for infants.

The new OP-MEG sensors do not rely on cryogenics. They are small, lightweight, and can be mounted on the patient's head within a helmet. Because the sensors are closer to the head, OPMs afford vastly better performance, and removing cryogenics results in a much cheaper system. Based on this, we now have a unique opportunity to develop a MEG scanner for infants.
In this project we will look to solve the issues of different sensor arrangements according to head size and develop appropriate, tolerable helmets for the new wearable OP-MEG system.

What this means: The different head sizes of children and infants present a challenge to MEG scanning and we hope to develop a series of appropriate, comfortable and tolerable helmets for children aged 0-15 years.

Workstream 3 – Outstanding Support

Epilepsy Carers Uniting with Researchers (E-Cure) PPI network

Aim: Strengthen the voice of children and young people with epilepsy in our research by establishing the UKs first network of parents, carers and young people who volunteer to shape childhood epilepsy research

Investigators: Amy Muggeridge, Samantha Chan, Amy McTague, Helen Cross

Summary: The sole purpose of the network is to consult on the development of research ideas, methodologies, and delivery to ensure research reflects the true needs of patients and families. Members choose their level of participation and interests. Roles for members can be as simple as participating in surveys, up to becoming formal members of project management groups as patient representatives. The network currently has almost 140 members.

What this means: Working with patients and their families is critical to the success of research. This network is a key component of research design across the unit.

Epilepsy Pathway Innovation in Africa (EPInA)

Aim:

- Diagnose: improve the rate of accurate diagnosis of epilepsy by refining app-based technologies
- Treatment: increase the adherence to medication using text messaging
- Societal change: ensure an enduring, positive change by improving public awareness and reducing the stigma experienced by people with epilepsy in sub-Saharan Africa.
- Prevent: reduce the incidence of infection and peri-natal injury in an endemic region in Tanzania and the subsequent risk of epilepsy

Investigators: Charles Newton, Helen Cross, Arjune Sen, David McDaid, Albert Akpalu, Damazo Kadengye, Gershim Asiki, Patrick Adjei, Sloan Mahone, Symon Kariuki, Tarun Dua, Thomas Kwasa, Mohammed Mnacho, John Geddes, Josemir Sander, Richard Walker, William Matuja

Summary: Epilepsy is one of the most common serious neurological conditions and is particularly widespread in sub-Saharan Africa (SSA). This high incidence is, in at least a quarter of cases, because of preventable factors, yet many people who may have had seizures are not diagnosed and even fewer receive appropriate treatments. These factors are compounded by enduring social stigma that can make it hard for Africans with epilepsy to obtain employment, form relationships or feel valued. We have chosen to work in three countries – Ghana, Kenya and Tanzania. We will bring together work across all three countries to better understand the history of epilepsy, investigate why people with epilepsy are so disadvantaged and then set out to improve things. We will develop an app to help healthcare workers to better diagnose epilepsy, and pilot a text messaging scheme to help people to remember to take their medication. We will train local people in epilepsy care and develop epilepsy healthcare specialists to lead future projects. In Tanzania, which has a higher incidence of epilepsy, possibly due to onchocerciasis infection, we are also going to see if reducing the rate of onchocerciasis infection can lower the number of people with epilepsy.

What this means: By implementing measures to improve the prevention, diagnosis, treatment and cultural understanding of epilepsy, we think this project can dramatically change the lives of people with epilepsy in sub-Saharan Africa. If successful we will use all that we learn to ensure similar work is carried out across other low-income countries.

Ongoing Projects

Workstream 1- Understanding Childhood Epilepsies

The neuropathology of focal epilepsy in children

GOAL 01

Project Aim: To understand the biology underlying the diseases that cause focal epilepsy.

Investigators: Tom Jacques, Helen Cross, Martin Tisdall, Darren Hargrave

Update: We are focussing on brain tumours and on malformations of cortical development. This is leading to changes in our diagnostic practice for children undergoing epilepsy surgery and is improving our understanding of how these diseases develop.

What this means: This is a group of new projects which aim to define the causes of focal epilepsy. This work is vital to obtaining faster, more accurate diagnoses and also to improving and developing successively better treatment options. Currently, most epilepsy treatments are symptomatic and focus on seizures. We need to understand more about what causes epilepsy to be able to develop and offer curative rather than symptomatic treatment.

Effect of paroxysmal events in early onset neurological disease on cerebral tissue oxygenation & metabolism: a NIRS pilot study

GOAL 01

Project Aim: To better understand energy consumption during epileptic seizures.

Investigators: Helen Cross, Aikaterini Vezyroglou, Ilias Tachtsidis, Rachel Thornton, David Carmichael

Update: We are using broadband Near Infrared Spectroscopy (bNIRS) to investigate the changes of oxygenated and deoxygenated haemoglobin, as well as of cytochrome c oxidase during epileptic seizures alongside EEG. As cytochrome c oxidase is part of the mitochondrial respiratory chain, any changes in cytochrome c oxidase during epileptic events might be a biomarker of energy consumption during seizures. We designed headgear to record bNIRS simultaneously with routine EEG and recruited 15 patients to this pilot study. We were lucky to capture seizures in 9 patients. Analysis of our bNIRS and EEG data during repeated seizures in one of our patients showed a significant increase in blood oxygenation adjacent to the epileptic focus and a significant decrease in cytochrome c oxidase in the region of the epileptic focus. This might indicate a relative brain tissue hypoxia and energetic deficiency in the region of the epileptic focus during seizures.

This project has been delayed by the COVID-19 pandemic and data analysis in further patients is ongoing.

What this means: We are investigating how the bNIRS, and especially the cytochrome c oxidase measurement, is affected during an epileptic seizure. Better understanding of energy consumption during seizures will help us understand how seizures affect the brain in the long term.

Memory profile and reorganisation after epilepsy surgery in children with intractable Temporal Lobe Epilepsy (TLE)

Project Aim: The project aims to 1) characterise the memory profile of children and young people with TLE as well as their post-surgical memory outcome and 2) depict functional and structural reorganisation of memory networks in temporal lobe epilepsy before and after surgery, using functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI) magnetic resonance. We hope this may help to refine the prognostic accuracy of the preoperative workup, guide neurosurgical resection, and reduce the risk of memory impairment after surgery.

Investigators: Filipa Bastos, Faraneh Vargha-Khadem, Helen Cross, Jonathan Clayden, Sarah Buck

Update: Medically intractable temporal lobe epilepsy (TLE) is the main indication for epilepsy surgery in both adults and children and yields good outcome regarding seizure freedom. However, due to the medial temporal lobe's central role in memory, long-term memory and learning, difficulties are reported in patients with TLE.

Routine pre-operative memory assessment in children with TLE consists of behavioural testing with protocols with suboptimal sensitivity to detect deficits in the paediatric population.

Furthermore, memory lateralisation predictions are extrapolated from language lateralisation even though the interdependence of these two functions in children is not well documented, particularly in children with temporal lobe pathology.

This project involves memory testing using an application on a tablet developed by Sarah Buck as well as undertaking an MRI. Patients are seen before surgery and again 4 and 12 months after surgery.

Patient recruitment, which was due to continue until Spring 2020, was cut short in February 2020 because due to the COVID-19 pandemic. Patient follow up is currently on hold for the same reason. We hope to be able to resume patient follow up in the Spring of 2021, and hopefully present results during the second trimester of 2022.

What this means: We want to ensure that children with TLE undergoing surgery will have the best possible outcomes with regard to their memory function. To do this we have developed an app-based test to be used by the child, alongside MRI imaging which will help us to better understand how memory works and is organised in the brains of children rather than relying on evidence from adult research. This will enable much more accurate understanding of how the surgery could affect an individual and therefore, thus continually improving the process of surgical evaluation.

The genetics of early onset epileptic encephalopathy

Project Aim: The project aims to identify novel early onset epileptic encephalopathy genes which will contribute to the understanding of the disease mechanisms involved in such epilepsies.

Investigators: Amy McTague, Helen Cross, Dimitri Kullmann, Rod Scott, Manju Kurian

Update: Investigation of this cohort is ongoing and our results have led to several publications including a Gene Reviews summary of *SLC12A5* and a review of the genetic landscape of epilepsy-dyskinesia. In addition, we have taken part in an international cohort study on the genetics of Epilepsy of Migrating Focal Seizures of Infancy and have identified a novel gene for epilepsy-dyskinesia, *CACNA1B.*

What this means: We want to know what has caused the epilepsy so we can better understand the processes in the brain that have gone wrong. We hope to use some new treatments for these processes that might not only apply to this rare epilepsy but also to some more common epilepsies. Recently, we have identified a new gene which causes both a severe early onset epilepsy and a movement disorder.

A natural history of Pyruvate Dehydrogenase Complex deficiency

Project Aim: To describe the natural history of Pyruvate Dehydrogenase Complex (PDC) deficiency from childhood to adulthood, including the spectrum of molecular diagnoses in affected patients in order to identify genotype/phenotype correlations and predictors of poor prognosis.

Investigators: Nandaki Keshavan, Shamima Rahman

Summary: PDC deficiency is one of the most common mitochondrial disorders. Patients with this condition develop a combination of problems including seizures, neurodisability and have a reduced life expectancy. It is essential to understand the mechanisms underlying the disease in order to identify new treatments, and to understand the natural history of disease in order to prepare for clinical trials. To date, a natural history study of PDC deficiency has not been undertaken in the UK. In collaboration with the Freya Foundation and tertiary paediatric metabolic and neurology centres nationally, we will undertake a multicentre retrospective study to describe the spectrum of symptoms, disease severity, molecular diagnosis, management and outcomes in both children and adult patients with PDC deficiency. We will then collate the data and analyse it to determine whether there are any correlations between clinical/laboratory findings and outcomes.
We will also biobank patient blood samples for future multi-omic studies in order to elucidate pathophysiological mechanisms.

What this means: We want to understand what are the predictors of poor outcomes in patients with PDC deficiency by undertaking the first natural history study of PDC deficiency in the UK. It is important that we understand how patients are currently being treated at different tertiary centres to inform best practice. At present we know little about the mechanisms that cause disease symptoms and in future aim to investigate this further in hope that we may be able to identify new effective treatments.

Epilepsy in Infancy: relating phenotype to genotype (EPIPEG)

Project Aim: To identify and follow-up a cohort of children with new onset of epilepsy under 12 months of age to enable definition of neurobehavioural phenotypes; identify risk factors for neurodevelopmental problems and later intellectual disability; determine novel genetic mutations as a cause for early onset epilepsy, and relate to clinical presentation.

Investigators: Helen Cross, Manju Kurian, Rod Scott, Christin Eltze, Finbar O'Callaghan, Michelle De Haan, Elaine Hughes, Jane Kung, Manuela Pisch, Katy Barwick, Aikaterini Vezyroglou

Summary: We received 185 referrals, of these 163 were eligible and a further 119 were recruited to the assessment arm of the study. We are currently investigating the genetic aetiologies in patients from the study suspected to have an underlying disorder of genetic origin. A cohort of patients were recruited for whole exome triome analysis. To date, several genetic diagnoses (e.g. SCN-related genes, *PRRT2*) have been established in approximately 15% of the cohort. Variants of unknown significance in known epilepsy gene, requiring further evidence for proof of pathogenicity have been reported in 42%, and analysis for novel mutant genes is ongoing in 43%. We plan to collect developmental follow up data from the 119 recruited participants in as and begin to establish a long term data set or these individuals.

What this means: We have been looking at children following first presentation with seizures from the EPIPEG cohort. In some patients, we suspect that their epilepsy may be 'genetic', that is related to a fault or spelling mistake in their genetic makeup. We've investigated a number of children now and so far, found a genetic problem in 1/6 of the cases. We want to understand the specific areas of need in the early onset epilepsies and how to spot the earliest possible signs of epilepsy so that we can better help families know what to expect, and help doctors to understand what to look for and treat. Many people with epilepsy never learn what causes their epilepsy, which is why we are looking at the child as a whole, including a wide range of genetic testing to find an answer. Research like this aims to understand the unknown causes of epilepsy in the hope of paving the way to new and better treatments. This project will provide the basis for a longer study, which will follow these children as they grow up.

