Protocol V4 (26/02/17)

Near-Infrared spectroscopy for Monitoring brain Oxygenation in Premature infants (NIMO-Prem)

Study type: Prospective observational two-centre study

Note: This two-centre study will run in collaboration with Texas Children's Hospital. However, this protocol is only applicable to the study based in Wellington Regional Hospital, Wellington NZ.

Objectives:
Objectives of this research are to determine in extremely premature infants:

1. The cerebral hypoxia and/or hyperoxia burden associated with an increased mortality and morbidity rate and an increased incidence of neurovascular injuries
2. High and low cerebral perfusion pressures that are associated with an increased mortality and morbidity and an increased incidence of neurovascular injuries
3. The effect of routinely measured physiological parameters on cerebral perfusion and oxygenation. These parameters are:
    a. Cardiovascular function (cardiac output, ductal haemodynamics, systemic blood pressure)
    b. Peripheral oxygen saturation
    c. End-tidal carbon dioxide levels
4. The effect of common neonatal interventions on cerebral perfusion and oxygenation. These interventions are:
    a. Indomethacin for closure of patent ductus arteriosus
    b. Caffeine citrate for prevention of apnoea of prematurity

Inclusion criteria: Preterm infants (<30 weeks gestation) with extremely low birth weight (<1000g) who are born in Wellington Regional Hospital will be considered for recruitment into the study.

Exclusion criteria: Infants with complex congenital abnormalities (significant cardiac or central nervous system malformations, or known chromosomal abnormalities), hydrops fetalis, poor skin integrity, and those for whom a decision for palliation has been made due to their extreme condition will be excluded from the study.

Study methods:
This is a non-invasive observational study, and as such all clinical decisions will be made solely by the attending clinical staff. All relevant clinical information gathered in the study will be shared with the attending clinicians.

Identification of potential participants: Following patients will be identified through daily discussion with the obstetrics and neonatal clinical teams:

- Mothers who are less than 30 weeks pregnant and are admitted to the Wellington Hospital antenatal / labour wards, AND
- Mothers who are in preterm labour or threatened preterm labour, OR
- Mothers for whom a decision for delivery before 30 weeks gestation has been made, OR

- Mothers who are admitted to the antenatal ward for monitoring of maternal or fetal condition for whom the obstetric team are considering delivery before 30 weeks to optimise maternal or fetal condition.

Consent: In all cases prospective consent will be obtained from parents of potential participants. Parents will be approached antenatally on the mother's admission to Wellington Hospital so that there is plenty of time for them to consider whether they wish to participate in the study.

Study timeline and tests:

Time	Tests
As soon after birth as possible (within 4hrs)	Initiate the following continuous physiological measurements (<u>total duration 72hrs</u>): • Cerebral regional oxygenation • Arterial blood pressure (**routine clinical practice**) • End-tidal CO_2 (**routine clinical practice**) • Peripheral arterial saturation (**routine clinical practice**) Perform the following investigations: • Cranial ultrasound scan (CUSS) • Transcranial Doppler (TCD) ultrasound – 15 minutes • Urine test for biomarkers of hypoxic/ischaemic brain injury (S100B and Activin A)
Within 12hrs of birth	• Cardiac echocardiography (**routine clinical practice**)
Day 2-3	• CUSS, TCD and urinary biomarkers (S100B and Activin A) on day 2 and day 3 of life
1 week	• CUSS (**routine clinical practice**)
1 month	• CUSS (**routine clinical practice**)
Term-equivalent age	• MRI brain ('feed and wrap' technique, i.e. <u>no</u> sedation will be used)
12-24 months of age	• Bayley Infant Neurodevelopment Scales (**recommended as routine clinical practice**)

<u>Continuous physiological measurement during the first 72hrs:</u>

1. *Cerebral regional oxygenation*: This will be measured using INVOS™ 5100c/ OXYALERT™ NIRSensor (Infant/Neonatal) as its safety and reproducibility have already been validated in extremely premature and/or low birth weight infants. If the skin condition of the infant is considered to be fragile the adhesive surface of OXYALERT™ NIRSensor will be covered using a sterile Tegaderm® and the probe will be place over the forehead using a soft crepe bandage or a CPAP hat (if the infant is on CPAP). The skin underneath the probe will be checked regularly during the infants' routine 4 hourly cares.

