Benefits of Analysing Brain

Biomarkers in perinatal care: a prospective observational cohort study

Short Name: BABBIES Trial

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Protocol Version # **1**

Protocol Date: **29/05/2022**

Ethics Statement

The study will be conducted in accordance with the *National Statement on Ethical Conduct in Human Research* (2007), the *CPMP/ICH Note for Guidance on Good Clinical Practice* and consistent with the principles that have their origin in the Declaration of Helsinki. Compliance with these standards provides assurance that the rights, safety and well-being of trial participants are respected.

Contents

Summary

Study title:	**B**enefits of **A**nalysing **B**rain **Bi**omark**ers** in perinatal care: a prospective observational cohort study (**BABBIES Trial**)
Protocol version	V 1, dated 29/05/2022
Objectives	
Primary objective	1) Provide feasibility data on the testing of umbilical cord blood for NfL and tau
Secondary objectives	1) Provide a "normal range of plasma NfL and tau" associated with normal healthy deliveries 2) Provide preliminary data linking cord blood NfL and tau to adverse perinatal outcomes 3) Compare cord blood NfL and tau in elective caesarean deliveries to other deliveries involving a period of labour 4) Provide preliminary data linking cord blood NfL and tau to foetal developmental abnormalities 5) Provide preliminary data linking cord blood NfL and tau to abnormalities on intrapartum monitoring (CTG, scalp lactate) 6) Assess the impact of gestational age on plasma NfL and tau 7) Assess the impact of birth weight on plasma NfL and tau 8) Assess the impact of the duration of the 2nd stage of labour on plasma NfL and tau 9) Determine the proportion of consented patients in whom inadequate cord blood is not collected
Study design	Prospective observational cohort study
Planned sample size	110
Selection criteria	Caesarean deliveries and deliveries involving a period of labour
Study procedure	Umbilical artery and vein cord blood samples (3mL) will be obtained from births at RPAH by the midwife (when feasible)
Statistical considerations	A sample size of 92 placentae (24 elective caesareans, 68 laboured deliveries) is required to ensure that the value for the mean plasma NfL has a 95% confidence interval not exceeding 3pg/mL, with an added 20% (18 patients) to account for issues with biospecimen collection and storage and non-healthy deliveries.
Duration of the Study	6 months

1. BACKGROUND AND INTRODUCTION

1.1. DISEASE/PROPOSED INTERVENTION BACKGROUND

Hypoxic–ischaemic encephalopathy (HIE) is a common cause of neonatal encephalopathy (NE), affecting 1–2 in every 1000 live births[1,2]. Approximately 60% of those with moderate–severe HIE will die in the neonatal period, and one quarter of those who survive will experience long-term neurocognitive deficits[3-7].

Therapeutic hypothermia is the mainstay of treatment in moderate and severe HIE[8-11]. If applied appropriately, it increases the rate of survival with normal neurological outcome at 18 months from 24% to 40% (relative risk: 1.63, 95%CI: 1.36–1.95)[11]. Early identification of possible HIE is crucial, as hypothermia must be induced within 6 hours post-delivery[12]; so critical is this time window that definitions of HIE severity have evolved over time to reflect this urgency of diagnosis[13]. However, identifying at-risk neonates is difficult, because current practice relies on clinical signs, cardiotocography and acid-base monitoring all of which are limited in their sensitivity in HIE detection[14,15]. Furthermore, the manifestation of clinical signs is significantly influenced by the timing of the hypoxic insult, with recent hypoxia more likely to be subclinical, allowing the neonate with early HIE to slip undetected through the 6-hour detection time-limit[16]. The shortcomings of current HIE detection methods are in part because none of them detect neuronal injury directly. Neuronal injury biomarkers may have prognostic significance and assist with patient selection for future neuroprotective HIE therapies[17,18].

It was traditionally believed that neonates with mild HIE have comparable long-term neurological function to their non-encephalopathic counterparts[19,20]. However, recent evidence suggests that HIE severity and long-term outcome may exist on a continuum[21-24]. Mild HIE cases are more difficult to detect using current clinical criteria [15], and may actually represent an evolving HIE due to a recent hypoxic insult. Biomarkers may help identify such patients who will benefit from therapeutic hypothermia despite being classified as having 'mild' HIE as per current clinical criteria [15,25], which will need to be assessed in future clinical trials.

Biomarkers of neuronal injury obtained from umbilical cord blood represent a tantalising addition to the toolkit for HIE detection and risk stratification. Many plasma and cerebrospinal fluid (CSF) biomarkers obtained in the hours and days post-delivery have been shown to be elevated in HIE compared to controls[26-34]; however, the time delay to obtain serum or CSF samples from a neonate risks jeopardising eligibility for therapeutic hypothermia. Studies of umbilical cord blood biomarkers in HIE have been scarcer than those of neonatal plasma biomarkers, but the findings are nonetheless promising[35-38]. We propose that monitoring the neuronal injury biomarkers, neurofilament light (NfL) and tau, may prove a useful decision aid in peripartum care.