Novel network analysis of intracranial stereoelectroencephalography (SEEG)

Project Aim: To characterize interictal abnormalities in single unit neural dynamics and to establish whether the regions that display abnormal dynamics are consistent with the epileptogenic zone.

Investigators: Rod Scott, Martin Tisdall, Aswin Chari, Rachel Thornton

Summary: Epilepsy surgery is a neurosurgical operation to remove parts of the brain that generate seizures. A proportion of children being evaluated for surgery have electrodes inserted into their brains as part of their clinical assessment, termed stereoelectroencephalography (SEEG), to help localise these regions. Subsequent surgery is not always successful - up to 40% of children will have ongoing seizures 5 years after surgery.
The purpose of this study is to assess the utility of specially designed SEEG electrodes which can measure signals from single brain cells. These electrodes record the same clinical information as normal SEEG electrodes and are implanted in the same way, but can give the research team extra information at the same time. The investigators aim to assess whether studying the changes in the firing of individual cells, both during and between seizures, improves our ability to localise seizures and therefore improve outcomes following surgery. This study will be carried out in children undergoing invasive recordings as part of evaluation for epilepsy surgery. The project has gained ethical approval and, over the course of late 2019 and 2020, has recruited 4 patients. The project's progress has been slow due to a number of technical challenges involved in recording these signals and the temporary pause on intracranial recordings necessitated by the COVID-19 pandemic but we look forward to making progress in the near future with some new equipment and new strategies!

What this means: We want to know if data gathered during and between seizures can improve the use of SEEG electrodes to find the epileptogenic region.

Multiscale modelling of epileptic networks from SEEG recordings

Project Aim: Epilepsy surgery aims to change epileptic brain networks in a way that will reduce the likelihood of future seizures. In this project we aim to use state of the art network modelling approaches to characterise these epileptic brain networks from intracranial EEG recordings, and in future help in predicting the effects of surgical intervention on those networks.

Investigators: Richard Rosch, Rachel Thornton, Martin Tisdall, Karl Friston, Ulrich Stoof

Summary: Resective surgery is an effective treatment for many focal epilepsies. Yet epilepsy is increasingly understood to be a disorder of brain networks, with abnormal brain activity emerging not from the isolated activity of individual regions, but from concerted activity of many coupled sources. Understanding this integrated epileptic network is far from intuitive – even apparently simple networks can show complex dynamics that are difficult to predict.
Computational models may offer a strategy to improve our understanding of epileptic networks. In this project, we are fitting computational network models of neuronal coupling to stereotactically recorded intracranial EEG (SEEG). Through the use of computational models, we are able to test what the network organisation that underlies epileptic dynamics on the SEEG is. This can be done at the level of microcircuits around focal brain abnormalities (e.g. looking at local coupling between tuber cores and peritubular cortex in tuberous sclerosis patients), and at the level of whole brain circuits (e.g. identifying whole-network changes after interventions in patients undergoing therapeutic radiofrequency thermocoagulation).
A new PhD student has been appointed with funding awarded by the Oakgrove Foundation to develop the computational tools necessary for this analysis.

a disorder of networks across the brain rather than the result of a single disruptive section. This means that entire networks must be considered when evaluating someone's suitability to undergo epilepsy surgery. This project sets out to really understand the workings of these networks so that the pre-surgical team can have a better grasp of the effect that any surgery, however relatively 'simple' may have on a person's functioning.

Landau-Kleffner syndrome: Patterns in the recovery phase

Project Aim: A retrospective case note review examining cognitive and language trajectories across different phases of Landau-Kleffner syndrome (LKS).

Investigators: Maria Clark, Christina Hawkins, Gemma Wilson, Harriet Holmes

Summary: LKS is a rare epilepsy which has an active phase, characterised by the loss of language skills and a distinct sleep EEG abnormality, referred to as Continuous Spike and Wave in Sleep (CSWS) or Electrical Status Epilepticus during Sleep (ESES). The active phase is followed by the recovery phase which continues for many years but in that time a child may regain skills. We have been asked to write a practice paper about LKS for the Paediatrics and Child Health Journal.

What this means: We are investigating past data to better inform future management and treatment of LKS.

Non-invasive modulation of brain network dynamics to suppress epileptic activity and improve cognition (EPICONN TM)

Project Aim: A pilot study to measure a reduction in epileptiform activity associated with transcranial electrical stimulation (TES). We look to modulate brain connectivity and understand its relationship to epileptiform activity reduction. We hypothesise that in epilepsy brain networks can be targeted by weak electric fields applied to the scalp (TES) to modulate the brain's connectivity to reduce epileptic activity.

Investigators: David Carmichael, Frederike Moeller, David Sharp, Helen Cross, Mirja Steinbrenner, Martin Tisdall, Mark Richardson, Ines Violante, Rory Piper

Update: This project is funded by an ERUK pilot grant to commence study in patients with Juvenile Myoclonic Epilespy. We have obtained first data in a few patients just before COVID struck and are analysing the results as the basis for larger research grants.
Rory piper a surgeon training in Oxford performed a research placement investigating thalamic connectivity in epilepsy with us and has recently been awarded a PhD to continue to work with us.

What this means: We want to know more about how non-invasive electrical stimulation of the brain affects the brain and how this may be used to control seizures. We know surgery is not always successful and not everyone responds to antiepileptic drugs (AEDs). This project looks at a pioneering, and cost effective, new treatment as an addition or alternative to surgery/ASMs.

Neurodevelopment in Hypothalamic Hamartoma

Project Aim: To review the developmental profiles of children with hypothalamic hamartoma in relation to their medical presentation and treatment.

Investigators: Hanna Richardson, Leah Bull, Varsha Siyani

Summary: Hypothalamic hamartoma is a rare epilepsy caused by a benign tumour-like formation on the hypothalamus. The growth causes very difficult to control seizures, early puberty and developmental and cognitive problems. Children with hypothalamic hamartoma have high levels of comorbidity and their profiles can change over time. The behavioural impact can be very severe and there are plans to look at this further with neuropsychiatry at GOSH.
We conducted a case note review of children with hypothalamic hamartoma to better understand how their development links to their medical presentation and treatment.

What this means: The more we understand about how hypothalamic hamartoma affects development, the better we will be able to treat all aspects of the condition. This is particularly important in cases where we are unable to remove the hamartoma by surgery.

Workstream 2- Outstanding Treatments

Modelling neuronal dysfunction in early onset epilepsies; a patient-centric approach

Project Aim: We have three overarching aims:

- To create and characterise a patient-derived induced pluripotent stem cell (iPSC) organoid model of Epilepsy of Infancy with Migrating Focal Seizures (EIMFS).The creation of patient-derived cerebral organoids will enable study of the effects of the mutations in their native neuronal and genetic milieu. Fibroblasts from patients with *SLC12A5, KCNT1* or *SCN2A* mutations have been transformed into induced pluripotent stem cells (iPSCs) and are being differentiated into cerebral organoids. Currently we are validating organoids for layer specific and regional markers of neuronal identify and maturity. In the next year patient lines will also be differentiated into medial ganglionic eminence-like organoids containing interneurons, which will be fused with the cerebral organoids.

- To investigate the neuronal phenotype of EIMFS at a cellular and network level A number of assays will be undertaken to investigate disease mechanisms including Western blotting and immunofluorescence to assess cell surface expression, patch clamping and multi-electrode array analysis to assess impact on channel and transporter function, multi-electrode array analysis to measure network formation and single-cell RNA sequencing to evaluate gene expression differences.

- To investigate the impact of novel therapies. We will use a gene therapy approach or antisense oligonucleotides to rescue the phenotype as an initial proof of concept. If successful, these approaches will be developed in future funding applications.

Investigators: Amy McTague, Dimitri Kullmann, Gabriele Lignani, Jenny Lange, Manju Kurian

Summary: In Epilepsy of Infancy with Migrating Focal Seizures (EIMFS), affected babies have very frequent seizures, often up to sixty per day, which usually do not respond to currently available medications. Abnormalities in three genes, known as *KCNT1, SLC12A5* and *SCN2A* can cause EIMFS. These genes make important proteins in the brain that, when abnormal, cause seizures in young babies. However, it is not clear how they lead to epilepsy. Using a new state-of-the art brain cell model made from skin cells taken from patients in the study, we will investigate how abnormalities in these genes lead to epilepsy and developmental problems in patients. Skin cells from each patient will be converted into stem cells. Stem cells have the potential to convert into any of the cell types in the body. The stem cells will be converted into three dimensional structures, or organoids, which after maturation for several months will be made up of layers of neurons. If we can work out precisely how the abnormal genes cause seizures, this may help us identify better drugs for both this form of epilepsy and other epilepsies.

What this means: We want to improve our understanding of how these abnormal genes lead to epilepsy and development problems which will help in the development of new treatments, with the ultimate aim of improving quality of life for patients and their families.

The infant baby enrichment research programme (ENRICH)

Project Aim: To explore the possibility of measuring the cortical response from the scalp of infants using standard non-invasive EEG techniques, due to the activation of C Tactile (CT) afferents and how the cortical response changes in regard to age.

Investigators: Ronit Pressler, Geraldine Boylan

Update: A total of 24 infants were recruited into the study, of which 20 attended both somatosensory nervous system pathway (SSEP) assessments at 4 weeks and 4 months of age and developmental assessments at 4 months. Group analysis of potentials during gentle stroking did not reveal a clear reproducible response. We are currently improving the test protocol and aim to test a further 20 infants. This second phase will be conducted in Cork, Ireland.
ENRICH was run by UCC (Cork) and GOSH was involved in a small part which was called Gentle Touch – evaluating the cortical response to gentle touch (like stroking or massage) using evoked potentials. We finished the clinical part but unfortunately were not able to see a clear response. This was probably due to technical problems, so UCC had planned to take this further by using our data to make changes to the recording set up but this was impossible due to COVID-19 pandemic.

What this means: This study seeks to understand how responses in the brain to certain sensory stimuli are developed over the first four months of life. We want to understand whether if a pleasant touch is administered to a baby's forearm in the supine and prone positions, will we observe a cortical response, and if so, can it be recorded and how does it develop over time.

A multicentre, open-label, single-arm study to evaluate the pharmacokinetics, efficacy, and safety of Brivaracetam in neonates with repeated electroencephalographic seizures (PETITE)

Project Aim: The purpose of the study is to evaluate the pharmacokinetics of Brivaracetam in neonates who have seizures that are not adequately controlled with phenobarbital treatment and to identify the optimal Brivaracetam dose (Exploratory Cohort) for the treatment of subjects enrolled into the Confirmatory Cohorts of this study.

Investigators: Ronit Pressler, Marios Kaliakatsos

Update: PETITE is a European, UCB Biopharma-led neonatal study exploring the efficacy of Brivaracetam. The study has now been set up and at present 6 sites are active across Europe (two UK sites - GOSH and Cambridge) and we have recruited our first participant.
The 'Exploratory Cohort' will receive a low dose of Brivaracetam intravenous (iv) solution for injection following one or multiple therapeutic doses of midazolam. 3 additional iv Brivaracetam doses, up to a total of 4 can be administered during the 48-hour Evaluation Period.
The dose and dosing frequency of Brivaracetam will be adjusted for the 'Confirmatory Cohorts' based on the analysis of the data collected for the Exploratory Cohort.
The study has now successfully included 5 babies (within Europe) and concluded the exploratory phase. The study has been reviewed by the Data Management Committee and they approved the start of the confirmatory phase which will start in 2021. GOSH will not be recruiting but UCLH will.

