Centre for Perinatal Neuroscience
Annual Report 2014
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Message from the Director

Pioneering research into neonatal brain has been conducted at Queen Charlotte’s and Chelsea and Hammersmith hospitals for several decades.

To further advance neonatal brain research requires a far wider and cross cutting collaborative approach. We need sophisticated technologies, specialist expertise, close involvement of scientists, engineers and industry to develop newer technologies for preventing, monitoring and treating brain injury. And, of course, we need large clinical and magnetic resonance biomarker collaborative networks for evaluation of these therapies, particularly in settings where the disease burden is high.

The establishment of the Imperial Centre for Perinatal Neurosciences (CPN) as a part of the Centre for Translational Medicine chaired by Professor Andy Bush, is the first small step in this direction. The Centre is hosted jointly by Imperial College London, Imperial College NHS Trust, and Imperial Academic Health Science Centre, and is funded by the Weston Chair endowment grant, National Institute for Health Research and Imperial Biomedical Research Centre.

The CPN aims to bring together the expertise of clinicians and academic researchers so that they can contribute to the delivery of translational medicine, innovative research and ultimately, excellence in neonatal research and clinical practice.

Our research focuses on deploying a number of quantitative magnetic resonance biomarkers in understanding perinatal brain development and injury, and in evaluating the treatment effects of novel neuroprotective therapies in first-in-human clinical trials. We also have a strong interest in neonatal evidence based medicine, and in systematic reviews of existing research evidence.

In this edition, we will reflect on the highs and lows of our busy first year, celebrate our achievements and present our future plans.

We hope you enjoy reading our first annual report!

Best wishes for 2015

Sudhin Thayyil
January 2015
Our Team

We are a small and multidisciplinary group of highly committed, driven and motivated individuals sharing a common passion – improving the neurological outcome of babies. Our team’s backgrounds range from underwater hockey and football refereeing to physics and imaging, gained from exotic shores such as Martinique, India, Singapore and Italy to highlight a few, and of course the UK.

Centre for Perinatal Neuroscience Team

Director and Head of Weston group  Sudhin Thayyil (Reader & NIHR Clinician Scientist)
Academics  Denis Azzopardi, Honorary – Frances Cowan, Ravi Swami, Mani Chandrasekheran
Associate Director  Badr Chaban
MR Physics  Pete Lally (Lead; NIHR fellow), Marc Rhea (MR Safety Advisor), Alan Bainbridge (MR advisor)
MR Radiographers  Julie Fitzpatrick (Lead), Guiliana Durighel
Clinical Research Fellows  Paolo Montaldo, Shreela Pauliah, Shea Addison
Academic Taster Trainees  Rebekah Gnanaratnem, Thomas Niccol, Audrey Soo, Syed Taha, Faith Zhu
Research Nurses  Vania Oliveira (Lead) Nelly Ricofranca, Albert Mallari, Josephine, Merla Medina, Llorana Sissons
Pediatric Neurology  Nigel Sheikh Basheer
Neuroradiology  Bynmore Jones, Olga Kirmi, Afshin Alawi
Clinical Engineer  Steve Forman
Ambulatory Unit Consultant  Nicky Coote
Senior Neonatal Research Manager  Nabila Youssouf
Personal Assistant  Belinda Smith

NHS Consultant Neonologists  
Sunit Godambe (Clinical Lead), Gerardine Ng, Alexander Rakow, Jenny Ziprin, Aniko Deierl, Emma Porter, Latha Srinivasan, Lidia Tyszczuk, Victoria Jowett (Cardiology), Gaurav Atreja (Locum), Libuse Pazderova (Locum), Jay Banerjee (Locum) Virginie Meau-Petit (Locum)
Imperial College: Academic Excellence

Imperial College London is consistently rated in the top 10 universities in the world (QS 2014/15 ratings) and has the greatest concentration of high impact research of any major UK university, according to the Research Excellence Framework (REF) 2014.

- 91% of Imperial research is classed as “world-leading” or “internationally excellent” – the highest proportion of any major university.
- Imperial was ranked top or joint-top for providing an environment conducive to producing “world-leading” or “internationally excellent” research in all of the Units of Assessment to which it made submissions.
- Imperial research quality has improved significantly since the Research Assessment Exercise 2008, with the proportion of 4* or 3* classified research moving from 73% to 91%, and 4* graded research increasing from 26% to 46%.

Neonatal research at Queen Charlottes and Chelsea was highlighted as an area of “Outstanding practice” in the 2014 Care Quality Commission report. The neonatal clinical service received a “good rating” in being effective, responsive and caring.

CQC feedback and grading of Neonatal Services, 2014
MR Governance

We are one of the very few hospitals in the world to have a dedicated 3 Tesla Phillips MR scanner inside the neonatal unit, which allows us to safely perform serial MR imaging of critically unwell newborn babies on cardio-respiratory support. Our dedicated team of research MR radiographer, MR physicist, research nurses and clinical fellows offer a unique and optimal system for neonatal MR imaging/spectroscopy and governance.