Neurofilament light is a structural protein of neurons that is released at the time of many types of neuronal injuries[39], ranging from ischemia (e.g., stroke)[40], to inflammation (e.g., surgery or multiple sclerosis)[41,42] or dementia (e.g., Alzheimer's disease)[43]. We have conducted a systematic review and identified two observational studies that have shown that NfL is raised in the umbilical cord blood of babies with adverse perinatal outcomes compared to healthy babies[36,37]. Toorell et al. [36] found that the level of NfL in the umbilical cord blood was 39.2 pg/mL in 10 neonates with asphyxia compared to 23.3 pg/mL in 18 healthy controls (p=0.016). Depoorter et al.[37] showed that the level of NfL in the umbilical cord blood was inversely correlated with body weight, gestational age, and 5- and 10-min APGAR scores in a cohort of 203 term and preterm neonates. A published abstract (with no full-text article) also demonstrated that levels of cord blood NfL were lower in neonates delivered in the context of an elective caesarean section than those born via a vaginal delivery[44]. These findings are

supported by studies of CSF NfL in asphyxia[26] as well as those from neonatal intensive care[45]. Altogether, these studies support NfL as a predictive biomarker of HIE and perinatal morbidity.

Tau is a phosphoprotein critical to microtubule stability in neuronal axons that is released into the bloodstream in the setting of CNS injury. Tau has been shown to be elevated in blood of patients with various neurodegenerative diseases[46], brain metastases[47], and obstructive sleep apnoea[48]. Our systematic review revealed three studies that analysed plasma tau levels in umbilical cord blood. Turc et al. found that umbilical cord blood tau was lower in neonates delivered by caesarean section rather than vaginal deliveries[49]. Another study has shown that levels of tau in the cord blood are higher in very-low birth weight (VLBW) neonates with foetal growth restriction (FGR) compared to VLBW neonates without FGR, but this difference between groups was not present in serum samples from days 1–5 of life[50]. Toorell et al, who also looked at NfL, noted a higher plasma tau concentration in 10 neonates with intrapartum asphyxia compared to 18 healthy neonates (48.0 vs. 11.7pg/mL, p=0.03)[36]. Together, these findings suggest that umbilical cord blood tau may be reflective of perinatal stress and neuropathology.

We propose to test whether collection of umbilical cord blood is feasible at RPA, as a forerunner for clinical trials in the use of NfL and tau as a decision aid in obstetric care, as a prognostic outcome in neonatology, or as a probe to study the safety of obstetric anaesthesia approaches.

1.2. RATIONALE FOR PERFORMING THE STUDY

Any approach to reduce the burden of adverse perinatal outcomes would be a major advance. A decision aid that directly measures brain injury could represent a major advance over current indirect approaches, such as measuring CTG or scalp lactate. In the future, we hope to develop a point-of-care NfL and tau measure that may be used as an adjunct or as a replacement to scalp lactate testing of the foetus, for decisions in labour ward regarding the optimal timing of delivery.

Our focus is on improving perinatal outcomes. A better decision-making aid may enhance:

1. De-escalation of care through confirming the baby is healthy
2. Escalation of obstetric care in a vulnerable baby
3. Understanding the treatment needs in neonatology
4. Improving the safety of anaesthetic care

This study will provide feasibility for a district-wide research cohort study of NfL and tau cord blood levels and perinatal outcomes. A Sydney-based NfL-SIMOA service is being developed in Sydney and with academic and industry partners we will develop a point-of-care testing device for use across peripartum units.

2. HYPOTHESIS

We hypothesise that the range of the 95% confidence interval for the true mean of plasma NfL will be <3pg/mL in the 110 umbilical cord blood samples.

3. STUDY OBJECTIVES

3.1. PRIMARY OBJECTIVES:

1) Provide feasibility data on the testing of umbilical cord blood for NfL and tau

3.2. SECONDARY OBJECTIVES

1) Provide a "normal range of plasma NfL and tau" associated with normal healthy deliveries
2) Provide preliminary data linking cord blood NfL and tau to adverse perinatal outcomes
3) Compare cord blood NfL and tau in elective caesarean deliveries to other deliveries involving a period of labour
4) Provide preliminary data linking cord blood NfL and tau to foetal developmental abnormalities
5) Provide preliminary data linking cord blood NfL and tau to abnormalities on intrapartum monitoring (CTG, scalp lactate)
6) Assess the impact of gestational age on plasma NfL and tau
7) Assess the impact of birth weight on plasma NfL and tau
8) Assess the impact of the duration of the 2nd stage of labour on plasma NfL and tau
9) Determine the proportion of consented patients in whom inadequate cord blood is not collected