2. *Arterial blood pressure*: Arterial blood pressure via umbilical arterial catheter (UAC) is **routine clinical practice** in this cohort of patients. Physiological Pressure Transducer/ Disposable Clip-on Domes™ (ADInstruments) will be integrated into the existing circuit and data will be acquired in real-time using PowerLab/LabChart system (ADInstruments). The data collection will continue for 72hrs *or less if the UAC is no longer clinically indicated (*i.e. the UAC will NOT be kept in-situ purely for the purpose of this study)

3. *End-tidal CO_2*: Measurement of end-tidal CO2 (capnography) is **routine clinical practice** in this cohort of patients while they are on mechanical ventilation. Once they are extubated the capnography will be attached to the 'exhaled air' pipe of the CPAP/SiPAP circuit to non-invasively capture this data. The ADInstruments Gas Analyser and Philips Filter-H set (sidestream microstream capnography) will be used to capture this data, and an equipment validation study in a neonatal population of patient is current underway (Ethics ref: 16/CEN/82).

4. *Peripheral arterial saturation*: Continuous measurement of peripheral saturation is **routine clinical practice** in this cohort of patients. This data will be captured using the ADInstruments Oxymeter Pod.

Other investigations

1. *Biomarkers of hypoxic/ischaemic brain injury (S100B and Activin A)*: A piece of cotton wool will be placed in the nappy to non-invasively collect the first urinary sample, and repeated on day 2 and day 3 of life. The specimen will be stored securely within the University of Otago laboratory until batch analysis using commercially available ELIZA kits.

2. *Brain perfusion pressure*: Middle cerebral artery blood flow velocity (MCA-BFV) will be measured using the ST3 Transcranial Doppler Ultrasound System (Spencer Technologies). A Doppler ultrasound probe will be gently held by hand on the infant's scalp to measure the MCA-BFV for 15mins. This measurement is repeated once a day over the first 3 days.

3. *Cranial ultrasound (CUSS)*: This is **routine clinical practice** in this cohort of patients in order to detect intraventricular haemorrhage and/or periventricular leukomalacia (IVH/PVL). In non-participating infants, these scans are routinely performed at 1 week and 1 month of age with additional scans performed in the first few days of life if clinically indicated. Participating infants will routinely receive three scans in the first 3 days of life (once daily) in addition to 1-week and 1-month scans, and all relevant

clinical information will be shared with the attending medical team to help guide infants' clinical management.

4. *Cardiac echocardiography*: This is **routine clinical practice** in this cohort of patients. Initial scan findings, as well as subsequent scan findings (if they are performed for clinical reasons) will be recorded as part of this study.

5. *MRI brain*: MRI brain performed at term-equivalent age (around the infants' 'due-date') could detect subtle white matter injuries that are not visible on cranial ultrasound. MRI will be performed using 'feed and wrap' technique without sedation either in Wellington Hospital or at their local institution if MRI facility is available. All relevant clinical information will be communicated with the attending medical team to help guide infants' clinical management.

6. *Bayley Infants Neurodevelopmental Scales*: A formal neurodevelopmental assessment of all infants born extremely preterm is **recommended as routine clinical practice** in order to screen for neurodevelopmental disabilities and to institute appropriate multidisciplinary interventions. However, due to logistical difficulties only half of extremely preterm infants born in Wellington Regional Hospital currently receive formal neurodevelopmental assessments (local audit data, 2015). Infants participating in this study will be proactively followed up with a formal neurodevelopmental assessment using the Bayley Infants Neurodevelopmental Scales, and all relevant clinical information will be shared with the attending medical team to help guide the infant's clinical management.

Patient characteristics

The following demographic and clinical information will be gathered as part of the study (only after informed consent has been obtained).

- Maternal demographics
- Relevant maternal past medical, antenatal and perinatal history
- Infant's perinatal and postnatal history

Outcome measures and power analysis:

The primary outcome measure is the cerebral hypoxia/ischaemia and hyperoxia burdens that are associated with an increased mortality rate and an increased incidence of neurovascular injuries. As per recommendation by our biostatistician (Prof. Greg Atkinson) the Receiver Operating Characteristics (ROC) curve will be used for statistical analysis of the primary outcome measure. A sample size of 120 infants will be required to detect 12% difference with the Area Under the Curve (AUC) of 0.75.

Anticipated duration of study:

Wellington NICU have achieved 80-90% recruitment rates in previous studies in the same cohort of extremely preterm infants (e.g. APTS, Provide study) We anticipate a similar participation rate in this study, and a total duration of 2 years will be required to complete the early phase. The neurodevelopmental follow-up phase (the Bayley neurodevelopmental scales) will occur with a 12-24 month time lag.