The ongoing costs for the entire system are met by research funding, and we are using our generated income to deliver clinical MR service for Imperial’s Neonatal Units. Our aspiration has been to utilise our team and research facilities to provide optimal holistic patient care in the Neonatal Unit and beyond.

If you think running an MRI inside an NICU is fun and easy, think again!!

- Following the exodus of the previous MR team in 2012, our first challenge was to set up a critical mass for MR safety and governance to establish a maintenance contract with Phillips. We also set up remote monitoring, linked up data with PACS, repaired oxygen sensors, chillers and ventilators, replaced ferromagnetic support devices with MR compatible systems, optimised the accuracy of quantitative MR measurements, and finally we started scanning again in April 2014.
- Then the gradient coil failed, and was replaced, soon followed by a failure of head coil, again replaced by Phillips.
- Ongoing issues with generator failure and power interruptions in the Trust, creates several problems with the scanner and chiller. Pete Lally set up a 24/7 e-mail automated system via raspberry to regularly alert him of the scanner and chiller status, so that scanner dysfunctions from power failures can be identified and rectified immediately. This means Pete is a frequent midnight visitor to the MR scanner and chiller.
- Disaster strikes again when an MR quench (helium is leaking requiring emergency repairs near the quench pipe). Our MR physics team trained and supported the NHS contract team to undertake these repair work in a safe way, although the scanner had to be shut down for several weeks.
- Then the neonatal unit roof started leaking requiring emergency repairs near the quench pipe. We MR physics team trained and supported the NHS contract team to undertake these repair work in a safe way, although the scanner had to be shut down for several weeks.

3T Neonatal MR Governance Group
Sudhin Thayil (Head), Pete Lally (Designated MR responsible person), Marc Rhea, Julie Fitzpatrick, Nabila Youssouf (finance and regulatory aspects)

The group meets fortnightly to discuss all MR governance and safety issues. We also discuss various governance issues at the monthly Trust wide MR safety meetings chaired by Iain Colquhoun (Consultant Radiologist) and Marc Rhea (NHS MR Safety advisor).

All staff involved in MR must complete:

- Training log book: all sessions attended must be logged and submitted for sign-off
- SOPs: sign as ‘read and understood’ on SOPs reading List

Data Governance & Reporting

We take Information Governance very seriously:

- Images must be put on NHS systems (PACS and RIS) so there is a record of scans for clinicians as well as researchers
- Anonymised images are stored on College system which are then archived
- All images are reviewed by a neuroradiologist for quality control and reporting of any incidental findings.

The above applies to both clinical and research scans.

Clinical MR Scan Requests

Complete the ‘MR Request form’ downloadable from the SOURCE and email to ICHC-tr.cpn@nhs.net – a CPN team member will acknowledge receipt and confirm the next available slot. Ensure that a request is made on the Cerner as well prior to the MRI. For urgent requests contact 0774173 8336.
Impact of our Past Research

Total Body Cooling – TOBY Trial and TOBY Children study
Sponsor: Imperial College London
Funding: Medical Research Council, UK

The TOBY Trial was a randomised controlled trial of whole body cooling in neonatal encephalopathy, led by Prof Denis Azzopardi, which confirmed the findings of the earlier Cool Cap trial (Gunn et al NEJM 2005) and NICHD whole body cooling trial (Shankaran et al NJEM 2005). The pooled data from these three clinical trials provided conclusive evidence for the safety and efficacy of whole body cooling in reducing death and improving survival with normal neurological outcome after neonatal encephalopathy in high-income countries. Cooling therapy is now the standard of care in neonatal encephalopathy in all high-income countries. A total of 11 papers have been published from these studies so far; high impact publications are given below.


Magnetic Resonance Imaging Autopsy Study (MaRIAS)
Sponsor: University College London
Funding: Department of Health, UK

The MaRIAS study was Dr Sudhin Thayyil’s PhD work (2007 to 2010; Supervisor: Prof Andrew Taylor, UCL) where he compared the accuracy of whole body MR imaging with conventional autopsy in 400 fetuses, newborns and children. This work demonstrated that whole body MR imaging can be used as an accurate alternative to autopsies in fetuses, newborns, and infants, however the accuracy was poor in older children, where histological sampling of visceral organs by an endoscopic approach was important. The Royal College of Pathologists and Radiologists have adopted this study to develop national guidelines. Based on the MaRIAS study, the Department of Health has now commissioned further work to explore endoscopic sampling alongside MR imaging, prior to rolling this out as a clinical tool in the NHS in the near future. A total of 20 papers have been published from this work so far; high impact publications are given below.