What this means: We are working with UCB Biopharma to understand the best way to use Brivaracetam in newborn babies with seizures who do not respond to Phenobarbital.

Is pyridox(am)ine 5'-phosphate oxidase deficiency, an eminently treatable cause of epilepsy, under-recognised in children?

Project Aim: Improve diagnosis and treatment of children with pyridox(am)ine 5'-phosphate oxidase (PNPO) deficiency by using a novel rapid screening dry blood spot assay.

Investigators: Peter Clayton, Philippa Mills, Helen Cross, Ronit Pressler

Update: This project has been granted ethical approval and is currently awaiting funding before work can begin. The COVID-19 pandemic has delayed progress.

What this means: The research team has developed a new, quick test to check if someone has an epilepsy disorder called pyridox(am)ine 5'-phosphate oxidase (PNPO) deficiency which responds to treatment with vitamin B6. We want to see how employing this test in clinical practice improves the diagnosis and treatment of children with PNPO as it is often overlooked. Early detection and treatment with vitamin B6 will help to prevent disability. We also hope this study may uncover other causes of epilepsy which may benefit from vitamin B6 treatment.

Ketogenic diet in Infants With Epilepsy (KIWE)

Project Aim: Determine the effectiveness on seizure control of the ketogenic diet compared to alternative further antiepileptic drug treatment.

Investigators: Helen Cross, Laura Lyons, Sally Halsall, Natasha Schoeler, Maryam Balogun, Christin Eltze, Simon Heales, Helen McCullagh, Rachel Kneen, Tim Martland, Jeen Tan, Andrew Mallick, Andrew Lux, Alasdair Parker, Helen McCullagh, Archana Desurkar, Penny Fallon, Helen Basu, Anita Devlin, Rajib Samanta, Shakti Agrawal, Manish Prasad, Rohini Rattihalli, Elma Stephen, Andreas Brunklaus, Martin Kirkpatrick, Ailsa McLellan, Nick Freemantle, Louise Marston, Irwin Nazaret

Update: Since last year we have received 2 extensions for KIWE from the National Institute of Health Research (NIHR) which allow us to continue the study until 30 June 2021. We have opened 6 new sites, so now have a total of 18 centres open across England and Scotland. We have recruited 119 patients to date, and aim to get as close as possible to the project's original 160 patient target.

What this means: We want to know if the ketogenic diet is an effective treatment for infants with drug resistant epilepsy.

The "Pair Test": an App to diagnose learning and memory impairments in children with Temporal Lobe Epilepsy

Project Aim: The aims are to 1) provide better informed diagnosis of memory impairments in children with epilepsy and 2) predict outcome after surgery in the temporal lobe, using the Pair Test.

Investigators: Sarah Buck, Torsten Baldeweg, Filipa Bastos, Faraneh Vargha-Khadem

Update: The "Pair Test" uses a tablet-based paired-associate learning paradigm to disentangle impairments in different memory processes, and different components of the neural network within the medial temporal lobes. The test provides behavioural evidence regarding the functional integrity of the hippocampi and their interaction with the neocortical learning system. The Pair Games can be used to (a) diagnose the status of memory and learning, (b) monitor progression of disease, (c) assess the efficacy of pharmacological and/ or surgical interventions by providing pre- and post-treatment measures of function. Overall, the test provides better informed diagnoses than standardised tools, with more precise indication of the types of memory deficits and the underlying processing impairment.

What this means: The Pair Test is an app-based tool which will better help clinicians understand the type and complexity of learning and memory problems in children with Temporal Lobe Epilepsy (TLE). For instance, we may know that someone has trouble with their memory but we don't know if this is one memory problem or several. This test helps clinicians to see the full picture. They hope that this will not only lead to better support and treatment but also to make a more accurate predictions of how epilepsy surgery may affect someone's learning and memory.

Optimisation and bioperformance of a novel formulation of pyridoxal 5'-phosphate for treatment of pyridox(am)ine 5'-phosphate oxidase deficiency induced epilepsy in children

Project Aim: To test the efficacy of a new treatment for children with pyridox(am)ine 5'-phosphate oxidase deficiency induced epilepsy.

Investigators: Catherine Tuleu, Peter Clayton, Philippa Mills, Emma Footitt, Ahad Rahim, Simon Heales

Update: Some children have a specific type of epilepsy, called pyridox(am)ine 5'-phosphate oxidase deficiency induced epilepsy, which can be treated with a form of vitamin B6 called pyridoxal-5-phosphate (PLP). However, the current medication is not ideal. PLP is only available as a nutritional supplement in tablet or capsule forms. Unlike pharmacy-only medicines, this product is not regulated and can be problematic for clinical use. It is difficult to prepare and administer, unpalatable and unstable. Additionally, our preliminary data has shown that there is a high risk of inaccurate dosing and when mixed in water, these products are not stable, forming compounds that may be dangerously toxic to the liver. We have developed a more stable, formulation and have evaluated the purity and taste of this new drug. We are currently evaluating whether this product meets the safety requirements (i.e. not liver toxic) for administration to humans.
This work has been delayed by the COVID-19 pandemic, and we are still evaluating the new formulation having done some toxicity studies in mice models.

What this means: We hope to produce a tolerable and regulated formulation of PLP which will improve both safety and quality of life for children who are taking PLP.

Antisense oligonucleotides for the treatment of *ALDH7A1*-deficiency

Project Aim: A proof of principal project to show that antisense oligonucleotide therapy can prevent the accumulation of the toxic metabolites that occur in patients with a-aminoadipic semialdehyde dehydrogenase (*ALDH7A1*) deficiency, a vitamin B6-dependent epilepsy disorder.

Investigators: Philippa Mills, Haiyan Zhou, Paul Gissen

Summary: Humans rely on vitamin B6 for the proper functioning of their nervous, endocrine and immune systems. They are not able to make this micronutrient themselves and must therefore get it from their diet. There are many different dietary forms of vitamin B6 which our bodies convert to the active form of this vitamin. This is known as pyridoxal phosphate (PLP). PLP is essential for enzymes involved in metabolism of proteins, fats and carbohydrates to work properly.
Whilst a dietary deficiency of vitamin B6 is rare, there are several genetic disorders which result in insufficient PLP within the cells of the body. PLP plays an important role in the brain therefore children with these disorders present with epilepsy.
The most common of these epilepsy disorders occurs when there are mutations in a gene that is responsible for making an enzyme called a-aminoadipic semialdehyde dehydrogenase. This enzyme is involved in the pathway which converts lysine, an amino acid which is present in the food we eat, into energy. Mutations in this gene result in an accumulation of metabolites which interact with PLP thereby reducing the amount of PLP available for the brain. The resulting epilepsy can be treated by giving supraphysiological doses of vitamin B6.
Unfortunately, the compounds that accumulate, besides interacting with PLP, are also toxic to the brain. This toxicity results in intellectual disability and developmental problems. Treatment with B6 does not correct this. One way of preventing the accumulation of these compounds is to restrict the amount of lysine in the child's diet. Children do not like this diet and the improvements seen have only been partial. Better treatments are therefore needed.
We will investigate the use of antisense oligonucleotides as a way of preventing an accumulation of these toxic compounds in this disorder.
We are currently looking to see if we can patent the work we have been doing but the COVID-19 pandemic has caused delays.

What this means: We are looking to develop a more tolerable treatment for *ALDH7A1*-deficiency.

Workstream 3 – Outstanding Support

European Reference Network on rare and complex epilepsies (EpiCARE)

EpiCARE is a European Reference Network (ERN) for rare and complex epilepsies, coordinated by Professor Alexis Arzimanoglou, Director of the Epilepsy, Sleep and Paediatric Neurophysiology Department at the University Hospitals of Lyon, France. Advances in brain scanning as well as genetic and metabolic investigations have determined an increasing number of causes behind epileptic seizures, resulting in the description of more than 130 rare diseases.
The European Reference Networks (ERNs) were launched in 2017. They involve more than 900 highly specialised health care teams, located in more than 300 hospitals in 26 European countries. The main mission of the ERNs is to help patients with rare or low-prevalence complex diseases.
The ERN EpiCARE brings together highly specialized health centres (28 full members and 15 affiliated partners) in 24 European countries with expertise in rare and complex epilepsies. The centers closely collaborate with the scientific societies (ILAE, EAN, EPNS, Epilepsy Alliance Europe) and a number of other epilepsy teams in the EU with expertise in specific domains. EpiCARE offers a coordinated approach for epilepsy diagnostics and treatment by using e-tools and cross-country e-consultancy.

One of 24 approved ERNs on rare disorders, EpiCARE aims to improve access for patients to diagnostic and therapeutic expertise, by engaging multidisciplinary experts through the network.

EpiCARE aims to:

- improve accessibility of detailed diagnostics to individuals of all ages with rare and complex epilepsies across Europe, including clinical evaluation and investigation
- develop treatment protocols and monitor standardised outcomes of rare and complex epilepsies
- improve awareness and accessibility to protocols for physicians and individuals with rare and complex epilepsies across Europe for treatment
- enhance educational activities and training opportunities across Europe by interchange across the network
- enhance opportunities for registries, and collaborative research for the benefit of individuals with rare and complex epilepsies across Europe

Multicentre Epilepsy Lesion Detection (MELD) Project

Project Aim: Create open-access, robust and generalisable tools for understanding and detecting focal cortical dysplasias (FCDs) that can assist the pre-surgical evaluation of patients with drug-resistant epilepsy.

Investigators: Sophie Adler-Wagstyl, Kirstie Whitaker, Armin Raznahan, MELD consortium,Helen Cross, Torsten Baldeweg, Konrad Adler-Wagstyl

Summary: The MELD project has created the largest neuroimaging cohort of FCDs to date, including data from over 580 patients and 380 controls. Using this unique dataset alongside statistical and machine-learning techniques, we are currently working on 3 projects: 1) Mapping the distribution of FCDs across the brain and creating predictive models of lesion location and seizure freedom. 2) Linking the distribution of FCDs across the cortex to the underlying brain structure. 3) Creating machine-learning algorithms to automatically detect FCDs on MRI scans.

What this means: Through the MELD project we hope to better understand this important cause of medication-resistant epilepsy and create tools that can be used to inform clinical decision making. These include predictive maps of lesion locations, deep-learning tools for the detection of FCDs and models for the prediction of post-surgical seizure freedom. These tools will be validated on data from 20 hospitals and will be made openly accessible for any hospital to use when evaluating a patient with a suspected FCD.

Prevention of Epilepsy by reducing Neonatal Encephalopathy (PREVENT) study

Project Aim: Our aim is to examine if a care bundle approach to improve the maternal care around delivery will reduce the number of babies sustaining serious birth related brain injury and epilepsy.

Investigators: Sudhin Thayyil, Helen Cross, Ronit Pressler, and many more

Summary: Led by Imperial College London, the PREVENT study is the world's largest study on babies with brain injuries. Brain injury during labour or childbirth is one of the leading causes of epilepsy in babies. The proportion of babies sustaining serious brain injury around the time of birth (40 per 1000 livebirths) in public sector hospitals in India is 10 times higher than that of the UK. Approximately 12 million people with epilepsy live in India. Although epilepsy is not curable in most cases, by reducing birth related brain injury and substantial number of these cases can be prevented. In many cases, this can be prevented by simple, evidenced based and low-cost interventions tailored to the local needs. Our aim is to examine if a care bundle approach; a series of simple and interventions administered consistently, which includes intelligent foetal heart rate monitoring, an e-partogram, brain oriented neonatal resuscitation, and birth companions, will improve the maternal care around delivery will reduce the number of babies sustaining serious birth related brain injury and epilepsy.
We have assembled a team of experts in neonatal brain injury and neuroimaging, obstetrics, midwifery, qualitative research, epilepsy, global health, electrophysiology, care bundle development, health economics, public health, statistics, implementation research from leading academic centres in the UK and India, along with parent representatives to undertake this work.
The study will be conducted over 4 years in two adjacent public sector hospitals in Tamil Nadu, India, where the total number of babies sustaining birth related brain injury is the same as the total UK annual burden of birth related brain injury. During the first year of the study, we will collect accurate base-line data on brain injury, and develop and pilot the care bundle. The care bundle will be then implemented during the second year, and the outcome evaluated during the 3rd and 4th years. The main outcome is to assess whether the proportion of babies (per 1000 live births) developing birth related brain injury is different before and after the introduction of this care bundle. We will also examine and compare the number of infants that develop epilepsy by their first birthday before and after the introduction of the care bundle.
We will compare our findings with data from 44 nonparticipating public sector hospitals to identify any natural reduction in the incidence of brain injuries. Finally, we will examine the views of the stakeholders and cost-effectiveness of this care bundle for adoption into the national health policy in India.

