Who wants to be a millionaire?

Pete Lally (MR Physicist and NIHR doctoral research fellow at CPN) continues his lucky run with grants and awards – an NIHR Clinical Trials Fellowship with Imperial Clinical Trials Unit; a project grant from Cerebral Palsy Alliance to examine the effect of perinatal infection on brain injury in neonatal encephalopathy; and a travel award for a platform presentation at the prestigious ISMRM (International Society for Magnetic Resonance in Medicine) at Paris (June 2018) on the MARBLE paper.

Pete has also invented a new post-processing method for accurately quantifying cerebral metabolites by MR spectroscopy which is currently being prepared for a patent application. If lucky, he may well be the next Imperial ‘millionaire’. He has been appointed as the senior MR Physicist at the CPN starting March 2018.

CPN Terminator

Nothing stops Paolo Montaldo (MRC doctoral research fellow at CPN) from working - not even a fractured right arm. Typing with his left hand in the hospital bed, Paolo completed his late stage PhD assessment in December 2017.

Paolo is researching gene expression profiles in neonatal encephalopathy under the supervision of Jethro Herberg and Myrsini Kafarou to see if we can categorise the babies with encephalopathy into various subgroups based the underlying disease mechanism.

In most diseases a ‘one size fits all’ approach does not work and personalised therapies are required; neonatal encephalopathy is no exception. So watch this space…
**A Global NHS Trust**

Dr Ravi Swamy, a Consultant Neonatologist at Imperial NHS Trust and the International Bayley Trainer for Pearson conducted his 30th Bayley III course in India. He is training his 600th candidate on Bayley III in the photo below. No wonder he is looking bored!

International Conference on ‘Recent Advances in Neonatology’ organised by Dr Ravi Swamy in Bangalore, March 2018 (photo below).

Ravi is also the director of the Perinatal Trials Unit in Bangalore that co-ordinates the HELIX trial. In between his neonatal intensive care and global health work, he also works as a football coach.

Please note that on most Saturdays Ravi work from a plane (British Airways, London – Bangalore, Seat 12A).

**Key notes........**

Vania Oliveira, a perinatal neurology research nurse and NIHR doctoral research fellow at CPN, delivers key note lectures at the Neocon, New Delhi, December 2017.

Vania has had fellowships from Imperial Charity and the Wellcome Trust previously and is currently undertaking a PhD at Imperial College with an NIHR doctoral research fellowship. She is trying to develop a bedside tool for quantifying brain injury in neonatal encephalopathy using heart rate variability under the supervision of Professor Danilo Mandic at the Electrical and Electronic Engineering Group, Imperial College London.

Good luck, Vania.

**Josephine on a Cool Mission**

Josephine Mendoza, CPN Research nurse training the Sri Lankan and Dhaka (below) HELIX sites on therapeutic hypothermia.
Can magnetic resonance biomarkers accurately predict the long-term outcomes after neonatal encephalopathy?

Easy – if your are doing single centres studies using the same MRI scanner.

Using these with different MR scanner makes is the Holy grail. It took us 7 years to crack this and finally the hard work has paid off.

Pete Lally developed the first ever cross platform (Phillips, Siemens and GE) 3T cerebral MR spectroscopy sequences for multi-centre trials.

We then validated these sequences in the MARBLE (Magnetic Resonance Biomarkers in Neonatal Encephalopathy) study – the largest ever prospective study of MR biomarkers in neonatal encephalopathy. A total of 223 babies were recruited from 8 tertiary centres in the UK and USA over a three-year period. Recruited babies had 3T MR imaging and spectroscopy within 2 weeks of age and neurodevelopmental outcome assessments at 2 years.

Using these sequences, thalamic N-acetyl aspartate [NAA] (a chemical that is only found in neurons) predicted long term neurological outcome after neonatal encephalopathy with an AUC of 0.99 (sensitivity 100%; Specificity 97%).

The study results will be published by Autumn 2018.

We can now use [NAA] as a surrogate biomarker in multi centre trials to speed up the clinical translation of novel drugs. We believe MARBLE will revolutionise the way we do early phase clinical trials in the next decade.

COMPLETED STUDIES

Why do babies die in the womb?

The result of the recently published CiCUS (cardiac ion channelopathy in unexplained still birth) study led by Sudhin Thayyil at Imperial College, in collaboration with researchers at the Barts Genome Centre, UCL and Boston Children Hospital suggest that a small proportion of these deaths could be related to a mutation in KCMJ2, a gene controlling heart rhythms.


These mutations are often genetic (AD), and the risk of sudden death in family could be reduced by appropriate therapy.