Current Research Projects

OBSERVATIONAL STUDIES

Magnetic Resonance Biomarkers in Neonatal Encephalopathy (MARBLE)
Chief Investigator: Dr Sudhin Thayyil
Funding: National Institute for Health Research and Biomedical Research Centre, Imperial College London
Sponsor: Imperial College London

Cooling therapy reduces brain injury after neonatal encephalopathy only to a certain extent, we need better treatments that can reduce the brain damage further. There are several drugs that are effective in animal studies when used together with cooling therapy, but to know if these combinations really work in babies, we need to study thousands of babies with this condition over several years. Assessing the effectiveness of new additive treatments is a slow process because the effects of brain injury and indeed any treatment may not be apparent until early school age, delaying the evaluation and introduction of these novel therapies into routine clinical practice. More importantly, drug failures occurring in a phase III trial results in substantial loss of research time, funding, and exposing babies to ineffective therapies, whilst depriving them of an effective one. Hence, rigorous evaluation of promising adjunct therapies to cooling in phase II trials using robust quantitative surrogate MR biomarkers and optimising trial protocols is vital before these drugs are tested in phase III trials.

MARBLE is a large multi-country study, comparing the prognostic accuracy and incremental benefits of a number of MR spectroscopy and diffusion tensor imaging based biomarkers, in babies with hypoxic ischemic encephalopathy. Once qualified, this MR biomarker platform would be ideal for conducting phase II randomised controlled trials of various neuroprotective therapies, and will be the first of its kind. MARBLE has recruited 145 (total 180 required) cases to date, and is expected to complete recruitment by mid-2015. The MARBLE platform will then start recruitment into trials evaluating N-acetyl cysteine and Vitamin D as adjunct neuroprotectants to cooling therapy.

Evaluation of MR imaging to predict neurodevelopmental impairment in preterm infants (ePRIME study)
Chief Investigator: Professor David Edwards
Funding: National Institute for Health Research
Sponsor: Imperial College London

Preterm birth is the leading cause of perinatal mortality and morbidity in developed countries, and leads to neurological impairment in a significant proportion of survivors. Targeting follow-on services to children who need them is difficult, particularly with inaccurate early diagnosis of neurodevelopmental impairment. In a research environment, MR is more accurate at detecting
cerebral abnormalities than standard care cranial ultrasonography and might provide a more accurate neurological prognosis and improve overall care. ePRIME is a large prospective study comparing the utility of MR imaging with cranial ultrasound in preterm babies. The study has completed recruitment, and the results will be published in due course.

**Quantitative MR biomarkers of Preterm brain injury**

Chief Investigator: Dr Sudhin Thayyil  
Funding: National Institute for Health Research and Biomedical Research Council, Imperial College London  
Sponsor: Imperial College London

One of the biggest stumbling blocks in understanding and reducing preterm brain injury is the lack of robust quantitative biomarkers for predicting long term outcomes. MARBLE preterm project is a large prospective study to quantify the preterm brain injury using novel MR spectroscopy and diffusion based biomarkers. We will then use these MR biomarkers to evaluate various therapies aimed at improving neurological outcomes in preterm babies.

**Cardiac Ion Channelopathies in Unexplained Stillbirths Study (CICUS)**

Chief Investigator: Dr Sudhin Thayyil  
Co Investigators: Prof Patricia Munroe (Barts and London)  
Sponsor: University College London  
Funding: Well being of Women and Biomedical Research Centre, Imperial College London

Worldwide, approximately 3.2 million stillbirths occur every year. Despite a detailed autopsy, as many as one third of stillbirths remain ‘unexplained’. Cardiac ion channelopathies account for approximately 10 to 15% of sudden infants deaths and sudden cardiac deaths in adults, however, it is not known if a similar disease process occurs in fetuses. The CICUS is a large prospective study into post-mortem genetic testing for cardiac ion channelopathies in unexplained stillbirths. Recruitment and data analysis is now complete and the study results will be published in the near future.

**The Neonatal Microbiome (NeoM) study**

Chief Investigator: Professor Simon Kroll  
Funding: Weston family  
Sponsor: Imperial College London

The Neonatal Microbiota Study (NeoM) examines the relation of gut microbiomes and necrotizing enterocolitis in premature babies. The study completed recruitment and sample collection in January 2013. 369 infants born at <32 weeks gestation were recruited and over 10,000 faecal samples were collected. The findings of the study in relation to NEC have been published in the journal Clinical Infectious Diseases, and a second manuscript outlining our results with respect to infants with late-onset bloodstream infection is in preparation. The study infants are being follow up at two years of age, to assess the impact of their NICU stay on the maturation of the GI microbiota towards a stable “adult” pattern.
Magnetic Resonance Imaging in Infection Primed- Neonatal Encephalopathy (MARINE study)
Investigator: Peter J Lally (NIHR fellowship; Supervisor: Sudhin Thayyil)
Funding: National Institute for Health Research and Biomedical Research Centre, Imperial College London
Sponsor: Imperial College London

Emerging evidence suggests that encephalopathic infants exposed to infection prior to birth may not benefit from rescue hypothermic neuroprotection. This may partly explain why up to 50% of cooled infants still go on to display abnormal neurological outcomes. In this work, we are developing specific magnetic resonance biomarkers of such dual hit injury. Techniques for rapid acquisition and automated post-processing of MR spectroscopy will also be developed so that hospitals without access to specialist MR physics expertise can use these techniques in routine clinical practice. The study will start recruiting in early 2015.