What this means: There is a high incidence of epilepsy in India due to complications during birth. We want to address the issues surrounding safe childbirth and through this aim to reduce the incidence of epilepsy due to birth complications.

Assessment of profound intellectual disability in complex epilepsy

Project Aim: To develop a robust assessment tool for children with complex epilepsy

Investigators: Maria Clark, Gemma Wilson, Lucy Pepper

Summary: We have been awarded a small grant through the Patient Public Involvement scheme at GOSH to allow us to run some focus groups with families to advance the project.

What this means: Current assessments do not capture the skills of children with complex epilepsy and are not sensitive enough to record change over time or after intervention. We are trying to develop new ways to assess this group that is meaningful for their families and allows them to be in research or outcome data (as they are often excluded).

Mental Health in Children with Epilepsy (MICE)

Project Aim: Establish the feasibility of routine screening and brief telephone intervention for mental health disorders in paediatric neurology clinics so children and young people with difficulties are able to access the support they need.

Investigators: Roz Shafran, Helen Cross, Sophie Bennett, Sarah Byford, Bruce Chorpita, Anna Coughtrey, Emma Dalrymple, Caroline Dore, Peter Fonagy, Tamsin Ford, Isobel Heyman, Rona Moss-Morris, Colin Reilly, Jonathan A Smith, Terence Stephenson, Sophia Varadkar

Update: Our NIHR funded Programme Grant began in October 2017. At therapists' requests we hosted a booster training session in March 2019 which gave therapists the opportunity to feedback on their experience on delivering the intervention during the training phase and discuss key learning points in preparation for the trial. During this session, we conducted qualitative interviews which provided further insight into their experience and the practicalities of physical healthcare staff delivering a telephone-based psychological intervention within epilepsy services. We also obtained participants' perspectives of receiving the intervention and the impact it has had on both their child's mental wellbeing and quality of family life. We received very positive, promising feedback from both therapists and families, and incorporated any feedback and suggestions into our planning for the main trial where appropriate.
In April 2019 we were awarded the second half of our funding based on successful outcomes from the 6-month training phase. The trial commenced in May 2019, when the first participant was recruited, and screening is now underway across all 7 sites.

To meet demand we have trained additional therapists and staff to help with screening at other sites. We continue to meet with our Patient and Participant Involvement Research Advisory Group and Health Professionals Advisory group every 2-3 months. They advise on trial related procedures, for example the recruitment process in clinics and have contributed to plain English summary for families. We are currently opening St Piers School at Young Epilepsy as a study site.
We started recruiting patients into the main trial in 2019 and have now recruited over 130 participants of our planned 334. We were very pleased to be able to continue our research and support families during the COVID-19 pandemic as all of the assessment and treatment is completed over the telephone or via video conferencing. We've had some really good feedback from participants so far.

What this means: Children and young people with epilepsy are more likely to have emotional or behavioural difficulties than children and young people who do not have a chronic illness. There are lots of studies showing that there are effective treatments for emotional and behavioural difficulties in children, but we don't know whether they also work in children who have epilepsy. We want to know if an online assessment and a talking treatment delivered over the telephone can help us to pick up and treat emotional and behavioural difficulties in children and young people with epilepsy.

Physical Activity in Childhood Epilepsy (PACE)

Project Aim: The primary aim is to compare levels of physical activity in secondary school-aged children with 'active' epilepsy, and matched healthy controls, using both survey methods and activity trackers.
A secondary aim is to understand factors (e.g. age, gender, seizure related factors, sleep, behaviour-emotional functioning, school learning and parent wellbeing) which may be associated with physical activity, including structured exercise/sports participation, in children with epilepsy.
A third aim is to gather pilot data on physical activity levels in children with epilepsy and explore the feasibility of implementing an intervention to improve levels of physical activity in children with epilepsy.

Investigators: Colin Reilly, Emma Johnson, Helen Cross, Lauren Sherar, Monica Lakhanpaul, Kerry Robinson, Amit Bali, Patricia Atkinson, Natalie Pearson, Kathryn Simpson

Summary: Anecdotal evidence suggests that children with epilepsy engage in less physical activity than their peers. This does not mean engagement in team sports, rather, just being active.

There is, however, limited research on this and no previous studies in the UK. We will compare levels of physical activity in 150 secondary school-aged (11-15 years) children. Half of them will have epilepsy and the other half do not have epilepsy. Of the 150 children, 50 of them will attend special schools and 100 attend mainstream schools.
Activity will be measured by using activity trackers. We also want to know whether factors other than just their epilepsy may affect how active they are – things like their age, gender, how they feel, and sleep quality etc.
Depending on what we find, we may use this evidence to explore strategies which may improve access to being active, for children with epilepsy.
This project is fully funded and ethical approval has been granted. The study was suspended due to the COVID-19 pandemic and is due to reopen as an entirely remote study in January 2021.

What this means: We want to understand the attitudes, barriers and enablers to children with epilepsy participating in physical activity in order to provide the best support.

PsyKD - Understanding of the impact of the ketogenic diet on child and parental quality of life

Project Aim: Gain an understanding of the needs and experiences of families considering a Ketogenic Diet Therapy (KDT) and the subsequent impact of the diet on children and their parents

Investigators: Colin Reilly, Natasha Schoeler, Helen Cross, Victoria Whiteley, Anita Devlin, Christin Eltze, Emma Williams

Summary: Adherence to a KDT may not always be easy and depends on physician, parental and healthcare system-related factors. Despite the range of prescriptible and non-prescriptible ketogenic products available, KDTs still require stringent dietary restriction, which places significant burden on families and requires major effort on the part of the child and family. Little is known about the impact of KDTs on child behavioural and emotional functioning and child quality of life.
In order to have a better understanding of the impact of KDTs on children with epilepsy and on parental functioning, we propose to conduct a pilot study assessing functioning and views before commencement of dietary treatment and at three months and one year follow up. The study would be the first of its kind and would make a significant contribution to the research evidence base for treatment of epilepsy with KDTs on psychosocial outcomes.
The project has been delayed by the COVID-19 pandemic and is currently seeking funding. It is a collaboration between Young Epilepsy, Matthews Friends, GOSH, Addenbrookes Hospital, Royal Manchester Children's Hospital and Newcastle upon Tyne Hospitals.

What this means: Adherence to a KDT is a lifestyle change and we want to better understand how to best support families to make the most of this treatment.

A wearable OP-MEG and Light Mu-Room System at Young Epilepsy

Project Aim: To develop and test the technical and clinical feasibility of the first lightweight magnetically shielded mu-room for use with cutting edge, wearable Opticallly Pumped (OP) magnetoencephalography (MEG) technology.

Investigators: Tim Tierney, Stephanie Mellor, Geroge O'Neill, Gareth Barnes, Helen Cross, Rosemarie Pardington, Amy Muggeridge, Megan Brady, Kelly St Pier, Mark Devlin, Niall Holmes, Elena Boto, Ryan Hill, Gill Roberts, James Leggett, Richard Bowtell, Matt Brookes, Nick Murby, Eliot Dawson, Nick van de Wydeven, Courtney Veenswyk-Colvin, Peter Fierlinger, David Woolger, Cassandra Hugill, Sophie Perry, Vishal Shah, Torsten Baldeweg, Sarah Buck, Umesh Vivekananda, Matthew Walker, Vladimir Litvak, Eleanor Maguire, Daniel Barry, Andrew Levy, Sven Bestmann, Leo Dunque-Munoz, Jose Lopez

Summary: Magnetoencephalography (MEG) is a functional neuroimaging technique with high spatial and temporal resolution. It has been shown to provide useful information for presurgical planning in epilepsy but is not a readily available clinical tool, due largely to its high cost and low tolerance to movement. The latter is particularly problematic with children. However, advances in magnetic sensor technology mitigate many of the issues associated with MEG. OP-MEG uses optically pumped magnetometers (OPMs) in the place of cryogenically cooled MEG sensors. They can be worn directly on the head, which allows the patient to move naturally during a recording.
Unfortunately, like cryogenic MEG, OP-MEG must currently still be performed in a bulky, costly magnetically shielded room (MSR). The MEG Project at Young Epilepsy is a collaboration between UCL, the University of Nottingham, Magnetic Shields Limited and Young Epilepsy to design and build a new, lightweight MSR, tailored to the clinical setting. The room is under construction and will be complete by spring 2021.

What this means: We have proven the technology and are building the world's first wearable OP-MEG and lightweight shielded room system which is the first MEG system accessible to children.

Realising the potential of 7T MRI for paediatric imaging

Project Aim: To enable the first 7 Tesla (7T) magnetic resonance imaging (MRI) of paediatric patients with epilepsy being evaluated for surgery at GOSH and Kings College London Hospital (KCLH)

Investigators: David Carmichael, Helen Cross, Martina Callaghan, Shaihan Malik, Thomas Booth, Sila Dokumaci, Fred Dick, Dr Simon Richardson

Summary: The current standard resolution for clinical Magnetic Resonance Imaging (MRI) in neurology is 1.5 - 3 Tesla (a measure of the power of the magnet used). This study will look into the practical application and benefit of the 7 Tesla (7T) MRI machines at GOSH and KCLH.
3T MRI machines can show details of the brain as small as 1mm, a 7T machine can show details 50% smaller than this; small enough to detail network connectivity in real time. We believe that the potential of this technology will enable a significant increase in our ability to detect and stratify structural abnormalities causing epilepsy, particularly those due to cortical abnormalities, and through greater accuracy, allow more children to be considered for epilepsy surgery.
We have been developing scan protocols for Paediatric Epilepsy patients, and although this was disrupted by the COVID-19 pandemic restrictions we are hoping to start patient scanning this year. In parallel, we have been developing patient friendly head cushions to improve scan performance and tolerance.

What this means: We are working to understand the potential of this enhanced imaging technology and how best to use it for children.

The fast without the spurious: developing a system for robust and rapid simultaneous EEG-fMRI measurements

Project Aim: To develop more advanced EEG-fMRI scans that may better detect brain areas active at the start of seizures. To do this we are trying new motion-correction technology that tells the scanner where the head is using a camera and a marker attached to a dental retainer and updates the scanner accordingly.

Investigators: Amy McDowell, Danilo Maziero, David Carmichael, Helen Cross, Kelly St Pier, Nikolaus Weiskopf, Mirja Steinbrenner

Update: This project is now being finalised. We have published our assessment of more rapid fMRI sequences for these and other fMRI studies. We have collected a small case series to test our new EEG-fMRI acquisition and are writing this up for publication. The COVID-19 pandemic has caused delays to this project but we have moved to the analysis stage.

What this means: This project has developed a system to improve the accuracy of brain imaging to better understand which parts of the brain are active just before and during a seizure. It has also been developed to improve accuracy when the patient is moving.
Any movement, no matter how small, will affect most imaging techniques but it is not always possible to get a patient to stay perfectly still for a length of time, particularly if the patient is a child or a child with complex needs. This work will greatly improve the accuracy of imaging for these patients.