4. STUDY DESIGN

4.1. DESIGN

4.2. EXPECTED PARTICIPANT NUMBERS

110 participants at Royal Prince Alfred Hospital

4.3. DURATION OF THE STUDY

6 months

4.4. ENDPOINTS

PRIMARY ENDPOINTS

95% confidence interval for mean umbilical cord plasma NfL of 3pg/mL or less

SECONDARY ENDPOINTS

Range of umbilical cord plasma NfL and tau values in healthy deliveries
Correlation of umbilical cord plasma NfL and tau with adverse perinatal outcomes
Correlation of umbilical cord plasma NfL and tau with intrapartum investigation results (e.g., CTG, scalp lactate)
Correlation of umbilical cord plasma NfL and tau with intrauterine developmental abnormalities
Influence of gestational age, mode of delivery, and birth weight on umbilical cord plasma NfL and tau

Influence of duration of 2nd stage of labour on umbilical cord plasma NfL and tau
Number of consented patients in whom an adequate sample for analysis is not collected

4.5. CENTRE

Royal Prince Alfred Hospital

5. STUDY PARTICIPANTS

5.1. INCLUSION CRITERIA

Inclusion Criteria:

Planned delivery at RPAH

Any route of delivery (vaginal delivery or elective/emergency caesarean sections)

Willingness to provide informed consent

English speaking to permit informed consent

5.2. EXCLUSION CRITERIA

Exclusion Criteria:

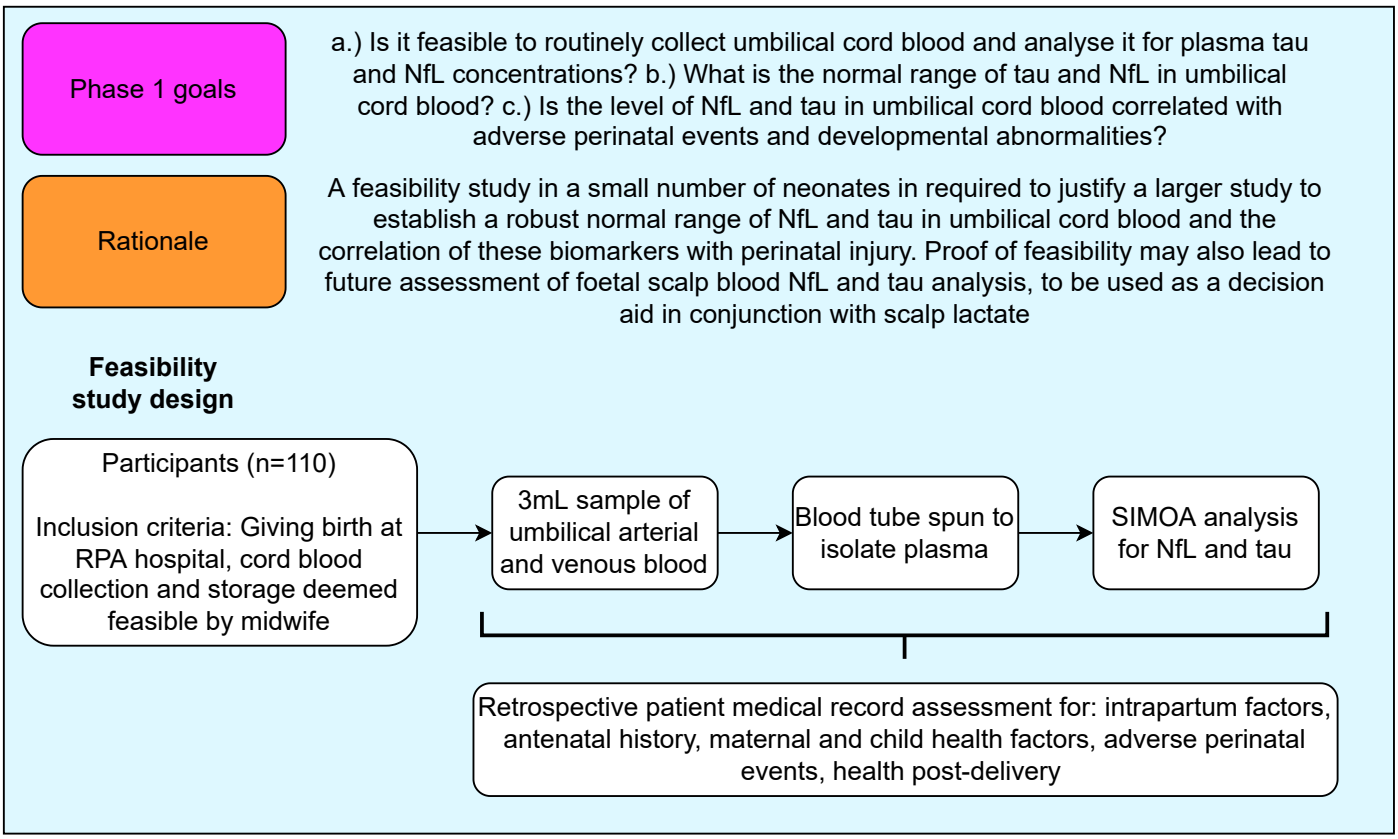
Expected infeasibility of sample collection (at midwife's discretion)