Prospective Research on Infants with Mild Encephalopathy: The PRIME study
Imperial Investigators: Sudhin Thayyil and Paolo Montaldo

PRIME is a prospective study examining the brain injury and long term outcome of 57 infants with mild encephalopathy (who were not cooled) involving a number of large centres in USA and Canada. Dr Guilherme M Sant'Anna at McGill University, Montreal is the chief Investigator. The study is now completing recruitment.

Breastfeeding infants receiving respiratory support (The BIRRST study):
Chief Investigator: Alexander Rakow

The usage of nasal continuous positive airway pressure (nCPAP) or humidified high flow nasal cannula (HHFNC) are common practice in neonatal care. Data from animal models suggests that nasal CPAP can affect swallowing behaviour and/or coordination of sucking, swallowing and breathing in newborns but the magnitude and clinical significance is still unclear even in animals. Studies in adults are also lacking but some have shown that swallowing can be impaired during CPAP therapy. In most places expert consensus has been that feeding should be delayed until respiratory support (including CPAP or HHFNC) is no longer needed. In our unit it has been common practice for decades to allow infants to breastfeed despite receiving treatment with either nCPAP or HHFNC. The BIRRST study will compare various physiological parameters during breastfeeding and nasogastric feeding in premature babies receiving CPAP of or HHFNC, to see if breastfeeding during CPAP or HHFNC is safe, and indeed beneficial. The parental perception of feeding with respiratory support will be assessed using a parental questionnaire. The study will be submitted for sponsorship in 2015.

Post-discharge breast milk fortification in premature babies
Investigator: Caroline King

Due the numerous benefits of human milk, preterm babies nursed on neonatal units in the UK are increasingly more likely to be fed human milk
than formula. During 2014 there was continued exploration of the Imperial Neonatal Units experience of using breast milk fortifier post discharge in breastfeeding preterm babies who are at risk of growth faltering. The risk of growth faltering carries with it the risk that mothers will introduce formula and that breast feeding will fail. Observational data was presented on 32 preterm babies in poster format at the Perinatal Medicine conference in June. This showed that using was associated with an increased prevalence of breastfeeding at 6 weeks (63%) corrected age, as opposed to 45% in 120 babies discharged without breast milk fortification. A case study was presented to illustrate the point at this conference.

INTERVENTIONAL TRIALS

TOBY Xenon Trial
Chief Investigator: Denis Azzopardi
Imperial Principal Investigator: Aniko Deierl
Funding: Medical Research Council, UK
Sponsor: Imperial College London

TOBY Xenon examined the feasibility of 30% Xenon started up to 12 hours of age as an adjunct therapy to whole body cooling. Imperial site enrolled 27 infants to this study. This study completed enrolment in 2014 with a total of 92 infants enrolled to the study, and the results are awaited.

Cool Xenon 3 Trial
Imperial Principal Investigator: Sudhin Thayyil
Co-Investigators: Badr Chaban, Pete Lally
Funding: SPARKS charity and Moulton foundation
Sponsor: University of Bristol

Following the completion of TOBY Xenon, we are now evaluating the neuroprotective efficacy of high dose early Xenon therapy (50% Xenon along with cooling started within 5 hours of birth) in the Cool Xenon 3 Trial. This work is done in collaboration with the Bristol Neonatal Neuroscience group (Ela Chakrapani, John Dingley), and Professor Marianne Thoresen is the Chief Investigator.

We will use the MR biomarkers qualified as a part of the MARBLE study to examine the neuro-protective effect of Xenon in this study. Cool Xenon 3 has recruited 5 babies at Bristol to date. Imperial recruitment will start early 2015. The TOBY Xenon and Cool Xenon 3 studies will provide the data required for designing the optimal treatment protocol for larger clinical trials of inhaled Xenon therapy.

N-acetyl cysteine and Vitamin D along with cooling (NAChiLD) study
Chief Investigator: Sudhin Thayyil
Funding: Biomedical Research Centre, Imperial College London
Sponsor: Imperial College London

Therapeutic strategies that reduce infection and inflammation-induced cerebral injury might benefit the neonates who do not completely respond to cooling and where the brain injury
seems to be linked to the release and circulation of pro-inflammatory bacteria-derived molecules that induce systemic inflammation. N-acetylcysteine (NAC) is an FDA-approved drug that has been used in multiple conditions for mitigating oxidative stress. Mechanisms of action include scavenging oxygen free radicals, serving as a precursor of the major intracellular antioxidant, glutathione and restoring intracellular redox potential, thereby reducing both oxidative stress and apoptosis.

In a transitional neonatal rat model, Vitamin D along with NAC promotes T regulatory cell proliferation and IL-10 secretion, brain Derived Neurotrophic Factor, Nerve Growth Factor, and NeuroTrophin-3 secretion by astrocytes, thus increasing neuroprotection.