Improving Care in Epilepsy (ICE) for children, young people, and families

Project Aim: To implement an innovative model of care that improves outcomes by better reflecting the broad impact epilepsy has on the individual person, by virtue of being young person and family-centred, integrated across different sectors providing care, and measured on meaningful outcomes.

Investigators: Amit Bali, Helen Cross, Monica Lakhanpaul, Kerry Robinson, Dougal Hargreaves, Christina Petropoulos

Update: This is a collaborative programme of projects between Young Epilepsy, UCL Great Ormond Street Institute of Child Health, UCL Partners and Whittington Health, led by Amit Bali. Current work streams include the development of a learning healthcare system for paediatric epilepsy, linked to individualised care plan; the co-creation of young people's networks; and the commissioning of an economic evaluation of the true economic impact of epilepsy at individual, family, service and national levels.

We have been struggling to fund the economic study. Bids are met with great interest and support but not with a dedication of funds. We are currently revising the approach to fund this study.
The development of a learning healthcare system has been incorporated into Young Epilepsy's Digital Strategy 2019-24 and will constitute one of two arms of the project. We aim to co-create and deliver a pilot patient held record in April 2020 for evaluation. This project will partner with the Epilepsy12 National Audit to record patient reported measures and we hope to integrate this as a patient held record and epilepsy registry within the NHS by 2024.

What this means: We want to ensure services for epilepsy are joined up, and are provided in partnership with young people and families and empowers them. We want to ensure they receive personalised, holistic care. Our work to date has told us this is imperative. This requires improved communication, understanding what outcomes really matter, tailoring care and thinking with a whole systems strategy across all sectors.

Completed Projects

Workstream 1- Understanding Childhood Epilepsies

Clinical and Molecular Genetic Investigation of Landau Kleffner Syndrome

Investigators: Adeline Ngoh, Maria Clark, Helen Cross, Dimitri Kullmann, Robert Harvey, Manju Kurian

The cost of epilepsy to an individual lies not just in the burden of having recurrent seizures but also in the condition's neurodevelopmental, cognitive, psychological and social co-morbidities. This study aimed to better understand the pathophysiological mechanisms underlying epilepsy and its neurocognitive co-morbidities through the clinical and molecular genetic study of a cohort of patients with Landau Kleffner syndrome (LKS), an epileptic encephalopathy characterised by seizures, and neurodevelopmental regression in the form of loss of speech and language skills.
Patients were recruited from a database of children referred for LKS at Great Ormond Street Hospital's Developmental Epilepsy Clinic. Clinical data was extracted through case note review. As mutations in *GRIN2A*, a gene encoding the N2A subunit of the Nmethyl-D-Aspartate (NMDA) receptor have previously been described in 8-20% of individuals with LKS and related disorders, recruited individuals were screened for *GRIN2A* mutations via Sanger Sequencing and multiplex-ligation probe amplification. Functional investigations exploring gene/protein expression, protein localisation and channel function were carried out on missense *GRIN2A* mutations identified. Individuals who screened negative for *GRIN2A* variants underwent whole exome sequencing or whole genome sequencing to identify novel genes associated with LKS.
Reflecting the rarity of Landau Kleffner Syndrome, this cohort of 91 patients accumulated over 30 years is one of the largest cohorts ever reported. This study has drawn conclusions that LKS is a neurodevelopmental disorder and clinical features influencing prognosis include age at onset of regression, non-verbal intelligence, and the presence of motor difficulties. The frequency of *GRIN2A* mutations in this cohort was consistent with that of previous literature reports. Our functional experiments demonstrated that *GRIN2A* mutations are likely to lead to LKS through overall NMDA receptor loss of function effects. Nonetheless, LKS may be a complex disorder with multi-factorial or oligogenic aetiology. Lastly, the long-term potentiation pathway, important for learning and memory mechanisms may feature strongly in the pathogenesis of LKS.

Using new quantitative MRI tissue parameter maps to detect and delineate Focal Cortical Dysplasia (FCD) – further update

Investigators: Sara Lorio, David Carmichael, Helen Cross, Nikolaus Weiskopf, Karin Shmueli, Thomas Jacques, Chris Clark, Kling Chong, Po-Wah So, Torsten Baldeweg

We aimed to develop better imaging methodology by investigating whether using quantitative MRI parameter mapping together with quantitative analysis can provide improved detection, delineation and classification of FCD lesions. This is the first application of these scanning and analysis methods to epilepsy and may lead to a change in local, national and international practice in imaging in childhood epilepsy.
We have published our study looking at diffusion changes in the cortex that demonstrated greater sensitivity of advanced diffusion maps to FCD lesions. We have also analysed quantitative susceptibility maps (QSM), a new MRI measure that has not been tested in many epilepsy patients before. QSM maps showed strong visual contrast in a handful of cases – and changes in cortical structure in FCD patients when evaluated quantitatively. Reduced susceptibility values were found across the cortex and an absence of a peak in susceptibility found in healthy cortex. Working with Po-Wah So at KCL we have compared our results to alterations in metal content using the diamond light source (https://www.diamond.ac.uk) to show changes in iron, calcium and zinc. This work is now available in preprint form from (https://www.medrxiv.org/content/10.1101/2020.09.15.20157123v1) and has been submitted for publication.

Koala Project: Plasticity of language networks after surgical resection in childhood epilepsy: implications of outcome

Investigators: Caroline Skirrow, Patricia Sanfilippo, Louise Weiss-Croft, Faraneh Vargha-Khadem, Frederique Liegeois, Helen Cross, William Harkness, Torsten Baldeweg.

The study is a major long-term outcome study in children who underwent epilepsy surgery, showing general cognitive improvements extending over a longer (>3-5 years) follow-up duration. It is also the first study to have used identical pre- and post-operative neuroimaging, together with detailed neuropsychological assessments. A total of 83 participants have been recruited into the study, including 18 sibling controls. The cognitive improvements seen in the surgery group were associated with cortical growth, both globally and in discrete frontal regions, known to be supporting intellectual functioning. This study also confirmed that extensive surgical removal of the language-dominant anterior temporal lobe can be associated with declines in verbal abilities. This calls for future exploration of more tailored or stepwise surgical techniques as well as further improvements in preoperative neuroimaging.

More specifically, epilepsy-related clinical factors (seizure control, medication reduction, duration of follow-up) contribute to cognitive outcomes after surgery. However, the current study shows that attention should also be paid to changes in brain structure. The left anterior temporal lobe is crucial for verbal reasoning and semantic memory development. Future outcomes may be improved if resections spare this brain region, whenever possible. Improvements in pre-operative imaging may help in a greater degree of tailoring of resections. At the same time, post-operative improvements are underpinned by grey matter growth in the lateral frontal cortex, a late-maturing region implicated in intellectual functioning. This supports the idea that successful epilepsy surgery in children can help initiate plastic processes in the brain, which underpin cognitive catch-up development.

Workstream 2- Outstanding Treatments

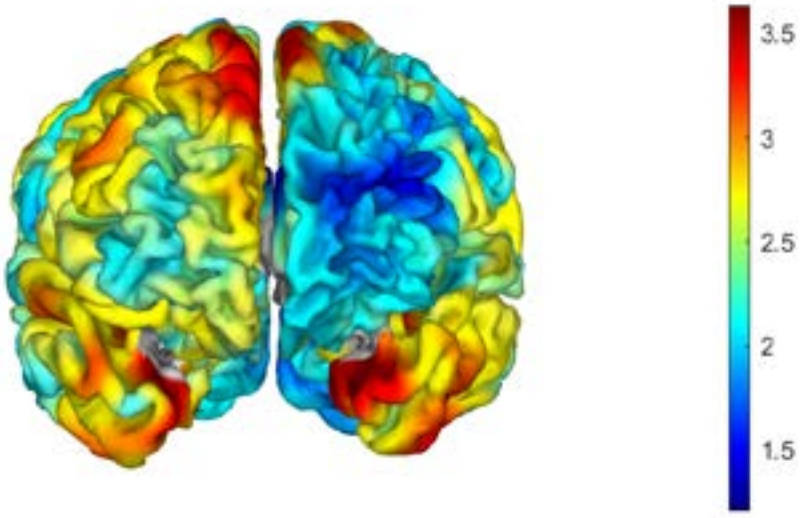
Rasmussen syndrome: Immunomodulation with Azathioprine therapy

Authors: Serena Pellegrin, Torsten Baldeweg, Suresh Pujar, Felice D'Arco, Gaetano Cantalupo, Sophia Varadkar, Helen Cross

This retrospective study aimed to verify safety and efficacy of the corticosteroid-sparing drug Azathioprine (AZA) in Rasmussen syndrome (RS). We compared outcomes in 30 RS patients who received AZA with 23 patients who were not treated with this drug. We used a multimodal approach to correlate therapy with clinical features (seizures, epilepsia partialis continua [EPC], hemiparesis) and neuroimaging markers of progressive brain atrophy. AZA was well tolerated; only one patient discontinued treatment due to pancytopenia. In 27/30 AZA patients, all of whom were corticosteroid responders, corticosteroid therapy could be weaned or reduced without worsening of seizures in 89%. AZA patients had a lower prevalence of EPC (42% vs. 67% in controls) and hemiparesis (64% vs. 92%, respectively). Cox regression showed for the AZA group compared to controls a delayed time to: 1) EPC (of about 2 years, 2) hemiparesis (about one year), and 3) surgery. However, there were no group differences in cognitive decline over time (IQ change per year) or in hemispheric grey matter atrophy on serial MRI scans.

We concluded that AZA treatment appears to slow clinical progression of Rasmussen syndrome in steroid responders; this will give most advantage in patients in the early stages of the disease in whom surgical decision-making may require further time.

Atrophy is in blue (showing loss of cortical thickness), viewed from front



Workstream 3 – Outstanding Support

What I Need in School (WINS) – Developing guidelines for best practice for young people with epilepsy in schools in the UK

GOAL 04

Investigators: Colin Reilly, Patricia Atkinson, Emma Johnson, Helen Cross, Amy Muggeridge

There is a lack of knowledge about epilepsy in schools and we aimed to gain an understanding of the views of parents of children with epilepsy regarding the process of securing educational and therapeutic supports and the changes they would like to make to this provision.

This study closed recruitment at the beginning of 2020 and results are currently being written for submission to academic journals at the end of 2020. Parents (n=68) of children (born between 2003 and 2014) with 'active' epilepsy (at least one seizure in last year) resident in the RH10-RH13 postcode areas of West Sussex, were interviewed using a semi-structured interview schedule The interviews were conducted between October 2018 and March 2020 and coded using Thematic Analysis by two independent raters.

Parents reported difficulties accessing both educational and therapeutic supports. They often felt that they had to drive the process to gain supports themselves. They reported little professional support, and inadequate communication regarding their child's needs with school staff and between school staff and/or medical/therapeutic professionals. Parents of children with severe intellectual disability (ID) and/or who attended a special school generally reported finding the process easier. Parents of children with mild to moderate ID who attended mainstream schools reported the most difficulties.

Regarding changes parents would like to make to their child's current educational and/or therapeutic supports, they highlighted the need for school staff to recognise the impact of epilepsy on learning and behaviour and to support their child more holistically. Many wanted greater access to assessment and therapeutic provision in relation to their child's learning and behaviour. They also highlighted the need for the child's schoolwork to be appropriate to their cognitive ability and profile.

Parents of school-aged children with epilepsy report difficulties accessing appropriate educational and therapeutic supports for their child and would like more support in the process. Parents also highlight the need for increased knowledge of the impact of epilepsy on learning and behaviour and want more resources for assessment in these areas.

This work will feed into the resources to education professionals provided by Young Epilepsy and we further hope to write guidelines for schools to support young people with epilepsy achieve their academic potential. We plan to test a screening instrument to help teachers and parents identify whether a child may have additional learning or behavioural needs, knowing this will lead to getting the right support at school.