Non-English speaking

Participants with a history of a psychological illness or other conditions which may interfere with their ability to understand the study requirements or provide consent

6. STUDY PROCEDURES

6.1. STUDY FLOW CHART



We will prospectively collect umbilical 3ml of cord blood from 110 placentae. Umbilical cord blood samples will be collected by midwives in theatre or the birthing suite. All patients giving birth will be eligible for inclusion in the study. The exclusion of specific patients (e.g., category 1 emergency caesarean cases) may be at the discretion of the midwife, if collection of umbilical cord blood samples is not feasible. Cord blood required for standard of care testing of rhesus and blood gas analysis will be taken as a priority. Only once the required sample volume for this purpose has been obtained will the additional blood for this study be collected. Cases where the patient was consent but an adequate sample of blood was not able to be taken, for whatever reason, will be recorded. Blood will be stored by the midwives in the fridge in a labelled box, for later collection by a member of the Department of Anaesthetics. Biospecimens will be sent to an external lab for analysis (see section 6.1.1).

We will access the medical records for all included patients. Data extraction will include: weight at birth, gestational age, duration of second stage of labour, mode of delivery, maternal and baby health history, antenatal care history, peripartum events and monitoring, and neonatal outcomes (see the Case Record form in the appendix).

6.1.1 BIOSPECIMEN EXPORTATION AND ANALYSIS

Each sample will be spun and plasma aliquots will be stored in the department's freezer. All cyrovials are de-identified and barcoded, a bio-specimen log is kept on the secure server on the lab computer, only authorised research staff will have access to this log. De-identified plasma samples will be sent to Dr. Henrik Zetterberg, University of Gothenberg, Sweden for analysis. Samples will be sent via TNT or Auspost and will adhere to the company guidelines for biological samples sent by air. Additionally we will ensure to follow the National Pathology Accreditation Advisory Council document- requirement for packages and transport of pathology specimens and associated materials. We will use the services of a company to provide cold chain packaging materials (CoolPac), to comply with the requirements for safe export of biological materials and dry ice. The required forms -UN 3373 and UN1845 - will be completed prior to exportation of biological goods.

The laboratory in Sweden is highly secure with restricted access to University employees only. Only University personnel performing analysis will have access to the de-identified plasma samples and to the de-identified data. University laboratory staff will analyse the samples sing SIMOA analysis of NfL and total tau. Additionally samples will be analysed for additional markers of injury (e.g. Glial Fibrillary Acidic Protein) and inflammation including cytokines (e.g. IL-6 and IL-8). The samples will placed in hazardous waste and be destroyed by incineration after analysis.

A Material Transfer Agreement (MTA) will be submitted as part of the RPAH Governance requirements.

6.2. INVESTIGATION PLAN

6.2.1. METHODOLOGY

Interventions	**Enrolment**	**Immediately post-delivery**	**2–4 weeks post-delivery**
Participant Consent	✓		
Inclusion / Exclusion criteria	✓		
Adverse Event & Serious Adverse Event Assessment		✓	
Umbilical artery + vein blood sample collection		✓	
Patient medical record assessment			✓

6.2.2 ADVERSE EVENTS/SERIOUS ADVERSE EVENTS

We anticipate no serious or non-serious adverse events with our study.

6.3. STUDY PROCEDURE RISKS

There is a risk of blood exposure to the midwife collecting umbilical cord blood samples. This will be minimised by standard blood precautions including the use of personal protective equipment. There is a possibility of damage to placenta in the process of collecting umbilical cord blood samples, which may interfere with placental histopathology, if it is indicated. The overall risk of this is very low. Both of the aforementioned risks of our study are offset by the fact that cord blood sampling is taken as standard of care in all patients giving birth at RPA—we will only be adding to the amount of blood taken, rather than affecting the decision of whether blood should be taken or not. The extra 3mL of blood obtained as part of this study is unlikely to represent any meaningful increase in the baseline risks of cord blood sampling described above. Blood will be taken for rhesus and cord gas analysis as a priority, and we will only assess blood that is provided in surplus of these requirements. We will not use cord blood that is otherwise required for essential investigations at the time of birth. As such, research activities will not disrupt any standard care.

6.4. PARTICIPANT RECRUITMENT AND SCREENING

All patients giving birth at RPAH will be eligible for recruitment. Screening and recruitment will take place on admission to the birthing suite at the discretion of the midwife.

6.5 RECRUITMENT OF ABORINGINAL AND TORRES STRAIGHT ISLANDER PATIENTS

In line with the National Best Practice Guidelines for Collecting Indigenous Status in Health Data Sets (AIHW 2010) we will be collecting demographic data on identification of Aboriginal or Torres Straight Islander origin.