The NAChilD project is in collaboration Dorothea Jenkins (Medical University of South Carolina) and is in three phases. In the first phase we are developing MRS techniques for accurate quantification of Glutathione levels in brain and investigating the acute (hours) and longer changes (days) in thalamic [NAA] following N-acetyl cysteine infusion in adult volunteers. The second phase will investigate the pharmacokinetic parameters and safety of low dose NAC and 1,25(OH)2 Vitamin D3 and to examine [NAA] levels at 1 week and 1 month after N-acetyl cysteine/Vit D therapy in babies with encephalopathy undergoing cooling. The final phase will be a phase II randomised control to examine the treatment effects of NAC and Vitamin D on neonatal brain injury.

**Hypothermia for Encephalopathy in Low and Middle-Income Countries (HELIX) Trial**
Chief Investigator: Sudhin Thayyil
Co-Investigators: Seetha Shankaran (Wayne State University, Michigan, USA), Ravi Swami
Funding: Gates Foundation, and Biomedical Research Centre, Imperial College London
Sponsor: Imperial College London

The benefits of cooling therapy are currently restricted to high-income countries however 99% of the burden from neonatal encephalopathy occurs in low and middle-income countries. Approximately 1 million babies die from neonatal encephalopathy in low and middle-income countries (LMIC) every year. There are a number of reasons why the safety and efficacy data on cooling therapy cannot be extrapolated to LMIC, including differences in population, higher incidence of perinatal infection, and lack of optimal tertiary intensive care. Furthermore, cooling requires expensive and sophisticated servo controlled devices unsuitable for use in low- and middle-income countries.

With funding from the Gates foundation, we have developed an inexpensive servo controlled cooling device – Tecotherm HELIX (~£500), in collaboration with Inspiration Health Care (UK). Tecotherm HELIX has a single switch operation mode to cool babies to a set temperature of 33.5°C. We are now organising a large phase III pragmatic clinical trial in low and middle-income countries a to see if cooling therapy would reduce death and disability in babies with neonatal encephalopathy in these settings. A total of 400 babies with moderate or severe...
neonatal encephalopathy will be randomised to whole body cooling or usual care, over an 18 month period. Neurodevelopmental outcomes will be assessed at 18 months of age. We will also undertake MR imaging and in depth infection screen on all recruited infants. Once completed, the HELIX trial will be the largest ever cooling trial in neonatal encephalopathy. If effective, cooling therapy may save thousands of babies in low and middle-income countries every year from death and disability.

PREMFOOD Study
Chief Investigator: Neena Modi
Co Investigator: Luke Mills (PhD student and Consultant Neonatologist, Chelsea and Westminster Hospital)
Funding: Biomedical Research Centre, Imperial College London

This is a pilot randomised controlled trial of fortified Human Donor Milk, unfortified Human Donor Milk or Preterm Formula in preterm babies, to make up any shortfall in the volume of Mother’s Own Milk. The Centre of Perinatal Neuroscience team are undertaking the MR imaging of PREMFOOD babies at our 3T MR scanner, and providing the MR physics expertise for the trial.

SYSTEMATIC REVIEWS AND META-ANALYSIS
We have a strong interest and expertise in systematic reviews and evidenced based neonatal medicine, particularly related to neonatal brain development and injury, and global health. Some of the ongoing work is given below:

• Long term neurological outcome after neonatal encephalopathy in low and middle-income countries (Lead: Mani Chandrasekheran)
• Prognostic accuracy of amplitude integrated electro encephalography (aEEG) in neonatal encephalopathy after rescue hypothermic neuroprotection (Leads: Mani Chandrasekheran and Badr Chaban)
• Morbidity and mortality after a premature birth in low and middle-income countries (Lead: Ravi Swami)
• Prognostic accuracy of Magnetic Resonance Biomarkers in neonatal encephalopathy after rescue hypothermic neuroprotection (Lead: Pete Lally)

OTHER RESEARCH WORK
In addition to our own and other collaborative research work given above, we also recruit Imperial babies into two other NIHR portfolio studies – PLANET study (comparing two different thresholds for platelet transfusion in premature babies with thrombocytopenia) and Mitogent study (examining genetic aspects of aminoglycoside induced hearing loss).
Academic Taster Program

Our academic taster program offers a unique opportunity for bright and motivated junior doctors/medical students with limited or no previous research experience, to undertake a short research project alongside their full time clinical work. The trainees will receive close research supervision and support to present their work at national and international meetings and in publishing their work in peer reviewed journals. Our ultimate goal is to help in securing competitive PhD programs/fellowship for gifted trainees to pursue a neonatal academic career. Current students give an insight into their aspirations and projects over the next few pages.

If you are interested in this program, please contact Dr Sudhin Thayyil, as soon as you join our neonatal unit.

Audrey Soo
As a paediatric ST2 trainee at Imperial College Healthcare NHS Trust, I have been able to join the research team at the Centre for Perinatal Neuroscience through the academic taster program. I have been working on fetal and neonatal MRI scans, tracking optic nerve development. The CPN team has been very welcoming and supportive during this academic taster. The academic mentoring and supervision has been excellent. I am currently writing up the project for a journal submission and am have submitted this work to the PAS conference, San Diego in April 2015.

In the future, I intend to pursue a PhD in clinical neurosciences and neuroimaging. This academic taster program has helped me further develop MRI post-processing skills and analytical research skills. It has also provided an inspiration to pursue a clinical academic career in the future.

Output:

Syed Taha
I am a year 5 medical student at Imperial College London. I have held an interest in paediatrics for a considerable time, which led me to join the team at the Centre for Perinatal Neuroscience. I am currently working on fetal and neonatal optic nerve development alongside a colleague within the CPN, with a view to furthering my interest in neonatology and paediatrics in general in the long-term.

Having conducted a search of the current literature, it was discovered that there was very limited data regarding fetal optic nerve development, especially with the use of Magnetic Resonance Imaging (MRI). 100 post-mortem MRI images from the MARIAS study were used, discarding images which were of poor quality and/or had congenital brain malformations that are known to affect optic nerve diameter. Two assessors blinded to gestational age and clinical data independently measured optic nerve diameters at 3 mm posterior to the optic globe using OsiriX Imaging Software. A Bland-Altman analysis showed good inter-observer reproducibility with 95% limits of agreement from -0.11 to 0.14mm between the two independent assessors. This study provides preliminary normographic MRI data for optic nerve development, which could be used for early identification of optic nerve abnormalities during the fetal and neonatal period.
Output:

Thomas Niccol
During the final year of medical school, I had the opportunity to chose an elective placement anywhere in the world. Similar to many other Australian’s I chose the UK, specifically to conduct a six-week term in neonatology at Queen Charlotte’s and Chelsea Hospital, London. My ambition is to become an obstetrician and therefore I utilised this time to expand my understanding of fields associated with obstetrics and gynaecology.

In addition to outstanding clinical exposure, this term allowed for involvement with one of Imperial’s research programs. After being introduced to Dr Sudhin Thayyil by my clinical lead I have been able to become engrossed in a research project, which I have continued to work on far past my departure from the UK. The intention of our project is to create a visual summary of the efficacy of Cochrane studied interventions for reducing neonatal mortality. Such a resource will allow clinicians to rapidly identify the effectiveness of interventions for specific conditions. I elected to become apart of this project as it is of personal interest, improves research skill and also aids in my pursuit to gain entry into specialty colleges.

The caliber of academics at Imperial and the programs that are offered result in a research culture which with nurture the keen student. The intention of my project is to create a visual summary of the efficacy of Cochrane studied interventions for reducing neonatal mortality. Such a resource will allow clinicians to rapidly identify the effectiveness of interventions for specific conditions. The visual summary will utilise a ‘bubble’ forest plot to display the risk ratio on the horizontal axis with associated confidence intervals, the central mark on that plot will display a circle proportional in size to the number of participants studied. At present the project is in the final stages of data collection and early stages of plot generation. It is anticipated that progress will accelerate in early 2015.

Rebekah Gnanaratnem
My name is Dr. Rebekah Gnanaratnem and I am a junior doctor with an interest in pursuing a career in Paediatrics, specifically Neonatology, in the future. For this academic year, I have been participating in the Academic Taster Programme here at Imperial College London's Centre for Perinatal Neuroscience in order to gain more experience in academic medicine as well as further insight into medical research processes. I've always had an interest in Paediatrics and Global Health and after hearing that this department has a strong interest in global perinatal health, I contacted them and enquired about getting involved in the research currently being done that focuses on understanding brain injury after neonatal encephalopathy in low- and middle-income countries and evaluating the safety and efficacy of the cooling device they have helped to develop, in these settings. I then joined the department and have since been working on the HELIX (Hypothermia for Encephalopathy in Low and Middle-Income Countries) project. I will also be going to south India to help with the current ongoing clinical studies using this device. Over the past few months I have learnt so much and continue to do so on a daily basis. The entire team have been very helpful and accommodating since I've joined the department. Imperial College's international reputation of providing excellent clinical care and pioneering new research has always impressed me and I am grateful to have this opportunity to be able to contribute to the ground breaking work being done at this institution.
Narayanan E, Rebekah Gnanaratnem, Kumutha Kumaraswami, Seetha Shankaran, Ravi Swamy and Sudhin Thayyil. Short-term outcomes following whole body cooling using an inexpensive servo-controlled cooling device in south India (Submitted to Paediatric Academic Society Meeting, San Diego 2015) – manuscript in preparation

Faith Zhu
Neonatology, and especially neonatal neurology, has always been my passion. When I learned that I was to join the team at Imperial as an ST2 clinical trainee, I was excited to have the opportunity to explore the research side of medicine. I approached the research team after hearing from them during my induction and have since been involved in a project which compares cranial ultrasound injury with fractional anisotropy of the whole brain white matter tracts using Tract Based Spatial Statistics (TBSS) in neonatal encephalopathy. We have demonstrated that infants with moderate injury seen on cranial ultrasound in the basal ganglia/thalami region have reduced whole brain fractional anisotropy in the white matter tract. Interestingly, the same outcome is not seen in those with white matter injury visualized on cranial ultrasound.

During this program, I have developed essential skills for an academic future through writing abstracts and presenting at The Neonatal Society meeting and I have been introduced to new techniques in neonatal cranial imaging which I will continue to develop in my future career.

Output:
New appointments, Events and News

Welcome

**Julie Fitzpatrick** joined as the lead research MR Radiographer in August 2014. Julie has over 18 years’ experience of MR imaging and previously worked as the lead MR radiographer at the Clinical Imaging facility at Imperial College London.

**Dr Nabila Youssouf** officially joined as the CPN senior neonatal Research Manager in November 2014, having previously been the lead Clinical Trials Manager at Imperial’s Joint Research Office.

**Vania Oliveira** was appointed as the lead neonatal neurology Research Nurse in January 2015. Vania is currently working as an MR Research Nurse at St Thomas Hospital, and will join the CPN in March 2015.

March 2014: Opening of the Centre for Perinatal Neuroscience
(Sponsored by Inspiration Health Care, UK)

May 2014: Pete Lally received an ISMRM travel award for his work on NODDI in south Indian population, Milan, May 2014

August 2014: Farewell to Shea Addison
After a successful and highly productive 2-year period with our research group, Shea returned to New Zealand in August. Shea will be dearly missed by all of us. Shea was the key person undertaking the genetic testing for the CICUS study in collaboration with Professor Patricia Munroe at the Barts Genome Centre.

October 2014: Farewell to Denis Azzopardi
The Unit organised a farewell breakfast get-together for Professor Denis Azzopardi, on his retirement in October 2014. Denis has been at the forefront of neonatal neuroprotection research for many years and we wish him all the best for a happy retired life.
November 2014: First CPN Open Research Day

Team members gave bite-size presentations of their research projects – the audience asked pertinent questions and the discussions and suggestions will help refine protocols to improve research.

The high attendance and positive feedback received showed that there is a demand for this type of open discussions with various professionals and specialties and we are looking to make the Open Research Day a recurrent fixture in the academic calendar.

December 2014: Pete Lally secures a prestigious NIHR doctoral fellowship

In this work Pete will develop rapid MR spectroscopy sequences that can be widely used within the NHS as a clinical tool, and will examine the interaction of perinatal infection on brain injury in encephalopathic infants.

December 2014: First ever UK Neonatal organ donation from Queen Charlottes and Chelsea hospital generated wide spread media interest.

The donation was facilitated by Dr Gourav Atreja and Dr Sunit Godambe, (Consultant Neonatologists), and was recently published in Archives of Diseases in Childhood and made headline news in the UK and abroad.
How to undertake a Neonatal Research Project

All Imperial neonatal research projects, internal or external, need to have ethics and R&D approvals, and a sponsorship agreement for indemnity, before starting recruitment.

Collaborations with the Centre for Perinatal Medicine are strongly encouraged both within and external to Imperial College London to explore magnetic resonance biomarker applications. We have a limited number of projects that can be conducted at any one time hence we will focus of high quality studies as evidenced by external peer reviewed funding by research councils or other major funding bodies. We are an academic centre and not just a ‘recruitment centre’ or ‘tissue sample collectors’, so if you do wish to collaborate with us, please discuss with us at the earliest opportunity, rather than when you are ready to recruit to avoid disappointment. Availability and priority will be given to collaborative projects with the Centre of Perinatal Neuroscience, although the imaging facilities can be made available purely as a resource. The cost of MR scanning is £500 per hour.

All project requests must be submitted electronically by completion of a Project Proposal form. The Chief Investigator will be invited to attend a teleconference with the CPN Management team within 1 week of submission of the form.

Project review

Collaborative funded projects take priority, but a limited number of unfunded pilot projects will be supported, if they are likely to lead to further grant applications or major publications. Criteria assessed for pilot and funded projects will include the quality of the science, alignment with the research interests of the division, the degree of in-house development required, timelines of the project in the context of current work load, overlap with any existing projects and data sharing for recruitment of babies into multiple studies, opportunities for undertaking nested projects and the scope for extended research and funding.

All investigators hoping to undertake any neonatal research projects at Queen Charlotte’s and Chelsea hospital or St Mary Hospital should contact Dr Nabila Youssouf (Neonatal Research Manager; E mail: Nabila.youssouf@imperial.ac.uk) in the first instance.

Once the project is accepted by the neonatal team, the Research Governance process can start in collaboration with the Trust Divisional Manager, Feasibility Officer, R&D and any other local department involved, with the view of obtaining NHS Permission within the applicable national timelines.
Presentations at major conferences


King C, Winter R. Use of breast milk fortifier in a preterm baby post discharge to avoid use of formula. Perinatal Medicine, Harrogate, June 2014

Weaver G, King C. The development of a clinical protocol for the analysis of donor breast milk fed to very preterm babies. Perinatal Medicine, Harrogate, June 2014

King C. Three year experience of using breast milk fortifier post discharge in preterm babies. Perinatal Medicine, Harrogate, June 2014

SS Pauliah, PJ Lally, A Bainbridge, DL Price, S Addison, FM Cowan, P Satodia, SC Wayne, A Soe, S Pattimayak, S Harigopal, IJ Abernethy, MA Turner, P Clarke, O Kirmi, J Cheong, SN
Basheer, B Jones, A Alavi, S Shankaran, EB Cady and S Thayyil. Neonatal Encephalopathy in the Cooling Therapy Era - Preliminary Cerebral Magnetic Resonance Results from the MARBLE Consortium, Pediatric Academic Society meeting, Vancouver, May 2014


Major Grants and other Academic Activities

Grant Income

We secured approximately £1.6 million grant income in 2014

- MARBLE Study (CI: Sudhin Thayyil; NIHR: £1 million (0.5m transferred to Imperial)
- NAChiLD and Cool Xenon trials (CI: Sudhin Thayyil; BRC and LCRN support: £0.8 million)
- MARINE study (PI: Pete Lally; NIHR fellowship: £0.3 million)

Supporting Academic Activities

- Denis Azzopardi, Aniko Deierl and Nigel Basheer talked at the London Neonatal Neurosyposium in May 2014
- Sudhin Thayyil gave key note lectures on neonatal neuroprotection at the International Neonatal Congress in Panama, September 2014
- Alexander Rakow and Nabila Youssouf are Experts panel members of research ethics committees.
- Sudhin Thayyil served on NIHR i4i and NIHR RfPB funding panels
- Ravi Swami conducted a number of Bayley III training workshops and neonatal simulation courses in India
- Sudhin Thayyil lectured on Imperial Pediatric MSc course on neonatal neurology
- Pete Lally gave invited lectures at C3N and University College London MR physics group
Publications

2014


2015

Atreja G, Godambe S. First neonatal organ donation in the UK. *Arch Dis Child Fetal Neonatal Ed.* 2015 Jan 19

Research Plans for 2015

Now that an effective research infrastructure is in place, 2015 is expected to be a year of high recruitment into existing studies and of more output in reputable journals. In addition, some of the new 2015 initiatives are given below.

**CPN starter Grants for MR Biomarkers**
These grants will fund cross cutting pilot studies using MR Biomarkers in newborn, children and adults. Each project will have £3000 worth of MR development/scan time.

**CPN Starter Grants for neonatal nurses**
These grants (£500 each) will fund short project/systematic reviews led by clinical neonatal nurses at Imperial neonatal service

**Neonatal MR Imaging and Spectroscopy Course**
A new national course on optimal neonatal MR scanning and spectroscopy, including hands on workshops. The course is intended for radiographers, nurses and doctors dealing with babies undergoing MR scans.

**Neonatal MR Spectroscopy Clinical Service**
This project will be initially piloted at selected large NHS neonatal units. Our MR team will train the local radiographers in acquisition and post-processing techniques for MRS.

**Ear Canal aEEG device for babies**
This is an exciting collaboration with Professor Danilo Mandic at the Imperial Signal Processing unit, to develop an ear plug device for remote monitoring of aEEG in babies

**Clinical research fellowships (MD/PhD)**
We have number of MD/PhD opportunities for neonatal trainees, and these will be advertised very soon. For more information please contact the CPN director.

**3 Telsa Fetal MRI and MRS**
Although 1.5T fetal MRI is widely used as a clinical tool, 3T fetal MR is challenging due to the difficulties in sequence optimisation and specific absorption rate issues. Along with the MR Physics teams at Wayne State University, Michigan and University College London, we are developing sequences for 3T fetal and placental MRI and MRS.

We also hope to provide a fetal MR clinical service for the fetal medicine team at Queen Charlottes and Chelsea and St Mary’s Hospitals in the near future.

**Research design and statistical advice clinics**
A quarterly clinic led by the CPN director and research manager to advice on study designs, sample size calculations, funding and governance aspects of neonatal research projects. The clinic will be open to all neonatal NHS staff at Imperial Neonatal Services. Please contact Nabila to make a booking.
Thank You

The CPN team wishes to thank all the collaborators mentioned in this report for their continued hard work and their commitment to conduct high caliber research projects. We would not be able to do our work without the support of our College and Trust colleagues and well-wishers, in the UK and internationally.

A special note of thanks to our funders, particularly the Weston family and the Imperial Biomedical Research Centre, without which none of our work be possible.
The School of Athens painting by Renaissance artist Raphael epitomises the Centre for Perinatal Neurosciences’ goal: to facilitate knowledge within a multidisciplinary team, where everyone’s input is highly valued, with the hope of positively impacting the wider population.

Discovering and understanding ourselves and the world around us is not optional. It is an ethical obligation. On these terms science is secular. It does not, nor cannot have denominational connotations.