Visit our online guide for schools:

www.youngepilepsy.org.uk/guide-for-schools/

The perceived impact of COVID-19 and associated restrictions on young people with epilepsy in the UK: young people and parent survey

Investigators: Colin Reilly, Amy Muggeridge, Helen Cross

We wanted to garner the views and experiences of young people with epilepsy and caregivers regarding the impact of the COVID-19 pandemic and subsequent restrictions in the UK.
An online survey was used to explore the views of young people (n=71) with epilepsy and caregivers (n=127) between 4th and 28th June 2020. It included sections on the impact of COVID-19 pandemic and associated restrictions on the child's epilepsy and on child and parental wellbeing.
One in 3 young people and one in four parents reported that the young person's seizures had increased during lockdown (only 7% of parents and 10% of young people reported a decrease). Half of young people reported that they were more reluctant to go to hospital for appointments. The majority of young people reported their sleep (73%), mood (64%) and levels of physical activity (53%) had deteriorated. However, 46% reported there had been positive aspects to the restrictions (e.g., spending more time with family). 19% of parents reported difficulties getting their child's medication whilst 25% reported their child had clinical procedures/investigations (such as EEG/MRI/surgery) cancelled during restrictions. Caregivers reported that their child's mood (60%), sleep (65%) and behaviour (50%) had deteriorated during the restrictions. The majority of caregivers experienced increases in stress (70%) anxiety (66%) and difficulties with sleep (58%). Epilepsy nurses, online support groups/ charity websites were seen as the most helpful supports for both young people and parents/ carers during the restrictions.
The survey results indicate that the pandemic and associated restrictions have had a negative impact on young people with epilepsy. Perceived increases in seizures and reluctance to go to hospital are likely to impact on epilepsy management. The wider psychosocial impact is also likely to be significant with increases in child and parent mental health problems in an already vulnerable group.

Research Funding

Central to the research programme is the ability to apply for and manage research grants and charitable donations.

Our collaborative funding strategy has enabled us to build the world's largest paediatric epilepsy research unit and network of multidisciplinary practitioners.

Between July 2019 and June 2020, research across the unit has secured over £24million in new research grants.

Alongside academic grants raised by the researchers and their academic institutions, we rely on the additional multidisciplinary fundraising by Young Epilepsy, which allow us to redirect funds where the need is greatest within a project. This flexibility is vital and provides stability during challenges such as delays.

The future of this programme rests on the ability to maintain and build the current infrastructure which allows us to maintain a base of operations to lead, coordinate and provide governance.

We remain ever grateful for the generosity and dedication of the organisations and individuals who support our work.

Thank you!

Action Medical Research
Autistica
Brain Tumour Charity
Cancer Research UK
Child Health Research Trust
Children with Cancer UK
Epilepsy Research UK
Ethypharm
European Association of Neurosurgical Societies
European Commission
Freya Foundation
Google Cloud Platform Research Credit Award
GOSH NIHR BRC
Great Ormond Hospital Children's Charity Research Leadership grant
Great Ormond Street Children's Charity
GW Pharmaceuticals
Innovate UK
James Lewis Foundation
Medical Research Council Clinician Scientist Fellowship
National Institute of Health Research (NIHR)
NIHR GOSH Biomedical Research Centre
NIHR GOSH BRC PPIE Small Grants
Novartis
Nutricia
Oakgrove Foundation
Rosetree's Trust
Sir Henry Wellcome Fellowship
UCB BioPharma
UCL Child Health Research CIO Strategic Initiatives Pump-Priming Fund
Veriton Pharma
Vitaflo
Waterloo Foundation
Wellcome Research Enrichment - Public Engagement
Wyfold Charity Trust
Young Epilepsy

Further Activities

E-CURe Network Launch

In February 2020, Young Epilepsy, Professor Helen Cross, Dr Amy McTague and Dr Samantha Chan hosted an information day for the parents of children with epilepsy to learn about E-CURe - the UK's first Patient and Public Involvement (PPI) network for childhood epilepsy. The event was held at ICH, London, and supported by PPI grants from both GOSH Children's Charity and Young Epilepsy.

Epilepsy in childhood: Carers Uniting with REsearchers ...join the conversation"

The Epilepsy in childhood: Carers Uniting with Researchers (E-CURe) initiative aims to recruit parents of children with epilepsy and young people with epilepsy to help shape epilepsy research. Members of the network are invited to consult on, and directly contribute to, research themes, design and management.

We welcomed 50 parents to the event which began with an introduction to research by Professor Cross, Dr McTague and Dr Chan. Guests were then free to visit and talk to representatives from 10 research groups which were looking to work with patient families to develop and improve their projects.

The day was a wonderful success and recruited all attendees to the E-CURe network as well as to individual project PPI initiatives. E-CURe now has over 140 members and an active Twitter account managed by Dr Chan and Dr McTague.

"I helped to secure the project funding and joined the research team as a co-applicant, which gave me a much better understanding of how the whole research process works. My main role is co-ordinating the research advisory group and co-chairing our quarterly meetings – the content of which varies depending on the phase of the project. The research team keep us regularly updated on how our insights and contributions have been implemented – from refining Plain English summaries and terminology to helping with approaches to recruit families into the project. As a result of this work I have completed Modules 1 and 2 of the NIHR INVOLVE PPI training. Outside of the organised sessions, we have an active WhatsApp group which is a place where we can find information or support from each other, which can be so difficult to find elsewhere."

E-CURe Parent Member

Young Epilepsy Paediatric Epilepsy Research Retreat 2020

The Young Epilepsy Research Retreat, hosted by The Prince of Wales's Chair of Childhood Epilepsy, is an annual gathering of researchers and collaborators across our research partnership. This meeting gives researchers, at all stages of their careers, the opportunity to discuss ongoing projects, completed projects and future directions of research with a unique diversity of epilepsy specialists.

2020 marked our 10th Research Retreat and to celebrate the occasion not only did Professor Cross present the data illustrating the growth of the unit over the past decade (some of which is included earlier in this report), but we were honoured to welcome two eminent Research Moderators to co-host the Retreat. Professor Alexis Arzimanoglou, Director of Epilepsy, Sleep and Paediatric Neurophysiology at the University Hospitals of Lyon, France, and Professor Matthias Koepp, Professor of Neurology at the UCL Queen Square Institute of Neurology. Professor Arzimanoglou's clinical and research activities are focused on the pharmacological and surgical management of childhood epilepsies, cognitive development and emotional regulation disorders in children with focal epilepsies. Professor Koepp runs specialist epilepsy clinics, with a particular focus on people with epilepsy and associated co-morbidities, in particular Learning Disabilities. His research focuses on difficult-to-treat epilepsy, co-morbidities, functional, molecular and structural imaging in epilepsy

This year we presented 34 research projects and welcomed 106 guests from over 20 organisations and 6 countries. Almost every attendee has a direct clinical role in supporting children and young people with epilepsy. Discussions at the end of each presentation give investigators the opportunity to receive comments and feedback from fellow researchers and principal investigators representing a vast array of different fields.

As well providing a unique networking opportunity, the meeting critically serves as a way of motivating early career researchers to recognise this diversity and to form the collaborations which underpin excellent science and practical outcomes.

The official photo from the very first Young Epilepsy Paediatric Epilepsy Research Retreat in 2011 for comparison!

Collaborative Awards

EPILEPSY RESEARCH UK & YOUNG EPILEPSY FELLOWSHIP AWARD

At the 2020 Young Epilepsy Paediatric Epilepsy Research Retreat, Young Epilepsy and Epilepsy Research UK were delighted to launch of our first joint venture - a £300,000 Fellowship Award for research into childhood epilepsy.

Epilepsy Research UK's vision is 'a life free from epilepsy'. They have raised and invested over £2million into epilepsy in childhood, and over £10million to all epilepsy in the UK. Their mission is to drive and enable life changing, lifesaving research into epilepsy. They have previously funded many projects under the Young Epilepsy research partnership.

Both organisations are thrilled to be working together to offer this support for research into the causes, diagnosis and treatment of childhood epilepsies.

Childhood epilepsies are associated with significant additional conditions which, over the course of someone's life, can have a much greater impact than seizures. Seizures are often the most obvious, or extreme symptom of the underlying cause of someone's epilepsy, but they are rarely the only symptom. Additional conditions of childhood epilepsy include ADHD, autism, learning difficulties, motor difficulties, behavioural difficulties and mental health/ emotional difficulties. It is well recognised that anti-seizure medications only go so far when seizures are not the only thing someone is facing.

We have kept the criteria for the award very open in order to maximise the breadth of opportunity in this field and the award processing is currently underway.

To ensure the voices and experiences of young people guide our work, both organisations have designed the programme a programme to involve the Young Epilepsy Young Reps into every stage of the award process. The Young Reps are a group of young people aged 16-25 who represent children and young people living with epilepsy throughout the UK and their input has been invaluable.

Young Epilepsy AUTISTICA EPILEPSY RESEARCH UK epilepsy and autism joint award

In spring 2020 Autistica, the UK's national autism research charity, Young Epilepsy and Epilepsy Research UK announced a joint award to create a dossier of evidence to better understand autism and epilepsy. We invited applications of up to £30,000.

The aim of the award is to create a dossier of evidence focusing on autism and epilepsy, outlining the scientific evidence and scale of the issue in human, social and economic terms. The dossier must highlight the gaps and barriers to progress to date, and strategic or collaborative action which can be taken to address this issue.

People who are autistic and have epilepsy face some of the starkest inequalities in the world. We know that worldwide approximately 8.4 million people have both conditions. Despite sharing some common mechanisms, autism and epilepsy remain virtually unstudied in combination. In fact, autism remains an exclusion factor in some epilepsy trials, and vice versa, in the UK and globally. We wish to set out the evidence which allows us to address the inequalities facing this population.

The grant was awarded to Dr Colin Reilly, Dr Sophie Bennett, Professor Roz Shafran and Dr Amy McTague in June 2020.

Research Team

The research team contribute to a wide spectrum of activities from basic science to patient care. The team consists of a multidisciplinary range of experts working across Young Epilepsy, UCL GOS - Institute of Child Health and Great Ormond Street Hospital for Children.