In accordance with the National Statement, Chapter 4.7, we will seek ethical approval from the HREC of the Aboriginal Health and Medical Research Council (AHMRC). Cultural differences and power differentials will be mitigated by being transparent in the consent process, engaging in open dialogue with participants and inviting cultural representatives/family members and social supports to guide the decision making process.

6.6. PARTICIPANT ENROLMENT

Participants will be enrolled into the study after the informed consent process has been completed and the participant has been assessed to meet all the inclusion criteria and none of the exclusion criteria. Study participants will receive a study enrolment number and this will be documented in the participant's medical (or personal) record and on all study documents.

6.7. INFORMATION AND CONSENT

Informed consent will be obtained from the eligible person giving birth on admission to the birthing suite or labour ward prior to their enrolment in the trial. The participant will be allowed time to discuss with family and a midwife prior to signing consent. The exportation of these biospecimens will be outlined in the Patient Information and Consent Form and all cryotubes sent internationally will be de-identified with barcodes.

A Patient Information Consent Form will be signed by the participant and a copy will be provided to the patient/person responsible as well a copy filed in their medical record. The original consent form will be stored with the study file in a secure locked location within Royal Prince Alfred Hospital. All paper source documents will only be accessible by midwives or research staff who require access.

6.8. RANDOMISATION PROCEDURE

No randomisation will take place as part of this study as per study design.

Blinding

No blinding will take place as part of this study as per study design.

6.9. END OF STUDY TREATMENT/WITHDRAWAL PROCEDURE

The study will end once patient medical records have been assessed.

6.10. PATIENT WITHDRAWAL

Patients or persons responsible may withdraw through proxy consent or if their treating clinician believes it in their best interest to not continue.

7. OUTCOMES

7.1. DEFINITION OF OUTCOMES

'Healthy delivery' will denote a neonate that does not require an emergency caesarean section, prolonged resuscitation at birth, admission to the special care baby unit (SCBU) or neonatal intensive care unit, any re-admission to hospital in the 2 weeks following birth, or has any other documented adverse outcomes (including APGAR score of <7 at 5 minutes[51]) or death in the perinatal period. Healthy deliveries will have no serious documented congenital abnormality, growth restriction or other developmental issue. Babies with no antenatal care data available will be assumed to be developmentally healthy unless there are documented perinatal adverse events.

An adverse outcome will be considered as the presence of any of the above. Intrapartum factors (e.g., abnormal foetal scalp blood sample lactate/pH and cardiotocography abnormalities) will also be considered an adverse outcome for the purpose of analyses.

APGAR scores from 1 and 5 minutes after birth will be collected from the medical record

Gestational weight will be obtained by the first recorded weight following birth

Gestational age will be recorded as per the medical record

Duration of the second stage of labour will be defined as the time from full cervical dilatation (as per progress notes) to the documented time of birth

8. STATISTICAL CONSIDERATIONS

8.1. SAMPLE SIZE OR POWER CALCULATION

On the basis of preliminary data showing that umbilical cord blood NfL is significantly lower in placentae of women undergoing elective caesarean than women who underwent laboured delivery[44], we decided to analyse these two populations separately. Based on one study of NfL in cord blood,[36] we anticipate the interquartile range (IQR) of umbilical vein NfL in non-elective caesarean deliveries to be 17pg/mL. We converted this is to a standard deviation (SD) using the rule of thumb SD = IQR/1.35. To ensure that the 95% confidence interval (CI) of the estimate of the true mean has does not exceed 3pg/mL, we calculated a required sample size of 68 patients. An additional 12 patients were added to account for issues with biospecimen collection and unforeseen emergencies that make collection unfeasible, for a total of 80 patients. For deliveries that were elective caesarean sections, based on another study that delineated caesarean sections from vaginal deliveries[37], we estimated the IQR to be 10pg/mL. This results in a sample of 24 participants required to establish a 95%CI of 3pg/mL for the true population mean. We increased this to 30 patients to account for issues with blood collection and storage. The total sample size including all modes of delivery is therefore 110. We will include consented patients in whom an adequate sample of cord blood is unable to be obtained in the 110 participants, in order to inform the feasibility and sample size calculation of a future study. However, given the NfL/tau concentrations will not be obtained, these patients will be omitted from the analysis.

8.2. PROVIDE A DETAILED ANALYSIS PLAN

Differences in plasma NfL and tau between healthy neonates and those with adverse outcomes will be assessed by independent samples t tests or Mann–Whitney U tests, depending on distribution.