Can high dose early Xenon therapy increase hypothermic neuroprotection?

TOBY Xenon trial (low dose late Xenon) led by Azzopardi et al did not show any neuroprotection. We don’t know if this was genuine lack of effect, inadequate Xenon dose/timing or due to inappropriate surrogate MR biomarkers.

Cool Xenon study (Phase II trial randomising to cooling alone or cooling + Xenon) examines the effect of high dose (50%) early (within 5h) of birth) Xenon on MR biomarkers using the MARBLE sequences. The trial is lead by Professor Marianne Thoresen at Bristol, with CPN providing the MR physics expertise, in addition to recruiting 2 babies from QCCH. The trial completed recruitment on 1st March 2018.

If Xenon improves thalamic [NAA] this will lead to a phase III trial and eventual clinical adoption. If not, this would be the final nail in the Xenon coffin.
Does N-acetyl cysteine infusion increase the brain anti-oxidant (glutathione) level in neonatal encephalopathy?

MARINAC (Magnetic Resonance Imaging and N-acetyl cysteine; Phase I trial) trial (Collaboration with South Carolina Medical University) completed the first part where we examined an extensive panel of oxidative stress biomarkers in neonatal encephalopathy (Sánchez, Thayyil, Montaldo et al., Analytica Chimica Acta 2018), change in cerebral MR spectroscopy glutathione levels during N-acetyl cysteine infusion in neonatal encephalopathy and pharmacokinetics.

The CPN team continuously measured the cerebral glutathione levels by 3T cerebral MR spectroscopy during N-acetyl cysteine infusion while providing ventilation and servo controlled therapeutic hypothermia inside our MR scanner in the neonatal unit.

The data are currently being analysed and will inform the next phase of the MARINAC trial.

12h NAC did not provide a sustained blood level, although it did get into the brain. The next step is to do another phase I study with a continuous NAC infusion, followed by a phase II RCT, and then a phase III clinical trial. If NAC survives all these steps, we have a new therapy for encephalopathy associated with infection.

Should low and middle-income countries offer cooling therapy as standard of care in neonatal encephalopathy?

This is a difficult one.

Ninety nine percent of encephalopathy burden occur in LMIC, and there is no other effective therapy.

Is it ethical to withhold such a effective therapy just because all cooling trials were conducted in high-income countries, and no evidence from LMIC is available? Most neonatal treatments in LMIC is extrapolated from high-income country data any way - so why should it be different with cooling?

We conducted a feasibility study of cooling using a low cost servo controlled cooling device on 82 babies with neonatal encephalopathy in India. Although the target temperatures were adequately maintained, almost half of the babies had gastric bleeds, and this was associated with high mortality.

These data suggest that cooling therapy should be considered experimental in low and middle-income countries, and should not be offered as routine care until more evidence from adequately powered randomised controlled trials are available (Oliveira et al., BMJ Paediatrics Open 2018)

Should we follow the Hippocratic oath we all took once “Do no harm first”? Well, it appears clinicians in LMIC have different ideas.

We undertook a national survey of the current cooling practices in India. More than 50% of neonatal units in India now routinely offer cooling therapy using a wide range of indigenous methods including Ice (Chandrasekeran et al., Indian Paediatrics 2018)

Well, well, so that much for the evidence based medicine........
New HELIX centre opened at Trivandrum

A new HELIX centre opened was opened at Trivandrum, Kerala, India in December 2017 in addition to existing eight centres from India, Bangladesh and Sri Lanka. Pete Lally and Vania at the site initiation visit undertaking the 3T MR spectroscopy harmonisation and cooling training.

HELIX trial recruits the 300th baby

HELIX (Hypothermia for Encephalopathy in Low and Middle-Income Countries) is the largest ever cooling trial in the world and is recruiting from several middle-income country public sector settings. All recruited babies have had 3 Tesla MR imaging and spectroscopy using the harmonised sequences developed by the CPN, and neurodevelopmental outcome assessments (Bayley III) at 18 to 22 months. We provide MR physics and governance support to these centres. Photos from the annual HELIX investigators meeting at Chennai below.

How far is too far?

See what Prof Jayashree Mondkar (Dean, Sion Medical College, Mumbai) and Dr Swati Manerkar (Associate Professor of Neonatology) did…….

- Performed Bayley in Dharavi (largest slum in the world featured in ‘Slum Dog Millionaire’) (left photo)

- Took a four hour flight to Calcutta to do Bayley of HELIX baby who migrated from Mumbai (right photo).

There are many things money can buy, but dedication and motivation is not one of them !
CPN Patient and Public Involvement (PPI) activities

Pete Lally discussing neonatal brain injury with general public during ‘Meet the scientist’ event organised by the Brain Sciences Division at Imperial in Dec 2017.

Discussing cooling therapy with penguins

Pete Lally explaining cooling therapy to penguins during an MRI Motion correction workshop at Cape Town (Sept 2017). Pete says penguins are very excited about cooling therapy.

HELIX trial PPI

PPI discussions with parents of babies recruited to HELIX trial at Chennai (March 2018) - Vania on skype at the top. Parents highlighted various difficulties in coming for follow up including loss of wages for the day, why do neurodevelopmental assessment if child is normal, feeling upset with the hospital if the child has disability, lack of permanent address etc.

HELIX Heroines

Indiramma, Monica and Mythili (HELIX research nurses from Bangalore, Institute of Child Health, Chennai and Institute of Obstetrics and Gynaecology) with Sudhin Thayyil in Chennai (March 2018). HELIX trial would not have been possible without the hard work and dedication of these three outstanding neonatal research nurses.
Ongoing and imminently starting CPN multi-centre studies

Heart Beat (heart beat variability in neonatal encephalopathy) study

Multicentre study recruiting from 8 NHS hospitals in the UK. First baby was recruited from Liverpool Women’s Hospital in 2017. Josephine recruiting the first Heart Beat baby from QCCH (photos used with parental consent). We have now recruited over 70 babies to the Heart Beat study.

Imperial PI is Dr Vijay Kumar (Neonatal Consultant)

GENIE (Genomic Imaging in Neonatal Encephalopathy) study

This multicentre study has started recruiting from 20 NHS hospitals. North Tees recruited the first GENIE baby. Total of 9 cases have been recruited so far. QCCH recruitment will begin soon.

Imperial PI is Dr Anup Kage (Neonatal Consultant).

COMET (Optimising Duration of Cooling in Mild Encephalopathy) trial

Cooling therapy is recommended by the NICE as standard of care for babies with moderate and severe encephalopathy, however, efficacy, risk benefits and optimal duration of cooling in mild encephalopathy is unknown.

COMET trial is using a novel trial design recently developed by the MRC Clinical Trials Unit in London for optimising treatment duration.

The primary outcome is thalamic N-acetyl aspartate concentration. Babies will be randomised to different cooling durations and a dose response curve will be created.

COMET, National Investigators Meeting

Left to right – Sudhin Thayyil (Imperial), Ajay Sinha (Royal London Hospital), Aung Soe (Medway), Samir Gupta (North Tees), Santosh Pattanayak (Medway), Neeraj Jain (North Middx), Gaurav Atreja (ICHT), Ujwal Kariholu (ICHT), Kiran Yajamanum (Liverpool)

Left to right – Lisa and Paolo Montaldo (Imperial), Paul Clarke (Norwich), Rachael Edward (UCL), Pete Lally (Imperial), Matteo Quartagno (LSHTM), Prakash Satodia (Coventry), Manobi Boorah (B’ham), Vania Oliviera (Imperial)
It is not always work, we do have a lot of fun at CPN......

CPN team (Sudhin, Vania, Pete, Paolo, Josephine) at the Muir Woods (left) and with the NICHD Neonatal Research Network Investigators in San Francisco cable car (right).

At Marina beech in Chennai (left photo) with Prof Shahidullah (Vice Chancellor, BSMMU, Dhaka) and Assoc Prof Swati Manerkar (Sion, Mumbai) (left). Paolo proposing to Lisa at the NICHD Neonatal Research Network mild encephalopathy investigators dinner in the USA (right). Lisa has now an international backup!

CPN Team at the Golden Gate Bridge (left) and Alcatraz, San Francisco (right). We love prisons!
Feel like joining the CPN family?

- Do you have a burning desire to be at the frontiers of scientific knowledge, and to be the first one to know?
- Are you passionate about improving outcomes of babies with brain injury worldwide?
- Do you enjoy working with data endlessly making your partner/children go mad?
- Do you enjoy writing?
- Are you a finisher?
- Do you get excited with new challenges?
- Can you work collaboratively and selflessly in a small team of highly committed academics supporting each other during good and bad times?

If so, please do get in touch with us (s.thayil@imperial.ac.uk) – we have MD/PhD positions available for dedicated and driven junior doctors and nurses/allied health professionals.

“Never doubt that a small group of thoughtful, committed citizens can change the world; indeed, it’s the only thing that ever has”

Margaret Mead