Principal Investigators

Professor Helen Cross OBE The Prince of Wales's Chair of Childhood Epilepsy and Head of UCL GOS - ICH Developmental Neurosciences Programme

Young Epilepsy; UCL GOS - Institute of Child Health and Great Ormond Street Hospital for Children

Additional Roles:

President Elect (2021-2025) - International League Against Epilepsy (ILAE)

Elected Treasurer (2017-2021) - International League Against Epilepsy (ILAE)

President - Epilepsy Research UK

UK Lead, Inaugural and Current Joint Co-ordinator - European Reference Network for Rare and Complex Epilepsies (EpiCARE)

Chair of the Medical Board - Dravet UK

Chair of Medical Board - Hope for Hypothalamic Hamartoma

Chair of Medical Board - Matthew's Friends

Chair of the Epilepsy Programme Board – Royal College of Paediatrics and Child Health (RCPCH)

Chair of the Clinical Research Network (Children) - National Institute for Health Research (NIHR) Neurosciences Clinical Studies Group

Elected to Board - International Child Neurology Association

Clinical Advisor - Children's Epilepsy Surgery Service (CESS)

Clinical Advisor - Epilepsy Action

Clinical Advisor to Revision of NICE Guidelines for Childhood Epilepsy - National Institute for Health and Care Excellence

Co-opted Member - Advisory Committee on Misuse of Drugs

Member of the Scientific Advisory Board - Lily Foundation

Member - MHRA Paediatric Medicines Expert Advisory Group

Member of the PhD Review Panel - UCL GOS – ICH

Theme Lead - NIHR Children and Young Person MedTech for Epilepsy, Muscle and Movement Disorders

Professor Torsten Baldeweg Professor of Developmental Cognitive Neuroscience, Deputy Head of UCL GOS - ICH Developmental Neurosciences Programme

UCL GOS - Institute of Child Health

Additional Roles:

External Expert to the French Higher Research Council - University of Amien

Chairman of Exam Board, MSc Paediatric Neuropsychology - University College London

Module organiser and lecturer, MSc Paediatric Neuropsychology - University College London

Editor (Until December 2019) - Journal of Developmental Cognitive Neuroscience

Professor Gareth Barnes Head of Magnetoencephalography

Wellcome Centre for Neuroimaging

Professor Chris Clark Professor of Imaging and Biophysics, Head of UCL GOS – ICH Developmental Imaging and Biophysics Section

UCL GOS - Institute of Child Health

Professor Michelle De Haan Professor in Infant and Child Development

UCL GOS - Institute of Child Health and Great Ormond Street Hospital for Children

Additional Roles:

Affiliated Scientist - British Autism Study of Infant Siblings Network

Course Speaker, MSc in Cognitive Neuroscience, Translational Research Module - University College London

Deputy Director, MSc in Clinical & Applied Paediatric Neuropsychology - UCL GOS - ICH

Director, MSc in Infancy and Early Childhood Development - UCL GOS - ICH

Membership of Steering Committees - Centre for Developmental Cognitive Neuroscience UCL

Professor Isobel Heyman Consultant Child and Adolescent Psychiatrist

UCL GOS - Institute of Child Health and Great Ormond Street Hospital for Children

Professor Tom Jacques Professor of Paediatric Neuropathology

UCL GOS - Institute of Child Health and Great Ormond Street Hospital for Children

Additional Roles:

Editor in Chief - Journal of Neuropathology and Applied Neurobiology

Lead - Paediatric Tumour Genomics England Clinical Interpretation Partnership (GeCIP)

Pathology representative on the Central Nervous System subgroup - National Cancer Research Institute (NCRI) Children's Cancer and Leukaemia Clinical Studies Group

Professor Manju Kurian NIHR Research Professor and Professor of Neurogenetics

UCL GOS - Institute of Child Health

Additional Roles:

Chair - BPNA Research Committee

Member of the Scientific Advisory Committee - Epilepsy Research UK

Professor Finbar O'Callaghan Professor of Paediatric Neuroscience, Head of UCL GOS - ICH Clinical Neurosciences Section

UCL GOS - Institute of Child Health and Great Ormond Street Hospital for Children

Additional Roles:

President - British Paediatric Neurology Association (BPNA)

Secretary and Board Member- European Paediatric Neurology Society (EPNS)

Professor Shamima Rahman Professor of Paediatric Metabolic Medicine

UCL GOS - Institute of Child Health and Great Ormond Street Hospital for Children

Additional Roles:

Adviser to Statutory Approvals Committee - Human Fertilisation and Embryology Authority

Contributor, MSc courses - UCL GOS - ICH and UCL Institute of Neurology and Genomics England

Coordinator of Mitochondrial Subnetwork - Metabolic European Reference Network (MetabERN)

Editor- Journal of Inherited Metabolic Disease

Lead of Mitochondrial Subdomain - Genomics England Clinical Interpretation Partnership (GeCIP)

Member of the Clinical and Scientific Review Panel - Mito Foundation, Australia

Member of the Evaluation Committee - 2020 European Joint Programme on Rare Diseases

Member of the External Advisory Board - North American Mitochondrial Disease Consortium

Member of the Medical Advisory Board - Freya Foundation

Member of the Medical Advisory Board - Lily Foundation

Member of the Scientific Advisory Board – Khondrion

Member of the Scientific Advisory Committee - Canadian Mitochondrial Network

Member of the Scientific Council of the AFM-Telethon - French Muscular Dystrophy Association

Member of the Steering Committee - Collaborative International Leigh Syndrome Task Force

Member of the Steering Group - Rare Mitochondrial Disorders Priority Setting Partnership, James Lind Alliance and Genetic Alliance UK

Senior Editor - Annals of Human Genetics

Training Advisor for Inherited Metabolic Medicine - Royal College of Paediatrics and Child Health

Professor Rosamund Shafran Chair in Translational Psychology

UCL GOS - Institute of Child Health and Great Ormond Street Hospital for Children

Professor Rod Scott Professor of Paediatric Neuroscience

UCL GOS - Institute of Child Health; Great Ormond Street Hospital for Children and University of Vermont, USA

Additional Roles:

Associate Editor - BMC Neurology

Member of the Basic Science Committee - American Epilepsy Society

Member of the Editorial Board - Epilepsia, Journal of the ILAE

Member of the Workshop on Neurobiology of Epilepsy (WONOEP) - ILAE Neurobiology Commission Conference

Reviewer - National Institute of Health Research (NIHR)

Professor Faraneh Vargha-Khadem Professor of Developmental Cognitive Neuroscience, Head of UCL GOS - ICH Cognitive neurosciences Section

UCL GOS - Institute of Child Health and Great Ormond Street Hospital for Children

Additional Roles:

Member of the Scientific Advisory Board - Max Planck Society

Dr Patricia Atkinson Consultant Community Paediatrician

Sussex Community NHS Foundation Trust

Dr Sarah Aylett Consultant Paediatric Neurologist

Great Ormond Street Hospital for Children

Additional Roles:

Caldicott Guardian Postgraduate Teaching - ICH-UCL

Dr Stewart Boyd Consultant Clinical Neurophysiologist

UCL GOS - Institute of Child Health and Great Ormond Street Hospital for Children

Dr David Carmichael Honorary Reader in Neuroimaging and Biophysics, Reader in Magnetic Resonance Physics

UCL GOS - Institute of Child Health and Wellcome / EPSRC Centre for Medical Engineering, Kings College London

Additional Roles:

Member of the MRI expert task force - E-PILEPSY E-PROCESSING

Dr Maria Clark Consultant Paediatric Neurologist

UCL GOS - Institute of Child Health and Great Ormond Street Hospital for Children

Dr Felice D'Arco Consultant Paediatric Neuroradiologist

Great Ormond Street Hospital for Children

Additional Roles:

Chair - GOSH MRI Safety Group

Honorary Senior Lecturer - UCL GOS - ICH and UCL Institute of Neurology

Lecturer - European Course of Paediatric Neuroradiology

Member - European Network for Brain Malformations

Member of the Editorial Board - Journal of the European Society of Neuroradiology

Dr Krishna Das Consultant Paediatric Neurologist

Young Epilepsy and Great Ormond Street Hospital for Children

Dr Christin Eltze Consultant Paediatric Neurologist

UCL GOS - Institute of Child Health and Great Ormond Street Hospital for Children

Mr William Harkness Consultant Paediatric Neurosurgeon

UCL GOS - Institute of Child Health and Great Ormond Street Hospital for Children

Dr Marios Kaliakatsos Paediatric Neurologist

Great Ormond Street Hospital for Children

Dr Amy McTague MRC Clinician Scientist Fellow and Honorary Consultant Paediatric Neurologist

UCL GOS - Institute of Child Health

Additional Roles:

Member of work package 2, Laboratory Diagnostics - EpiCARE

Scientific Adviser - Apollo London translational medicine network

Scientific Adviser - KCNT1 Epilepsy Foundation

Dr Philippa Mills Associate Professor of Inherited Paediatric Metabolic Disease

UCL GOS - Institute of Child Health

Additional Roles:

Course Contributor - UCL GOS - ICH

Treasurer - Society of the Study of Inborn Errors of Metabolism

Dr Friederike Moeller Consultant Clinical Neurophysiologist

UCL GOS - Institute of Child Health and Great Ormond Street Hospital for Children

Dr Ronit Pressler Consultant in Clinical Neurophysiology and Clinical Lead of GOSH Telemetry Unit, Honorary Associate Professor in Clinical Neuroscience

UCL GOS - Institute of Child Health and Great Ormond Street Hospital for Children

Additional Roles:

Affiliated Member- Paediatric Neurosciences Clinical Reference Group (CRG), NHS England

Chair of the Neonatal Guideline Task Force - Commission on Paediatrics of the ILAE

Co-chair of INC Seizures Workgroup - International Neonatal Consortium by Critical Path Institute, enabled by FDA/EMA

Council Member - British Society for Clinical Neurophysiology

Course Director, EEG in the First Year of Life teaching course - ILAE

International Secretary - British Society for Clinical Neurophysiology (BSCN)

Lead- Neonatal seizure working group of GAIA, Brighton Collaboration

Lecturer in Neonatal Seizures - ILAE

Member of the Editorial Board - European Journal of Paediatric Neurology

Member of the Medical Therapy in Children Task Force - ILAE

Web based teaching: e-brain: Epileptic Seizures and Syndromes in Neonates and Infants - ILAE

Dr Colin Reilly Educational Psychologist

Young Epilepsy and UCL GOS - Institute of Child Health

Additional Roles:

Annual workshops for trainee educational psychologists - University College London

Co-Chair Paediatric Psychiatric Issues Committee - ILAE

Co-Chair Paediatric Psychiatric Issues Committee – ILAE

Member of the Editorial Board - Epilpesy & Behavior

Dr Robert Robinson Consultant Paediatric Neurologist

UCL GOS - Institute of Child Health and Great Ormond Street Hospital for Children

Dr Richard Rosch Sir Henry Wellcome Postdoctoral Fellow

King's College London, University of Pennsylvania

Additional Roles:

Clinical Fellow - Great Ormond Street Hospital for Children

Dr Richard Scott Consultant in Clinical Genetics

UCL GOS - Institute of Child Health and Great Ormond Street Hospital for Children

Dr Rachel Thornton Consultant in Neurophysiology

UCL GOS - Institute of Child Health and Great Ormond Street Hospital for Children

Mr Martin Tisdall Consultant Paediatric Neurosurgeon and Honorary Associate Professor

UCL GOS - Institute of Child Health; Great Ormond Street Hospital for Children and National Hospital for Neurology and Neurosurgery

Additional Roles:

Honorary Senior Lecturer - UCL GOS - ICH and UCL Institute of Neurology

Dr Sophia Varadkar Consultant Paediatric Neurologist

UCL GOS - Institute of Child Health and Great Ormond Street Hospital for Children

Additional Roles:

Chair - North Thames Neurosciences Network for the Neurosurgical Child

Chair of the Steering Committee - BPNA Paediatric Epilepsy Training Programme

Co-Chair - UK Paediatric Vagus Nerve Stimulation (VNS) expert group

Council Member - ILAE British Chapter

Medical Advisor - Children's Trust, Tadworth

Medical Advisor and Trustee - Ring 20 Research and Support UK

Member - RCPCH Epilepsy Programme Board

Research Staff

Sophie Adler-Wagstyl Research Associate

Konrad Adler-Wagstyl Research Associate

Amit Bali Clinical Leadership Fellow and Young Epilepsy Trustee

Katy Barwick Genetics Associate - EpiPEG

Anne Brown Research Administrator

Sarah Buck Research Associate

Emma Dalrymple PPI Lead – MICE

Judit Germuska Senior Research Coordinator - EpiCARE group

Sally Halsall Trial Manager - KIWE

Emma Johnson Assistant Research Psychologist - WINS

Laura Lyons Trial Manager - KIWE

Elaina Maldonado Research Associate

Amy Muggeridge Research Manager, Young Epilepsy

Liz Neal Honorary Research Dietitian

Nicola Openshaw-Lawrence EpiCARE ERN Operational Helpdesk Coordinator and Data Manager

Manuela Pisch Research Associate

Mirja Steinbrenner Research Associate

Natasha Schoeler Senior Research Dietitian

Tom Stone Research Associate

PhD Students

Fatimah Almousawi *Pathways and mechanisms affected in individuals with vitamin B6-responsive epilepsy*

Sam Amin *An investigation into mTOR inhibitors in Tuberous Sclerosis Complex*

Filipa Bastos *Memory outcome after temporal lobectomy*

Victoria Bryant *Sudden Unexpected Death in Childhood; characteristics, autopsy findings and investigation*

Dominic Burrows *Brain-wide abnormal dynamics during epileptic seizures at single cell resolution*

Aswin Chari *Novel network evaluation of intracranial EEG to identify the epileptogenic zone*

Rosie Coleman *Functional and structural plasticity after epilepsy surgery*

Bianca De Blasi *Multi-parametric imaging using hybrid PET/MRI to investigate the epileptogenic brain*

Maria Eriksson *Cognitive outcomes after neurosurgical treatment for focal epilepsy: developing a neuroanatomical predictive model for clinical decision making*

Amy Fairchild *Characterisation of high-risk paediatric brain tumours and their aberrant gene networks*

Nandaki Keshavan *Gene Therapy for Deoxyguanosine Kinase Deficiency*

Mei-Ju Lai *Investigating cellular identity in childhood epilepsy*

Jane Kung *Epilepsy in infancy – relating phenotype to genotype*

Adeline Nogh *Molecular Genetic Investigation of Landau-Kleffner Syndrome*

Birgit Pimpel *Neurophysiological methods to aid decision making in paediatric epilepsy surgery*

Apostolos Papandreou *Investigation of disease mechanisms and screening for treatments in Beta-Propeller Protein- Associated Neurodegeneration (BPAN)*

Izabella Smolicz *The biology of paediatric central nervous system tumours at post-mortem*

Ulrich Stoof *Multiscale modelling of epileptic networks from SEEG recordings*

Aitkaterini Vezyroglou *Deep phenotyping of alternating hemiplegia in childhood*

Active Collaborators

Professor Alexis Arzimanoglou
Director of Epilepsy, Sleep and Pediatric Neurophysiology
University Hospitals of Lyon, France

Professor Ingmar Blümcke
Professor of Neuropathology
Universitätsklinikum Erlangen, Germany

Professor Richard Bowtell
Head of Sir Peter Mansfield Imaging Centre and Professor of Physics
University of Nottingham

Professor Kees Braun
Professor of Neurology and Neurosurgery
University Medical Center Utrecht, Netherlands

Professor Matthew Brookes
Professor of Physics
University of Nottingham

Professor Nick Freemantle
Professor of Clinical Epidemiology and Biostatistics
PRIMENT Clinical Trials Unit, UCL GOS – Institute of Child Health

Professor Simon Heales
Professor of Clinical Chemistry
UCL GOS - Institute of Child Health and Great Ormond Street Hospital

Professor Gregory Holmes
Professor of Neurology and Paediatrics
University of Vermont, USA

Professor Matthias Koepp
Professor of Neurology
UCL - Institute of Neurology

Professor Irwin Nazareth
Professor of Primary Care
PRIMENT Clinical Trials Unit, UCL GOS - Institute of Child Health

Professor Charles Newton
Cheryl & Reece Scott Professor of Psychiatry
University of Oxford

Professor Ingrid Scheffer AO
Paediatric Neurologist and Physician Scientist
University of Melbourne & Florey Institute of Neuroscience and Mental Health

Professor Sanjay Sisodiya
Professor of Neurology
UCL - Institute of Neurology

Professor Sudhin Thayyil
Professor of Perinatal Neuroscience and Head of the Weston Group for Academic Neonatology and Director of the Centre for Perinatal Neuroscience
Imperial College London

Professor Matthew Walker
Professor of Neurology
UCL - Institute of Neurology

Professor Robin Williams
Professor of Molecular Cell Biology
Royal Holloway Hospital

Dr Shakti Agrawal
Consultant Paediatric Neurologist
Birmingham Children's Hospital

Dr Helen Basu
Consultant Paediatric Neurologist
Lancashire Teaching Hospitals NHS Foundation Trust

Dr Bigna Bölsterli
Paediatric Neurologist
University Children's Hospital Zurich, Switzerland

Dr Richard Chin
Clinical Senior Lecturer
University of Edinburgh

Dr Archana Desurkar
Consultant Paediatric Neurologist
Sheffield Children's NHS Foundation Trust

Dr Anita Devlin
Trustee
Young Epilepsy
Consultant Paediatric Neurologist
Newcastle upon Tyne Hospitals NHS Foundation Trust

Dr Penny Fallon
Consultant Neurologist
St Georges Hospital

Dr Dougal Hargreaves
Health Foundation Improvement Science Fellow and Honorary Consultant Paediatrician
University College Hospital

Dr Elaine Hughes
Consultant Paediatric Neurologist
Evelina London Children's Hospital

Dr Judith Kalser
Paediatric Neurologist
Lausanne University Hospital, Switzerland

Dr Rachel Kneen
Consultant Paediatric Neurologist
Royal Liverpool University Hospital

Dr Andrew Mallick
Consultant Paediatric
Neurologist Bristol Children's Hospital

Dr Louise Marston
Trial Statistician PRIMENT Clinical Trials Unit,
UCL GOS - Institute of Child Health

Dr Helen McCullagh
Consultant Paediatric Neurologist
Leeds Teaching Hospital

Dr Ailsa McLellan
Consultant Paediatric Neurologist
Royal Hospital for Sick Children, Edinburgh

Dr Alasdair Parker
Consultant Paediatric Neurologist
Cambridge University Hospital

Dr Natalie Pearson
Senior Research Associate in Physical Activity and Public Health
Loughborough University

Dr Rajib Samanta
Consultant Paediatric Neurologist
Leicester Royal Infirmary

Dr Lauren Sherar
Reader in Physical Activity and Public Health
Loughborough University

Dr Jeen Tang
Consultant Paediatric Neurologist
Royal Manchester Children's Hospital

Dr Ruth Williams
Consultant Paediatric Neurologist
Evelina London Children's Hospital

Congratulations

Awarded PhDs

Yao-Feng (Derek) Li

2020

Modelling cell-cell interactions in developmental cortical lesions

Joyeeta Rahman

2020

Novel Diagnostic and Therapeutic Approaches for Mitochondrial Disorders

Professional Recognition and Awards

Rory Piper

Surgeon Scientist

2020

Great Ormond Street Hospital Children's Charity

Richard Rosch

Ronnie MacKeith Prize

2020

British Paediatric Neurology Association

Research Publications

Primary Research

1. Amin S, Mallick AA, Lux A, **O'Callaghan F** (2019) **Quality of life in patients with Tuberous Sclerosis Complex (TSC).** *Eur J Paediatr Neurol.* 23(6):801-807. DOI: 10.1016/j.ejpn.2019.09.006.

2. Annear NMP, Appleton RE, Bassi Z, Bhatt R, Bolton PF, Crawford P, Crowe A, Tossi M, Elmslie F, Finlay E, Gale DP, Henderson A, Jones EA, Johnson SR, Joss S, Kerecuk L, Lipkin G, Morrison PJ, **O'Callaghan FJ**, Cadwgan J, Ong ACM, Sampson JR, Shepherd C, Kingswood JC (2019) **Tuberous Sclerosis Complex (TSC): Expert Recommendations for Provision of Coordinated Care.** *Front Neurol.* 6;10:1116. DOI: 10.3389/fneur.2019.01116.

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Reviews, editorials and letters

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Glossary

Animal models
A non-human species used in medical research because it can mimic aspects of a disease found in humans

Assays
An investigative procedure in laboratory medicine for measuring the presence, amount, or functional activity of a target entity

Biophysical
Methods used in physics to study biological phenomena

Calcium imaging
A microscopy technique to optically measure the calcium levels in a cell or tissue

Chronic
Long term

Co-morbidities
Medical conditions that are simultaneously present in a patient

Computational modelling
A mathematical model to study the behaviour of a complex system by computer simulation

Copy number variants
When the number of copies of a particular gene varies between individuals

Cortical
Relating to the outer layer of the uppermost part of the brain

Cox regression
A statistical test

Cryogenic
The production of, and behaviour of, materials at very low temperature

Dietetics
Branch of knowledge concerned with the diet and its effects on health

Electroencephalography (EEG)
A test that detects electrical activity in your brain using small electrodes attached to your scalp. Your brain cells communicate via electrical impulses and activity shows up as wavy lines on an EEG recording

Epidemiological
The branch of medicine which deals with the incidence, distribution, and control of diseases

Epilepsy-dyskinesia
Disorders characterised by recurrent episodes of abnormal movements, co-occurring with epilepsy or other episodic neurological symptoms

Epileptiform discharges
Seen on an EEG, meaning spikes, polyspikes, sharp waves, or spike and slow-wave complexes without observed clinical seizures

Epileptogenesis
The gradual process by which a normal brain develops epilepsy or, the area of epileptogenesis is the area of the brain which causes a patient's epilepsy

Functional validation (of disease-causing genes)
The process of determining whether a particular genetic mutation is causing a disease

Genomics
The study of whole genomes of organisms, and incorporates elements from genetics

Genotype
An organism's set of heritable genes that can be passed down from parents to offspring

Health economics
The study and understanding of how society allocates resources to healthcare and the resource needs of specific healthcare issues

Hemiparesis
Weakness of one entire side of the body

Immunofluorescence
A method in biology that relies on the use of antibodies chemically labelled with fluorescent dyes to visualise molecules under a light microscope

Intractable
Untreatable, hard to manage

Language lateralisation
The phenomenon in which one hemisphere (typically the left) shows greater involvement in language functions than the other

Lesion
A region in an organ or tissue that is abnormal from injury or disease

Magnetoencephalography (MEG)
Functional neuroimaging technique for mapping brain activity by recording magnetic fields produced by electrical currents occurring naturally in the brain

Memory lateralisation
The phenomenon in which one hemisphere (typically the left) shows greater involvement in memory functions than the other

Miss-sense mutation
A point mutation in a gene in which a single nucleotide change results in a codon that codes for a different amino acid

Multi-omic
Or *integrative omics,* is a biological analysis approach in which the data sets are multiple "omes", such as the genome, proteome, transcriptome, epigenome, metabolome, and microbiome

Myoclonia
A form of epileptic seizure manifesting with jerks of the muscles

Natural history
The progression of a disease process in an individual over time, in the absence of treatment

Pancytopenia
A condition that occurs when a person has low counts for all three types of blood cells: red blood cells, white blood cells, and platelets

Pathophysiological mechanisms
The cause of a disease associated injury

Phenotype
An individual's observable traits, such as height, eye colour, and blood type. The genetic contribution to the phenotype is called the genotype

PPI
Patient and public involvement in research

Practice paper
Evaluative summaries of scientific and evidence-based information that address practice topics. Practice papers are often done in emerging areas that might not have sound scientific data yet

Putative variants
A segment of DNA that is believed to be a gene. Putative genes can share sequence similarities to already characterised genes and thus can be inferred to share a similar function, yet the exact function of putative genes remains unknown

Sanger sequencing
A method for determining the nucleotide sequence of DNA

Status epilepticus
A single seizure lasting more than five minutes or two or more seizures within a five-minute period without the person returning to normal between them

Structural correlates
Structural anomalies which correlate to symptoms

Targeted treatment
Treatments which target specific symptoms and potential causes of disease. These treatments are disease modifying

Therapeutic radiofrequency thermocoagulation
A technique of controlled thermal ablation of tissues

Trio whole genome sequencing
Whole exome sequencing is a comprehensive method for analysing entire genomes. Trio whole exome sequencing refers to the sequencing of the entire genome of a patient and their biological parents

Western blotting
A widely used analytical technique in molecular biology and immunogenetics to detect specific proteins in a sample of tissue extract

Young Epilepsy is the children and young people's epilepsy charity

We exist to create a society where children and young people with epilepsy are enabled to thrive and fulfil their potential. A society in which their voices are respected and their ambitions realised.

Let's work together.

For more information on our research or if you want to get involved please contact:

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