The area under the curve (AUC) of the receiver operating characteristic (ROC) curve will be calculated to assess the test characteristics of elevated cord blood NfL and tau in the prediction of adverse perinatal outcomes. Outcomes will be selected for ROC analysis if there is a statistically significant difference observed between healthy/diseased

neonates. The threshold elevation will be determined specifically for each outcome of interest, based on the observed difference in biomarker concentrations between groups. We will compare this to the AUC for CTG abnormalities (binary: present/absent) and scalp lactate elevation for the prediction of the same outcomes.

The normal range of plasma NfL and tau for healthy neonates will be established using the value range in which 95% of confirmed healthy neonates fall.

Scalp blood lactate concentrations with be compared to umbilical cord NfL and tau concentrations using linear regression. The correlation between the presence CTG abnormalities and NfL and tau concentrations will be assessed by independent samples t-test or Mann–Whitney U test, depending on distribution

Our initial analyses will be done independently for elective caesarean section deliveries vs. all other deliveries. However, further adjustments to baseline data may be required. Levels of tau and NfL for the above four analyses may be adjusted based on the multivariable regression analysis described below, if some factors (e.g., gestational age) are revealed to likely confound the outcome.

Linear regression models will be used to assess the correlation between gestational age, birth weight, and duration of 2nd stage of labour and plasma NfL/tau. The relationship between mode of delivery and plasma Nfl/tau will be compared using independent samples t test or Mann–Whitney U test, depending on distribution. All the aforementioned variables will be combined into a multivariable regression model for the prediction of plasma Nfl/tau to increase precision and adjust for confounders.

9. DATA COLLECTION

9.1. PARTICIPANT REGISTRATION

Participants will be registered/enrolled for the trial at the time of consent and will be provided with a study ID.

9.2. FORMS AND PROCEDURE FOR COLLECTING DATA

All data will be collected on a paper Case Report File (see appendix) or recorded directly to an electronic CRF. Any paper CRFs will be de-identified and labelled with patient ID number and data will be transcribed to REDCAP database. The RedCap database will be accessible only by approved members of the research team. Once the study has concluded the PI will be the custodian of the database. All paper documents will be securely stored in a locked cabinet as per legal requirements. Paper documents will be destroyed 15 years post-study.

9.3. CASE REPORT FORMS AND SCHEDULE FOR COMPLETION

A case report form will be provided in the appendix. This study is completed following patient medical record assessment.

9.4. DATA FLOW

Protocol → CRF Design → Patient data collected in CRFs → Patient data in CRFs converted into raw data sets → Raw data sets → Create Tables/Listings/Figures → Create Analysis → Report

10. QUALITY CONTROL AND ASSURANCE

10.1. CONTROL OF DATA CONSISTENCY

All data will be collected by research staff (see CRF). Data will be collected on paper CRFs and de-identified using patient study IDs. All data will be transcribed to RedCap with permission to access only granted to study doctors and authorised research staff.

If feasible eCRFs will be used to ensure direct entry to improve efficiency and reduce entry errors, reduce data queries, missing data and maximise completed data.

10.2. PROTOCOL AMENDMENTS

All protocol amendments will be submitted to the HREC for approval prior to use. Trial sites will follow their local governance protocols to gain approval to commence this trial.

11. ETHICS

11.1. INVESTIGATOR AUTHORISATION PROCEDURE

Ethics and Governance approval will be obtained via the local HREC and governance offices prior to commencement of the study.

11.2. PATIENT PROTECTION

Research doctors and staff will ensure that the study is completed in accordance with the guidelines set out in the *National Statement on Ethical Conduct in Human Research* (2007) (the *National Statement*) and the *CPMP/ICH Note for Guidance on Good Clinical Practice* and any other relevant legislation/guidelines.

12. SAFETY

12.1. ADVERSE EVENT REPORTING

Adverse event

The Australian Clinical Trial Handbook (*The Handbook*) defines an adverse event (drugs) as:

> any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign, symptom, or disease temporally associated with the use of a medicinal (investigational/experimental) product, whether or not related to this product. [1]

Adverse drug reaction

The Handbook defines an adverse drug reaction as:

> For unapproved medicines: all noxious and unintended responses to a medicinal product related to any dose should be considered ADVERSE DRUG REACTIONS. The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility.

[1] http://www.tga.gov.au/industry/clinical-trials-handbook.htm (definitions of adverse events are on 28-29).

For marketed medical products: a response to a drug which is noxious and unintended and which occurs normally used in man for prophylaxis, diagnosis or therapy of diseases of for modification of physical function.[2]

Serious adverse event (SAE) or Serious Adverse Drug Reaction is defined as:

Any untoward medical occurrence that at any dose:

- results in death;
- is life-threatening, (NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event/reaction which hypothetically might have caused death if it were more severe)
- requires in-patient hospitalisation or prolongation of existing hospitalisation;
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect; or
- is a medically important event or reaction.[3]

An adverse event or serious adverse reaction can also be any event or experience which compromises the ethical acceptability of the protocol. This can be a non-medical event for clinical trials that are not medical or testing drugs or devices, such as those clinical trials conducted in different fields such as psychology.

12.2. SERIOUS ADVERSE EVENT REPORTING

All serious adverse events will be reported immediately to the sponsor and the HREC. The reports will be followed by a detailed written report. Follow-up reports will identify the participant/s by unique code assigned to participants (rather than by name).

12.3. DATA SAFETY AND MONITORING BOARD (DSMB)

A DSMB compromising of independent experts will be assigned prior to trial commencement.

12.4. EARLY TERMINATION

If early termination of the research project is required the Principal Investigator Dr Dave Zalcberg will communicate with the HREC and Governance offices. All policies and procedures will be followed and documented.

13. BLINDING AND UNBLINDING

There will be no blinding as part of this study.

[2] Ibid.
[3] Ibid.

14. CONFIDENTIALITY AND STORAGE AND ARCHIVING OF STUDY

Electronic data will be stored in a secured online database (RedCAP) only accessible to those with authorised access to the data for analysis purposes. Any staff who no longer require access to the online data will be removed from the database.

Paper CRFs will be kept in a locked secure file cabinet within the locked Department of Anaesthetics and keys will be kept in a safe location for those who require access. All documents will be held for 15 years as per legal requirements.

15. TRIAL SPONSORSHIP AND FINANCING

This trial is being supported by the Department of Anaesthesia, Royal Prince Alfred Hospital.

16. REFERENCES

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17. APPENDICES

Data Collection Sheet/CRF

BABBIES Case Report File

Demographics **Date of Admission: _____ Date of Birth: _____**

Factor	Outcomes

DOB (Age) **Weight** **Height**	_____/_____/_____ _____ years old _____kg _____cm
Ethnicity	OCEANIAN NORTH-WEST EUROPEAN SOUTHERN AND EASTERN EUROPEAN NORTH AFRICAN AND MIDDLE EASTERN SOUTH-EAST ASIAN NORTH-EAST ASIAN SOUTHERN AND CENTRAL ASIAN PEOPLES OF THE AMERICAS SUB-SAHARAN AFRICAN
Indigenous	Aboriginal Torres Strait Islander Aboriginal and Torres Strait Islander Unknown Prefer not to say
Medications **(Name/Dose)**	
Diabetes	Type 1 diabetes Type 2 diabetes Gestational diabetes None Unknown
Multiple pregnancy	MCMA MCDA DCDA No Unknown
Alloimmunisation prophylaxis (28 + 36 weeks)	Required: yes/no Given: yes/no

	Unknown
Hypertensive Disorder	Gestational hypertension Chronic hypertension None Pre-existing
Previous miscarriage/loss of pregnancy	
Alcohol	Yes/No/Unknown Quantity (drinks/week) _____
Tobacco	Yes/No/Unknown Smokes/week _____
Other drug use	Yes/No/Unknown Type/Amount _____
Folate supplementation	Taken regularly Taken irregularly Not taken Unknown
Maternal health issues	Cardiovascular disease Thrombophilia Autoimmune disease Inflammatory Bowel Disease Asthma Obesity Malignancy Neurological disease (Description: _____) Other (Description: _____)
Number of previous births and Route of Delivery	

Prenatal screening

Factor	Outcome
Group B Streptococcus status	Positive Negative Not done Unknown
Prenatal fetal screening tests	1st trimester combined screening 2nd trimester combined screening NIPT None Unknown Results:
Prenatal ultrasounds	Abnormal (Description: _____) Normal Not done Unknown
Screened infections	HIV (positive/negative) HBV (positive/negative) HCV (positive/negative) Syphilis (positive/negative) Rubella (positive/negative) Varicella (positive/negative) None Not done Unknown
Other infections	Yes/No/Unknown 1. Description: _____
Maternal iron deficiency	Yes/No/Not done/Unknown 2. Ferritin (lowest): _____ ug/L

Maternal anaemia	Yes/No/Not done/Unknown 3. Haemoglobin (lowest): _____ mg/L
Midstream urine test	Asymptomatic bacteriuria UTI Normal Not done Unknown

Antenatal complications

Factor	Outcome
Hyperemesis gravidarum	Yes/No/Unknown
Pre-eclampsia	Pre-eclampsia Eclampsia HELLP syndrome None Unknown
Placental abruption	Yes/No/Unknown Notes:
Sepsis	Yes/No/Unknown Notes:
Placental abnormalities at birth	Subchorionic haematoma Placenta praevia Vasa praevia Single umbilical artery Velamentous cord insertion Circumvallate Other (Description:_____) None Unknown

Maternal embolism	Thromboembolism Air embolism Amniotic fluid embolism None Unknown
Polyhydramnios	Yes/No/Unknown
Oligohydramnios	Yes/No/Unknown
Antepartum haemorrhage	Yes/No/Unknown Notes:
Intrauterine growth restriction	Small for gestational age Fetal growth restriction None Unknown
Twin-to-twin transfusion syndrome	Present Absent Not applicable Unknown

Intrapartum factors

Factor	Outcomes
Prelabour rupture of membranes	PROM PROM >24 hours from birth None Not applicable Unknown
Preterm Birth (<37 weeks)	Yes/No/Unknown
Induction of labour	Required Not required Unknown Notes: (AROM, cervical ripening methods, etc.)

Duration of 1st stage of labour	4. _____ hours/not applicable
Duration of 2nd stage of labour	5. _____hours/not applicable
Fetal presentation	Cephalic Breech Transverse Oblique Unstable Unknown Fundic/cord presentation
Fetal distress	Yes/No/Unknown Notes:
Fetal lactate sample + result	Sampled/not sampled/unknown _____ mmol/L
Cardiotocography abnormalities	Present (Description:_____) Absent Not applicable Unknown
Pain management	Epidural Nitrous oxide Pethidine Other (Description:_____) None Unknown
Anaesthetic complications	Yes/No/Unknown 6. Description:_____
Caesarean section delivery	Category 1 – Reason: Category 2 Category 3

	Category 4 Not applicable Unknown
Uterotonic agent administration	Oxytocin (units) _____ Ergometrine (mg) _____ Syntometrine (units, mg) _____ Misoprostol (mcg) _____ Carboprost (mcg) _____ Carbetocin _____
Post-partum haemorrhage	Yes/no/unknown (text description)
Umbilical cord gas	pH: Base excess: pCO2: PO2:
Blood loss	_____mL
Complications	Uterine rupture Umbilical cord prolapse Chorioamnionitis Puerperal sepsis Other (Description:_____) None Unknown

Neonatal factors

Factor	Outcomes
Birth weight	_____ kg
Gestational age at birth	_____ weeks _____ days
Preterm birth	Spontaneous Iatrogenic Not applicable Unknown
Postnatal death (first two weeks)	Yes/No/Unknown Notes:

Injuries from birth	Cephalohaematoma Subgaleal haemorrhage Caput succedaneum Erbs Palsy Clavicle /humeral fracture Cranial nerve palsy Laceration Facial Bruising Other (Description:_____) None Unknown
Neonatal ICU admission	Yes/No/unknown Duration of Stay: _____ days
Special care nursery admission	Yes/No/unknown Duration of Stay: _____ days
Resuscitation at birth	Yes/No/unknown Notes:
APGAR score at 1 minute	_____ (0–10)
APGAR score at 5 minutes	_____(0–10)
Vaccinations	Yes/No/Unknown Description: _____
Resuscitation at any point in admission	Yes/No/unknown Description and Outcome: _____
TORCH infections	Toxoplasma (Yes/No) Rubella (Yes/No) Cytomegalovirus (Yes/No) HIV (Yes/No) Hepatitis viruses (Yes/No) Herpes simplex virus (Yes/No) Parvovirus B19 (Yes/No) Syphilis (Yes/No)

	Varicella zoster virus (Yes/No) None Unknown
Genetic disorders	Trisomy 21 Trisomy 18, 14, or 13 Klinefelter syndrome Turner syndrome Spinal muscular atrophy Fragile X syndrome Cystic fibrosis Other (Description:_____) None Unknown
Birth defects	Congenital heart disease Neural tube defects (Description: _____) Abdominal wall defects Congenital diaphragmatic hernia Tracheal abnormalities Oesophageal atresia Pulmonary hypoplasia Other (Description: _____) None Unknown
Neonatal sepsis	Early onset sepsis Late onset sepsis None Unknown
Metabolic complications	Hypoglycaemia Hypothermia Anaemia Polycythaemia Congenital hypothyroidism

	Metabolic bone disease of prematurity Haemolytic disease of the newborn Congenital adrenal hyperplasia Other (Description: _____) None Unknown
7. Neonatal jaundice	8. Present/Absent/Unknown 9. Peak serum bilirubin level: _____umol/L 10. Direct antibody test: Positive/Negative/Not done 11. Suspected cause: _____
Gastrointestinal complications	Necrotising enterocolitis Biliary atresia Neonatal hepatitis Other (Description: _____) None Unknown
Respiratory complications	Respiratory distress syndrome Apnoea of prematurity Bronchopulmonary dysplasia Transient tachypnoea of the newborn Pneumothorax Pneumonia Meconium aspiration syndrome Persistent pulmonary hypertension of the newborn Other (Description: _____) None Unknown
Neurological complications	Cerebral palsy Intraventricular haemorrhage Retinopathy of prematurity Hypoxic–ischaemia encephalopathy Periventricular leukomalacia

	Seizures Movement disorders Other (Description: _____) None Unknown
Haematological complications	Anaemia of prematurity Physiological anaemia of the newborn Other (Description: _____) None Unknown
Readmission to hospital in 2 weeks following birth	Yes/No/Unknown Description/length of stay: