Caffeine to improve neurodevelopmental outcomes in babies born late preterm: a randomised controlled trial

Short Title: The Latte Trial

Registration: The Latte Trial will be registered with ANZCTR

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Study Sites:

Secondary and Tertiary Maternity hospitals in Aotearoa New Zealand

This study protocol follows the SPIRIT checklist

Version Record

Date	Version	Updates to this version
12/09/22	1.0	
15/1/24	1.1	Addition of “Other” Serious adverse event.
27/5/24	1.2	Addition of signature page
14/6/24	1.3	Change to Open label caffeine

Name	Role	Signature	Date
Jane Alsweiler	Principal investigator		23/5/24
Liza Edmunds (Ngāpuhi, Ngāti Whātua),	Investigator		25/5/2024

Project Summary

Late preterm babies (34^{+0} to 36^{+6} weeks' gestational age (GA)) are the most common of all preterm babies, constituting 5% of all births or 3,000 births annually in Aotearoa New Zealand. Currently, systemic privilege and advantage in outcomes occurs for European women and their babies. Equity is a priority for all aspects of health and wellbeing, including late preterm babies, 20% of whom are Māori. Late preterm babies have a 30% increased risk of severe long-term neurodevelopmental impairment compared to babies born at term. While there has been progress in improving neurodevelopmental outcomes for babies born more preterm, it is only recently that late preterm babies have been recognised as being at risk of significant problems. Remarkably, there has been very little research on how to improve the long-term outcomes of babies born late preterm.

In very preterm babies, both apnoea (pauses in breathing) and intermittent hypoxaemia (recurrent drops in oxygen saturation (SpO2)) are common and are associated with worse neurodevelopmental outcomes. Treatment with caffeine not only reduces apnoea and intermittent hypoxaemia in very preterm babies but also improves long-term neurodevelopment. While apnoea of prematurity is less common in late preterm babies, we have recently identified that intermittent hypoxaemia is common.

In preparation for this study, we undertook the Latte Dosage Trial, which investigated the effect of different daily doses of caffeine citrate (5, 10, 15, 20 mg/kg or placebo) on intermittent hypoxaemia in late preterm babies. We randomised 132 late preterm babies, 12% Māori, over 20 months in two Auckland hospitals. Caffeine citrate reduced the incidence of intermittent hypoxaemia, with 20 mg/kg/day the most effective dose, halving the incidence of intermittent hypoxaemia 2 weeks after randomisation. Caffeine also increased the mean SpO_2 and reduced the amount of time spent with SpO_2 less than 90%. Caffeine citrate increased the incidence of tachycardia but did not reduce weight growth velocity.

Interventions are needed to improve long-term outcomes for late preterm babies. The Latte trial is a phase III, multi-centre randomised, parallel two-arm, placebo-controlled trial of oral caffeine citrate 20 mg/kg/dose from birth to term equivalent age in late preterm babies to improve neurodevelopmental outcomes at 2.5 years. Any interventions that improve outcomes for late preterm babies will have an important beneficial impact for the significant proportion of Māori babies born late preterm.

1. INTRODUCTION

1.1 Background

Late preterm babies have poorer neurodevelopmental outcomes. Babies born at 34^{+0} to 36^{+6} weeks' gestational age (GA), or late preterm, constitute 83% of the preterm population, and approximately 5% of all babies born annually in Aotearoa New Zealand, or 3,000 babies per year.[1,2] Currently, systemic privilege and advantage in outcomes occurs for European women and their babies.[3,4] Equity is a priority for all aspects of health and wellbeing, including late preterm babies, 20% of whom are Māori.[2] Despite late preterm babies making up by far the largest proportion of babies born preterm, the majority of research efforts have concentrated on improving survival and long-term outcomes of babies born very (<32 weeks' GA) and extremely (<28 weeks' GA) preterm.[5-7] Many late preterm babies are managed in a similar manner to term babies on postnatal wards, rather than neonatal units[8] and are not treated with the routine prophylactic interventions, such as caffeine, nutritional supplements and probiotics that are common practice in very and extremely preterm babies.

Recently, it has become apparent that late preterm babies have higher rates of mortality,[9,10] cerebral palsy,[11,12] developmental delay,[13,14] cognitive impairment,[15-17] behavioural disorders[18] and poor educational outcomes[2] compared to term babies (>37 weeks' GA). The identification of late preterm babies as a high-risk group has been described as an important public health breakthrough,[19] yet there have been few interventional studies designed to improve long-term outcomes in late preterm babies. A recently published trial of antenatal betamethasone for women at risk of late preterm delivery, demonstrating a reduction in respiratory morbidity in babies born late preterm when the mother had been prophylactically treated with antenatal steroids, is an example of a treatment known to be effective in very preterm babies[5] that is also effective in late preterm babies.[20] Any interventions that improve outcomes for late preterm infants will have a significant impact for the significant proportion of Māori babies born late preterm.[2,4]

Intermittent hypoxaemia may explain increased risk of neurodevelopmental impairment. Very preterm babies are at high risk of apnoea of prematurity and intermittent hypoxaemia.[21,22] Apnoea of prematurity refers to prolonged pauses in breathing, of 20 seconds or more, which may cause a reduction in the oxygen saturation and bradycardia and is associated with an increased incidence of brain injury[23] and neurodevelopmental impairment.[24] Late preterm babies also experience apnoea of prematurity, although less frequently than in very preterm babies.[21] Intermittent hypoxaemia are brief repetitive decreases in oxygen saturation not associated with apnoea, but potentially causing similar organ hypoxia. In an observational study of late preterm and term babies (8% Māori) published in 2019 we demonstrated that late preterm babies have more frequent episodes of intermittent hypoxaemia than term babies, peaking at 2 weeks' postnatal age, before reducing to baseline levels at term corrected age (Fig 1).[8]

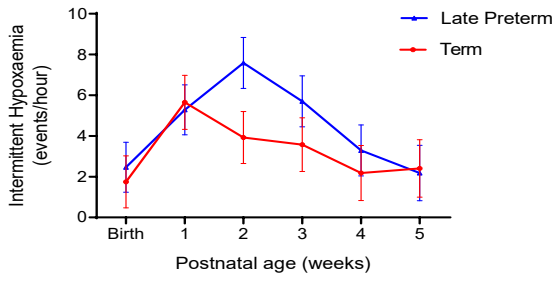

Figure 1. Intermittent hypoxaemia in late preterm and term babies in the first 5 weeks after birth.

Studies in adults have consistently shown that even brief exposure to hypoxia, whether from high altitude[25] or carbon monoxide poisoning,[26] can have long-term adverse effects on cognition. Even small changes in oxygen saturations in the neonatal period have been shown to significantly affect survival and neurodevelopment of very preterm babies.[27-29] Intermittent hypoxaemia is associated with altered brain development in neonatal mice[30] and reduced cognition and behavioural deficits in neonatal rats.[31] In humans, intermittent hypoxaemia is associated with poor neurodevelopmental outcomes in extremely preterm babies[32] and in children with sleep disordered breathing[33] and congenital heart disease.[34]

Caffeine may improve outcomes for late preterm babies. Caffeine is a respiratory stimulant which is effective in the prevention and treatment of apnoea of prematurity and intermittent hypoxaemia, and also reduces the incidence of chronic lung disease, cerebral palsy, and cognitive delay in very preterm babies.[6,35,36] Importantly, follow up to 11 years of age has recently shown that caffeine treatment reduces the risk of motor dysfunction by a third in babies born very preterm.[37,38] While some of the long term beneficial effects of caffeine may be due to its effect in reducing the incidence of chronic lung disease,[39] there is also benefit from reducing the amount of time that babies are hypoxic, independent of the effect on chronic lung disease.[40] Thus, caffeine has become the standard of care for very preterm babies and is in widespread use in neonatal units around the world as one of the few neonatal treatments that has been proven to have long term neurodevelopmental benefit, and very well tolerated. Similar benefits may exist for late preterm babies, but the long-term effects of caffeine therapy in this population have not yet been evaluated in clinical trials. While clinical studies in very preterm babies have been reassuring, there are some data from pre-clinical studies that caffeine may have detrimental effects on the developing brain,[41] therefore it is vital that clinical trials are conducted in late preterm babies before being introduced as a prophylactic therapy.

Latte Dosage Trial

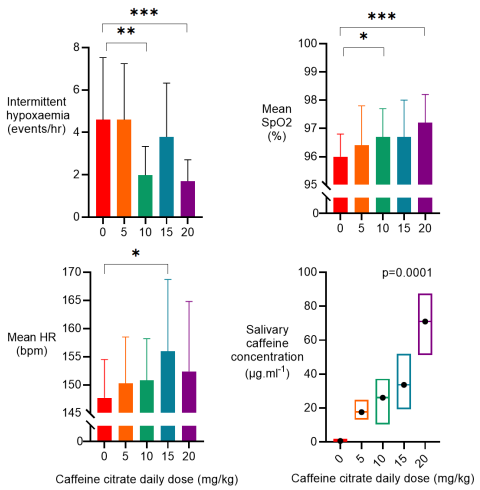

Figure 2. The effect of different daily doses of caffeine citrate on intermittent hypoxaemia (geometric mean (95%CI), mean SpO2, heart rate, and salivary caffeine concentration (median (IQR), in late preterm babies at 2 weeks of age. * p<0.05, ** p<0.01, ***p<0.005

Recently, we completed the Latte Dosage Trial, a multi-centre randomised, blinded, controlled dosage trial, which investigated the effect of different daily doses of caffeine citrate intermittent hypoxaemia in late preterm babies.[42] Babies were randomly assigned to receive a loading dose (10, 20, 30 or 40 $mg.kg^{-1}$) followed by 5, 10, 15 or 20 $mg.kg^{-1}.day^{-1}$ equivolume enteral caffeine citrate or placebo daily until term corrected age. The primary outcome was the frequency of intermittent hypoxaemia, defined as events/hour with oxygen saturation concentration ≥10% below baseline for ≤2 minutes, measured by overnight oximetry 2 weeks after randomisation. There were 132 babies (12% Māori) randomised over 20 months at two Auckland maternity hospitals (recruitment rate of eligible babies 132/337(39%)), mean (SD); GA 35.4 (1.2) weeks, birth weight 2418 (521) g.

Caffeine citrate reduced the incidence of intermittent hypoxaemia, with 20 mg/kg the most effective dose, halving the incidence of intermittent hypoxaemia 2 weeks after randomisation (primary outcome, Fig 2).

Caffeine also increased the mean SpO2 and reduced the amount of time spent with SpO2 less than 90%. There were no adverse effects of caffeine citrate on growth, feeding or sleep.

Interventions are needed to improve long-term outcomes for late preterm babies. The Latte trial is a phase III, multi-centre randomised, placebo-controlled trial of oral caffeine citrate from birth to term equivalent age in late preterm babies to improve neurodevelopmental outcomes at 2.5 years.

1.2 Aim

To determine if prophylactic caffeine citrate treatment, given to babies born late preterm (34^{+0} to 36^{+6}) from birth to term equivalent age improves neurodevelopmental outcome at 2.5 years' corrected age.

1.3 Hypothesis

Caffeine citrate administered to late preterm babies will reduce the risk of long-term neurodevelopmental impairment.

1.4 Study Design

A phase III, multi-centre, randomised, placebo-controlled, double-blind trial in which eligible late preterm babies will be randomised to oral caffeine or placebo daily from 3 days after birth to term equivalent age. We will follow the CONSORT Statement and checklist.

1.5 Study population

Babies born between 34^{+0} and 36^{+6} weeks' gestation. As Māori make up 20% of the late preterm cohort, we will intentionally place an emphasis on recruiting Māori whānau in this study to assist Mana Whakamārama (equal explanatory power) to occur.

2. METHODS

2.1. Participants, Interventions and Outcomes

2.1.1Study Setting

Participants will be recruited at secondary and tertiary maternity hospitals in Aotearoa New Zealand. Babies will be randomised and receive the loading dose of the study drug while in hospital. Once the infant is discharged home the parents/whānau will continue to give a daily dose of the study drug until term equivalent age (40^{+0} weeks gestational age).

2.1.1 Eligibility Criteria

Babies born between 34^{+0} and 36^{+6} weeks' GA without contra-indication to caffeine treatment.

Exclusion criteria

- Major congenital abnormality
- Minor congenital abnormality likely to affect respiration, growth, or development
- Previous caffeine treatment
- Renal or hepatic impairment
- Tachyarrhythmia
- Seizures
- Hypoxic ischaemic encephalopathy
- Maternal age less than 16 years
- More than 72 hours after birth
- Multiple births of triplets or higher

2.1.2 Recruitment

Potentially eligible late preterm babies will be identified on antenatal wards, neonatal units, and postnatal wards. We will intentionally place an emphasis on recruiting Māori whānau in this study to assist Mana Whakamārama (equal explanatory power) to occur and aim for 50% of participants to be Māori. To support recruitment of Māori participants we will allow more time to build relationships (whakawhanaungatanga and manaakitanga). Parents and whānau of eligible babies will be approached by a research nurse/midwife or investigator, or a member of the neonatal clinical team, either antenatally or in the first 72 hours after birth. We will ask Māori advisors at each DHB to assist with recruitment, and where possible we will aim for members of the local research team to be Māori. Parents and whānau will be informed about the trial and given the Participant Information Sheet (PIS). Parents will be given time to consider the trial, ask questions and discuss the study with whānau and friends. Parents/caregivers who agree for their infant to participate in the trial will be asked to sign the consent form, a copy of which will be provided to the parents/caregivers, usually by email, or hard copy if preferred. After completion of written informed consent, the infant will be randomised. Participation in the trial will be recorded in the baby's clinical record. With parent/caregiver permission, the baby's Lead Maternity Career (LMC) and Primary Health Practice will be notified about his/her participation in the trial.

To support recruitment of Māori, Māori whānau who have taken part in the pilot projects or who have been recruited to the Latte Trial will be asked if they agree to being approached for suggestions on how recruitment of Māori to the trial might be improved. Having already taken part in research, they will be well placed as hapū mama to contribute and guide the research team.

As the primary outcome of this trial is cognitive function at 2.5 years' corrected age, parents/caregivers will be asked to provide consent at recruitment for assessment of all primary and secondary outcomes. We will request consent (optional) to access medical records up to point of primary outcome assessment.

When then child approaches 2.5 years' corrected age parents and whānau will be sent an invitation letter containing further information about the follow-up assessment and will be given the opportunity to ask questions. Assent will be obtained from the attending parent or caregiver prior to conducting the assessment.

2.1.3 Study Interventions

Babies will be assigned randomly by online randomisation (1:1 variable block design) to caffeine citrate (loading dose of 40 mg/kg, then 20 mg/kg daily in a paediatric syrup formulation (cherry flavoured) or placebo group (equivalent volume of paediatric syrup formulation (cherry flavoured)), with stratification for groups of collaborating centres (Starship NICU, Middlemore NICU, Waikato NICU, Dunedin NICU, Upper North Island SCBU, Lower North Island SCBU, Other), gestational age (34, 35, or 36 weeks) and ethnicity (Māori or non-Māori). The study drug will be administered by parents or whānau once the baby is discharged from hospital, shown to be feasible during the Latte Dosage Trial.

The infant will be given a 2 ml/kg enteral loading dose of the study drug (40 mg/kg of caffeine citrate or placebo). The loading dose will be given at 7 to 9 am on a morning prior to the baby reaching 96 hours of age, followed by a daily dose of 1 ml/kg each morning (20 mg/kg of caffeine citrate or placebo) until term equivalent age (40^{+0} weeks' gestational age). The dose will be recalculated for the babies' weight gain weekly after the infant has regained birth weight while an inpatient, and at 3 weeks after randomisation if discharged. Two bottles of the study drug from the same allocated group will be allocated at randomisation. The first bottle will be used for the first 3 weeks, and then returned to the study centre to determine compliance. The second bottle will be used after the first 3 weeks.

The study drug is given via a nasogastric tube for babies with a tube *in situ*, and orally for babies who do not require a nasogastric tube. Babies who are not able to tolerate enteral medications will have the study drug withheld.

2.1.4 Open Label Caffeine Citrate

If an infant in the trial has apnoea or intermittent hypoxaemia clinicians will be encouraged to use low flow oxygen or positive pressure ventilation (high flow or CPAP) as a first line treatment, where appropriate. If necessary, clinicians can give a loading dose of caffeine citrate as an open label medication. If a clinician decides to continue caffeine treatment, then the Latte Trial Study Drug should be withheld until the open label caffeine has been stopped. Open label caffeine treatment will be recorded, and these babies will be included in the intention-to-treat analysis.

2.1.5 Reducing the Dose or Discontinuation of Study Drug

Permitted protocol deviation

The dose of the study drug may be reduced from 1 ml/kg/day (20 mg/kg/day) to 0.5 ml/kg/day (10 mg/kg/day) if the baby has tachycardia (heart rate consistently >180 bpm at rest) or if the parents or clinicians believe the infant is having side effects (at the discretion of the site principal investigator). If the parents or whānau report difficulty administering the full volume, this can be administered as two half doses in the morning, e.g., with two separate feeds.

The allocated treatment can be stopped at any time at the request of the parents, or by the clinician caring for the infant if (s)he feels that stopping the treatment would be in the best interest of the infant. If treatment is stopped due to an acute illness or problem that resolves, consideration should be given to restarting the allocated treatment. Babies should continue in the study and complete all planned assessments, regardless of treatment status, unless they are formally withdrawn from the study. Data collected up to the point of withdrawal will be reported (with consent) and analysis will be according to the intention-to-treat principle.

2.1.6 Compliance

The bottles of study drug will be collected at 3 weeks post randomisation (by courier if the baby has been discharged home) and the amount of study drug remaining in the bottle will be determined. Compliance will be defined as ≥ 80% of the predicted volume of the drug dispensed.

2.1.7 Co-interventions

All clinical care, other than study interventions and assessments, will be determined by the local clinical team, according to local guidelines.

Clinicians will be advised to use oxygen as first line treatment for persistent hypoxaemia, and positive pressure ventilation for apnoea. A one-off dose of caffeine citrate may be given for apnoea in an emergency, but ongoing use of caffeine citrate should first be discussed with the Site Principal Investigator (section 3.1.5).

2.1.8 Re-admission

Babies in the trial will have their participation recorded in their hospital discharge letter and a letter to file will be made to inform clinicians that the infant is in the trial and to give them the contact details of the Site Principal Investigator and Research Nurse. Clinicians will be asked to continue the study drug during the admission, unless there is a clinical indication not to do so, and to manage apnoea and hypoxaemia as per the protocol (section 3.1.5). They will also be informed that the infant may receive a loading dose of caffeine citrate, in addition to the study drug, if clinically appropriate and urgent without prior discussion with the Site Principal Investigator.

Before giving ongoing caffeine citrate the clinician should discuss unblinding (caffeine or placebo) with the Site Principal Investigator.

3.1.7 Outcomes

Primary Outcome

Bayley Scale of Infant Development 4th Edition (BSID IV) cognitive score at 2.5 years' corrected age (continuous variable).

Secondary Outcomes

Neonatal

1. Weight, and weight z score at term corrected age (40^{+0} weeks' gestational age)
2. Length of stay in hospital (primary neonatal admission)
3. Study drug dose reduced or discontinued due to side effects or poor tolerance
4. Fully breastfeeding (the baby has taken breast milk only, no other liquids or solids except a minimal amount of water or prescribed medicines, in the past 48 hours) at term corrected age (40^{+0} weeks' gestational age).

Early childhood (2.5 years corrected age)

5. Cognitive impairment, (BSID IV cognitive score more than one standard deviation (SD) below the test mean (<85, categorical))
6. Moderate-Severe cognitive impairment (BSID IV cognitive score more than two SD below the test mean, <70, categorical)
7. BSID IV language score (continuous)
8. Language delay (BSID IV language score more than one SD below the test mean, <85, categorical)
9. Moderate-Severe language delay (BSID IV language score more than two SD below the test mean, <70, categorical)
10. BSID IV motor score (continuous)
11. Motor delay (BSID IV motor score more than one SD below the mean, <85, categorical)
12. Moderate-Severe motor delay (BSID IV motor score more than two SD below the test mean, <70, categorical)
13. Social-emotional/behavioural delay (BSID IV Social-Emotional score or BSID IV Adaptive Behavious score more than one SD below the mean, <85, categorical)
14. Developmental delay (BSID IV cognitive or language score more than one SD below the test mean, <85, categorical)
15. Asthma/wheeze defined as wheeze or whistling in the chest in the past 12 months or doctor diagnosed asthma (yes to PARC #1/ISAAC #3 or ISAAC #7-8 questions)
16. Predicating Asthma Risk in Childhood (PARC) score ≥5 (high risk of school-age asthma)
17. Death before 2.5 years' corrected age
18. Anthropometry at 2.5 years' corrected age (weight, height, head circumference and body mass index (BMI) z scores)
19. Infant and Toddler quality of life score
20. Healthcare utilisation after primary hospital discharge (linkage to routine data from the Ministry of Health Manatū Hauora for emergency department visits, outpatient visits and hospitalisations, and parent questions on visits to primary healthcare providers)

3.1.9 Participant Timeline

The study schedule is as follows:

Table

	t-x	T0	Day 5-7	3 weeks	40 weeks gestational age	6 monthly newsletters and birthday cards	2.5 years Follow -Up
Screening	X						
Informed Consent		X					
Randomisation		X					
Loading dose		X					
Daily dosing			X	X	X		
Demographics		X					
Contact information		X				X	
Anthropometry					X		X
Heart rate check			X				
Dose adjustment for weight				X			
Compliance assessment				X			
Breastfeeding assessment					X		
BSID IV							X
Body size measurements							X
Parent/caregiver questionnaires							X

3.1.10 Sample Size

Cognitive scores at 2.5 years of age have moderate to high positive correlation with later intelligence quotient, and of all early developmental domains, cognitive scores are the most predictive of later neurodevelopmental outcome.[44,45] A recent publication found that late preterm babies have a BSID cognitive score 5.3 points lower than term babies, equivalent to approximately one-third of a SD (SD 15).[46] Exert consensus across the Interdisciplinary Maternal Perinatal Australian Collaborative Trials Network (IMPACT) judged that a ~0.3 SD difference in Bayley Scales cognitive score is clinically significant, and this has been selected as the primary outcome in other recent perinatal trials aimed at improving neurodevelopmental outcome (e.g., ACTRN12618000371291).

To detect a difference between caffeine and placebo groups of at least 5 points with 90% power (two-sided α=0.05) requires 191 babies in each arm (total 382). Allowing for a conservative 20% drop-out rate (withdrawal and loss to follow-up), we will recruit a total of 478 babies (239 in each arm). Babies from multiple pregnancy may be recruited and will be allocated to the same intervention to avoid accidental cross-over. Only one baby from a multiple pregnancy will be counted in the sample size but all enrolled babies will be included in the intention-to-treat analysis. Assuming a similar rate of multiple births to that seen in the Latte dosage study (average number of babies per mother = 1.065), we will expect to include a total of 510 babies if we achieve our target sample size of 478.

We will place an emphasis on recruiting Māori whānau in this study to assist Mana Whakamārama (equal explanatory power) to occur. To incorporate this principle, we will aim to recruit equal numbers of Māori and non-Māori pēpi (239 Māori, 239 non-Māori),

The Data Safety Monitoring Committee (DMSC) will monitor sample size assumptions (compliance and drop-out rates) and advise on the need for any sample size adjustment. It will not be possible for the DMSC to advise on the background rate of the primary outcome as most children will have already received the intervention prior to this time point.

3.1.13 Withdrawal

If a parent/caregiver wishes to remove their child from the study, they will be given the option of 1) discontinuation of study drug (if <40 weeks' postmenstrual age) and collection of minimum outcome data (as agreed with the parents); 2) withdrawal from the study and discontinuation of further data collection, with use of data collected prior to withdrawal; or 3) complete withdrawal from the study including previously collected outcome data. Withdrawal due to concerns about the intervention side effects or tolerance will be recorded.

2.2 Assignment of Interventions

2.2.1 Allocation Sequence Generation

The allocation sequence will be generated by the study statistician, with variable block sizes and priority stratification for groups of collaborating centres ((Starship NICU, Middlemore NICU, Waikato NICU, Dunedin NICU, Upper North Island SCBU, Lower North Island SCBU, Other), gestational age at birth (34, 35 and 36 weeks' gestational age) and ethnicity (Māori or non-Māori). Multiples will be allocated to the same study group because of the risk of medicine cross-over in a single household.

2.2.2 Allocation Concealment Mechanism

Babies will be assigned randomly via an internet randomisation service to the placebo or caffeine dose with equal allocation ratio (1:1).

2.2.3 Implementation

At randomisation the baby will be allocated a unique ID number and allocated to a study group (placebo or caffeine dose) that will correspond to a study drug bottle labelled with a random number, containing either caffeine citrate in an appropriate neonatal formulation at 20mg/kg, or an identical-appearing placebo. The baby's hospital sticker will be applied to the bottle and the drug will only be dispensed to that infant.

2.2.4 Blinding

The research team (investigators, nurses, coordinator, students, research assistants), clinical staff and the baby's parents/caregivers will be blinded to treatment allocation. This will be achieved by

dispensing caffeine in identical bottles with identical study drug solutions (caffeine and placebo). Only the Data Manager, Study Statistician and the compounding pharmacy team at Biomed will have access to the allocation sequence during the trial.

2.2.5 Emergency Unblinding

The baby's treatment allocation may be un-blinded if judged clinically necessary by the clinical team caring for the infant, in agreement with the Site Principal Investigator. To unblind the infant's study drug, the Site Principal Investigator will contact the Data Manager and ask them to contact the responsible clinician with the study allocation.

2.3. Neonatal Phase

2.3.1 Baseline Data Collection

We will collect the following demographic data at baseline for each baby:

- Sex
- Ethnicity, including hapū and iwi for Māori participants
- Estimated date of delivery (for calculating corrected age)
- Date of birth
- Birthweight
- Customised birthweight centile
- Birth length
- Birth head circumference
- Maternal height and weight
- Maternal age and parity
- Pregnancy complications: gestational diabetes, pregestational diabetes, pre-eclampsia, antenatally diagnosed fetal growth restriction, smoking and drug use in pregnancy, antenatal corticosteroid administration, induction of labour, mode of birth
- Current respiratory support

Contact information, including social media, will be obtained for the parents, another close friend or relative, and general practitioner. Parents/caregivers will be able to nominate multiple ethnicities for their baby. For the purposes of randomisation and analysis ethnicity will be prioritised: Māori (Māori), and Pacific people (including Cook Island Māori), Asian, Indian, European, Other (non-Māori). Direct identifiers will be stored separately to other study data.

A koha of a muslin wrap will be given to each baby at enrolment.

2.3.2 Neonatal Assessment

At one week (3-8 days) post-randomisation or pre-discharge (whichever occurs first, but at least 72 hours after randomisation), babies will have a spot check of their heart rate assessed during a period of quiet restfulness, either by direct auscultation using a stethoscope or by using a pulse oximeter (Rad 8, Masimo Corp., Irvine, CA). Babies with a heart rate of over 180 bpm will have the study dose reduced to 10 mg/kg/day and the heart rate will be assessed again one week later.

Date of primary hospital discharge will be recorded to calculate duration of admission post-randomisation. All other concurrent medications taken while the baby is receiving the study drug will be recorded.

At 3 weeks' post randomisation and at 40 weeks' (term equivalent age), if the baby is still in hospital, research staff will record the last weight from the clinical chart, or if the baby has been discharged, they will call the parent or whānau and ask them for the latest weight documented by

the baby's usual clinical care provider in the Well Child Tamariki Ora My Health Book. At 3 weeks' post randomisation the dose will be adjusted for the latest weight. At term equivalent age the parents/whānau will be asked if the baby is fully breastfeeding (the baby has taken breast milk only, no other liquids or solids except a minimal amount of water or prescribed medicines, in the past 48 hours).

2.4 Early Childhood Phase

2.4.1 Contact tracing

There can be significant movement of whānau across Aotearoa New Zealand and it will be important to maintain accurate contact details to be able to find the children at 2.5 years' corrected age. Whakawhanaungatanga (process of developing relationships) and manaakitanga (showing respect for others) will be vital for retention both in the recruitment and follow up phases of the trial. We will contact whānau every 6 months with newsletters and birthday cards. We will trace families for whom current contact information is not available via their primary health provider, midwife or other family members. A check will be made of NHI numbers to ensure we avoid contacting families whose baby(s) has died.

2.4.2 Assessment at 2.5 years' corrected age

1. Developmental status (BSID IV motor, language, cognition)
2. Social-emotional and adaptive behaviour function (BSID IV parent questionnaire)
3. General health (developmental disorders and therapy and doctor diagnosed asthma)
4. Physical size (height, weight, head circumference,)

We will assess the child at 2.5 years' corrected age. At this age children are sufficiently developed to allow a thorough investigation of cognitive, language and motor development not possible at earlier ages. These assessments will be undertaken by an assessor trained in developmental assessments.

Each child will be assessed at a research clinic, or if the family prefer, at home. We will provide reimbursement for travel, koha (gift), and kai (food). A koha of a muslin wrap will be given to the whānau at the time of enrolment, and an additional koha of a voucher will be given at the 2.5 year assessment. For children who are fluent in Te Reo Māori whānau will be given the option of the assessment being done in Te Reo Māori. The assessors will be unaware of the neonatal history of the child and allocated intervention. It is anticipated that the assessment will be conducted in a single session lasting up to 2 hours, with regular breaks to prevent fatigue and to maintain child interest and willingness to comply with the assessment process. However, additional follow-up appointments will be offered if the assessment cannot be completed in a single session and the parents or whānau request this.

Development

The psychological assessment includes the Cognitive, Language (receptive and expressive), Motor (gross and fine motor), scales of the Bayley Scales of Infant and Toddler Development, Fourth Edition (BSID-IV). Standard scores on these scales have a mean (SD) score of 100 (15) and will be calculated using corrected age from Aotearoa New Zealand normative data. Higher scores indicate better performance. Children unable to complete the Cognitive, Language or Motor Scales of the BSID-IV because of severe delay in these domains will be assigned scores of 49.

Developmental delay will be defined as:

- *Mild delay: Cognitive or Language composite scores 2 to <1 SD below the mean.*

- *Moderate delay: Cognitive or Language composite scores 3 to <2 SD below the mean.*
- *Severe delay: Cognitive or Language composite scores more than 3 SD below the mean.*

Growth

Height will be measured by a stadiometer to the nearest 0.5 mm, weight by electronic scales to the nearest 0.1 kg (minimal clothing) and head circumference to the nearest 1 mm. All equipment is portable and can be used for home visits.

Parent questionnaires
Emotional-behavioural function will be assessed by the Social-Emotional and Adaptive Behaviour scales of the BSID-IV.

The incidence and severity of current wheeze and future risk of asthma at school age will be assessed using the PARC questionnaire.[49]

Parents/caregivers will be asked about whether their child has been diagnosed with asthma, neurological or developmental conditions, or experienced traumatic brain injury (for sensitivity analysis).

We will offer support in completing the questionnaire for whānau where lower literacy may make this difficult.

Parent Feedback
Parents/caregivers of children who have taken part in the study will be sent a letter summarising the results of the assessments, with information about who to contact if they have any questions. If there are concerns about a child's health or developmental status, referral to an appropriate health agency, usually the child's primary health provider, will be made with the consent of the parents/caregivers. Parents, caregivers, and their health professionals will have the opportunity to request more detailed report of specific assessment results if required.

2.5. Data Collection and Management

2.5.1 Data Collection Methods

Data will be collected directly into eCRFs using the REDCap system. Branching logic and range checks will be used to reduce data entry errors.

Parent questionnaires will be completed online using the REDCap survey system. Hard copy forms will be available if internet access is difficult.

2.5.2 Data Management

A Data Monitor will review each form for completeness before locking forms. If needed, queries will be raised with the Site Principal Investigator, and tracked in REDCap.

2.6 Statistical Methods

2.6.1 Derived variables

Socioeconomic decile will be determined from the New Zealand Deprivation Index, calculated from the mother's address at trial entry.

Gestation and sex-specific z-scores for weight, length and head circumference at birth will be calculated using the Fenton population reference,[50]. Weight z-score at term equivalent age will also be calculated using the Fenton population reference.

Age and sex-specific z-scores at 2.5 years' corrected age for weight, length, BMI, and head circumference will be calculated using the WHO Child Growth Standards.

2.6.2 Descriptive Statistics

Categorical data will be presented as number and percent, and continuous data as mean and standard deviation or median and inter-quartile range, as appropriate. Denominators will be given for all outcomes.

2.6.3 Treatment Effect

The primary analysis will compare primary and secondary outcomes between the placebo and caffeine group using generalised mixed models with adjustment for the stratification variables of groups of collaborating centres, gestational age at birth and ethnicity (Māori or non-Māori); potential confounding by socio-economic status (NZ Deprivation Index) and sex; and non-independence of multiples (random effect). Treatment effects will be presented as mean difference, ratio of geometric means (positively skewed data) or risk difference with 95% confidence interval. For categorical data, an estimate of relative effect will also be given (odds ratio, 95% confidence interval). A hypothesis test will be conducted for the primary outcome (two-tailed α=0.05). The data will be analysed on an intention-to-treat basis. Missing data will not be imputed in the primary analysis.

2.6.4 Secondary Analysis

The following secondary analyses will be performed for the primary outcome:

Compliance
A sensitivity analysis will be performed for the primary outcome that includes only those babies who were compliant with the study drug (see section 2.1.6).

Open-label caffeine treatment
A sensitivity analysis will be performed for the primary outcome that includes only those babies who did not receive open-label caffeine treatment (see section 2.1.4)

Neurological conditions
A sensitivity analysis will be performed excluding children with developmental delay due to conditions unrelated to preterm birth and caffeine therapy, e.g., traumatic brain injury, genetic disorders, and congenital brain malformations.

Missing data

Multiple imputation techniques may be considered in exploratory secondary analysis of primary and critical secondary outcomes if there are concerns about bias in effect estimates, e.g., differential loss to follow-up among groups, especially if this is related to prognostic factors.

2.7. Data Monitoring

A Data Monitoring and Safety Committee (DMSC) consisting of a neonatologist and paediatrician experienced in large, randomised trials and a statistician will be convened. The DMC will monitor recruitment, sample size assumptions, completeness of data acquisition, and evidence for group differences in the safety outcome measures. The DMSC will convene prior to the first randomisation to review this protocol and the terms of reference, and then yearly to advise the Steering Committee on trial continuation or protocol modification. Once the intervention phase has finished the DMSC will remain an advisory body until publication.

Members of the DMSC:

- Professor Stuart Dalziel (Chair, Paediatric Emergency Medicine Specialist)
- Dr Kathryn Beardsall (Neonatologist)

- Mr Greg Gamble (Biostatistician)
- Prof Cass Byrnes (Māori academic)

2.7.1 Interim Analysis

It is envisaged that the trial will be completed as planned as the primary outcome will only be available after the assessment at 2.5 years' corrected age. There will be no interim efficacy analysis.

2.7.2 Harms

The following Serious Adverse Events and Adverse Events will be reported to the DSMC:

Serious Adverse Events (reported to the DSMC within 48 hours of the Site Primary Investigator being notified)

- Death before 2.5 years corrected age
- "Other" (defined as: immediately life-threatening; requires prolongation of existing hospitalisation or substantial escalation in care, or results in persistent or significant disability or incapacity

Adverse Events (reported to the DSMC at yearly intervals)

- Tachycardia requiring dose reduction
- Study drug stopped due to presumed side effects

2.8 Trial Monitoring

An independent trial monitor will ensure that the trial is conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

3. ETHICS AND DISSEMINATION

3.1 Research Ethics Approval

National ethical approval will be sought from the Health and Disability Ethics Committees (HDEC) and SCOTT.

3.2 Locality Approval

Locality Approval will be sought from the University of Auckland and recruitment sites.

3.3 Protocol Amendments

All amendments to the final version of this protocol will require review and approval of the Steering Committee and will be submitted to HDEC and DHB Research Offices, as appropriate. All amendments, including approval date, will be recorded with this protocol (Appendix 8.4).

3.4 Consent

Informed consent will be obtained by the research staff, PhD Student, Clinical Staff, or Investigators. When the child approaches 2.5 years of age parents and whānau will be provided with an information pack, containing further information about the assessments to be undertaken, and will be given the opportunity to ask questions. All information sheets will be reviewed for readability.

Parents/caregivers will retain the right to withdraw their baby from the study at any stage. Parents/caregivers who would like to withdraw their baby from the study will be asked the reason for withdrawal (optional). With parental permission, data collected up to the point of withdrawal will be used in the analysis.

3.5 Confidentiality

Electronic databases will be stored on secure servers at the University of Auckland and access will be controlled by unique user ID and password, with full electronic tracking log. In addition to the randomisation system, three separate databases will be used to protect participant privacy. The screening database will record NHI, date of birth and expected date of delivery (to calculate gestation length), birthweight, sex and eligibility criteria of participants considered for enrolment. This will enable the reporting of CONSORT data and assessment of external validity. Following randomisation, trial data will be stored in a separate database with eCRFs labelled only by randomisation ID. Contact information will be stored in a separate database, independently of the trial database. NHI will only be stored in the randomisation database but not the trial or contact database. Data Access Groups will be employed so that site personnel can only see data for participants at their site. The download of data will be restricted to the Data Manager, Study Coordinator and Principal Investigator, and only the Data Manager and Principal Investigator will be able to download direct identifiers.

Extracted data files will contain the indirect identifiers DOB and EDD, as these are necessary for analysis. No direct identifiers such as NHI, name or address will be combined with study outcome data.

Study reports will contain only summary data and individual participant data will not be reported. Direct identifiers and DOB or EDD will not be released to any third party. Research staff will be certified in best practice for clinical trials (ICHGCP E6 and PHRP).

At the completion of the study, all electronic data will be permanently digitally archived and accessible only to the study investigators. All hard copy records that have been digitally scanned will be added to the archive, and then destroyed.

3.6 Declaration of Interests

Investigators will declare any financial, intellectual, or other potential conflicts of interest, as outlined by the ICMJE, to the Steering Committee.[58] The Steering Committee will decide on how any conflicts of interest are to be managed.

3.7 Access to Data

The Steering Committee have access to the full dataset and oversee analysis, interpretation and reporting of results. Approval will be sought from the Latte Trial Steering Committee prior to publication of study data. Care will be taken to avoid duplication in reporting of results.

3.8 Authorship

The Council of Science Editors (CSE) standards for authorship will be applied (www.councilscienceeditors.org). The Steering Committee will be responsible for planning manuscripts and determining authorship. It is anticipated that Steering Group Members, Site Principal Investigators and students will qualify as authors. Professional staff who meet CSE standards will may also qualify as authors. Investigators and study personnel who do meet the criteria for authorship will be acknowledged as non-author contributors.

3.9 Dissemination

Results of the study will be presented at relevant conferences and hospital meetings and published in peer-reviewed scientific journals. We will also disseminate the results of the study to the community, and to the participants.

4. TRIAL ORGANISATION

4.1 Steering Committee

The Trial Steering Committee takes overall responsibility for all aspects of the study, meeting initially on a fortnightly basis, and then monthly. Matters arising between meetings may be dealt with by email. The Principal Investigator is responsible for maintaining a record of correspondence and minutes of meetings.

Members of the Steering Committee:
Assoc Prof Jane Alsweiler (Chair, Neonatologist)
Dr Chris McKinlay (Neonatologist)
Dr David McNamara (Paediatric Respiratory Specialist)
Dr Liza Edmonds ((Ngāpuhi, Ngāti Whātua, Neonatologist)
Ms Jenny Rogers (Ngāi Tahu, Kāi Tahu, Kaiarahi)
Dr Braden Te Ao (Waikato, Tainui ,Health Economist)
Dr Alana Cavadino (Statistician)
Ms Elizabeth Oliphant (Paediatric Pharmacist)

4.2 Management Committee

The Trial Coordinator will oversee day-to-day running of the study. They will be supported by a Management Committee that will meet regularly.

Members of the Management Committee:
Assoc Prof Jane Alsweiler (Chair)
Dr Chris McKinlay
Trial Co-ordinator
Other members of the research team may be requested to attend the Management Committee meetings as required.

4.3 Site Principal Investigators

The Site Principal Investigator will have overall responsibility for the running of the study at their local site, including completion of local governance requirements, and local promotion and staff education. They will be supported by the Management Committee and other research staff. The Site Principal Investigators will be added as named investigators to this protocol, and will included as co-authors in publications.

5. APPENDICES

5.1 Participant Documents

The following participant documents are to accompany this protocol:

Title	Version	Date
Participant Information Sheet and Consent		

5.2 Case Report Forms

The following case report forms (CRF) are to accompany this protocol:

Title	Version	Date

5.3 Ethical and Locality Approval

The following letters of approval are to accompany this protocol:

Title	Reference	Date

5.4 Protocol Amendments

Protocol version, Date	Amendment(s)	Date accepted by Steering Group	Date ethics notified (or NA)

5.5 Study Committee Terms of Reference

The following Terms of Reference are to accompany this protocol:

Title	Version	Date
Steering Group Term of Reference		
Data Safety Monitoring Committee Term of Reference		

REFERENCES

1. Ministry of Health. NZ maternity clinical indicators 2018. Wellington: Ministry of Health; 2020.
2. Berry M, Foster T, Rowe K, Robertson O, Robson B, N P. Gestational Age, health and educational oucomes in adolescents. Pediatrics. 2018;142(5):e20181016.
3. Filoche S, Cram F, Beard A, Sim D, Geller S, Edmonds L, et al. He Tamariki Kokoti Tau-Tackling Preterm: a data-linkage methodology to explore the clinical care pathway in preterm deliveries. BMC Health Serv Res. 2018;18(1):374.
4. Edmonds LK, Sibanda N, Geller S, Cram F, Robson B, Filoche S, et al. He Tamariki Kokoti Tau: Tackling preterm incidence and outcomes of preterm births by ethnicity in Aotearoa New Zealand 2010–2014. Int J Gynecol Obstet. 2021;155:239–46.
5. Roberts D, Brown J, Medley N, Dalziel SR. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev. 2017(3).
6. Schmidt B, Roberts RS, Davis P, Doyle LW, Barrington KJ, Ohlsson A, et al. Caffeine therapy for apnea of prematurity. N Engl J Med. 2006;354(20):2112-21.
7. Sharif S, Meader N, Oddie SJ, Rojas-Reyes MX, McGuire W. Probiotics to prevent necrotising enterocolitis in very preterm or very low birth weight infants. Cochrane Database Syst Rev. 2020(Issue 10):Art. No.: CD005496.
8. Williams LZJ, McNamara D, Alsweiler JM. Intermittent hypoxemia in infants born late preterm: a prospective cohort observational study. J Pediatr. 2019;204:89-95.
9. McIntire DD, Leveno KJ. Neonatal mortality and morbidity rates in late preterm births compared with births at term. Obstet Gynecol. 2008;111(1):35.
10. Mathews TJ. Infant mortality statistics from the 2006 period linked birth/infant death data set. National vital statistics reports: from the Centers for Disease Control and Prevention, National Center for Health Statistics. National Vital Statistics System. 2010;58(17):1.
11. Moster D, Lie RT, Markestad T. Long-Term medical and social consequences of preterm birth. N Engl J Med. 2008;359:262-73.
12. Odd DE, Lingam R, Emond A, Whitelaw A. Movement outcomes of infants born moderate and late preterm. Acta Paediatricia. 2013 102:876–82.
13. Darlow BA, Horwood LJ, Wynn-Williams MB, Mogridge N, Austin NC. Admissions of all gestations to a regional neonatal unit versus controls: 2-year outcome. J Paediatr Child Health. 2009;45(4):187-93.
14. Woythaler MA, McCormick MC, Smith VC. Late preterm infants have worse 24-month neurodevelopmental outcomes than term infants. Pediatrics. 2011;127(3):e622-9.
15. Talge NM, Holzman C, Wang J, Lucia V, Gardiner J, Breslau N. Late- preterm birth and its association with cognitive and socioemotional outcomes at 6 years of age. Pediatrics. 2010;126(6):1124.
16. Quigley MA, Poulsen G, Boyle E, Wolke D, Field D, Alfirevic Z, et al. Early term and late preterm birth are associated with poorer school performance at age 5 years: a cohort study. Archives of Disease in Childhood - Fetal and Neonatal Edition. 2012;97(3):F167.
17. Heinonen K, Eriksson JG, Lahti J, Kajantie E, Pesonen AK, Tuovinen S, et al. Late preterm birth and neurocognitive performance in late adulthood: a birth cohort study. Pediatrics. 2015;135(4):e818-25.
18. Huddy CL, Johnson A, Hope PL. Educational and behavioural problems in babies of 32-35 weeks gestation. Arch Dis Child Fetal Neonatal Ed. 2001;85(1):F23.
19. Adamkin DH. Late preterm infants: severe hyperbilirubinemia and postnatal glucose homeostasis. J Perinatol. 2009;29(S2):S12-S7.
20. Gyamfi-Bannerman C, Thom EA, Blackwell SC, Tita ATN, Reddy UM, Saade GR, et al. Antenatal betamethasone for women at risk for late preterm delivery. N Engl J Med. 2016;374(14):1311-20.

21. Henderson-Smart DJ. The effect of gestational age on the incidence and duration of recurrent apnoea in newborn babies. Aust Paediatr J. 1981;17:273-6.
22. Rhein LM, Dobson NR, Darnall RA, Corwin MJ, Heeren TC, Poets CF, et al. Effects of caffeine on intermittent hypoxia in infants born prematurely: a randomized clinical trial. JAMA Peds. 2014;168(3):250.
23. Butcher-Puech MC, Henderson-Smart DJ, Holley D, Lacey JL, Edwards DA. Relation between apnoea duration and type and neurological status of preterm infants. Arch Dis Child. 1985;60(10):953-8.
24. Janvier A, Khairy M, Kokkotis A, Cormier C, Messmer D, Barrington KJ. Apnea is associated with neurodevelopmental impairment in very low birth weight infants. J Perinatol. 2004;24(12):763-8.
25. Bahrke MS, Shukitt-Hale B. Effects of altitude on mood, behaviour and cognitive functioning. Sports Med. 1993;16(2):97-125.
26. Weaver LK, Hopkins RO, Chan KJ, Churchill S, Elliott CG, Clemmer TP, et al. Hyperbaric oxygen for acute carbon monoxide poisoning. N Engl J Med. 2002;347(14):1057-67.
27. Saugstad OD, Aune D. Optimal oxygenation of extremely low birth weight infants: a meta-analysis and systematic review of the oxygen saturation target studies. Neonatology. 2014;105(1):55-63.
28. SUPPORT Study Group. Target ranges of oxygen saturation in extremely preterm infants. N Engl J Med. 2010;362(21):1959-69.
29. Stenson B, Brocklehurst P, Tarnow-Mordi W. Increased 36-week survival with high oxygen saturation target in extremely preterm infants. N Engl J Med. 2011;364(17):1680-2.
30. Kanaan A, Farahani R, Douglas RM, LaManna JC, Haddad GG. Effect of chronic continuous or intermittent hypoxia and reoxygenation on cerebral capillary density and myelination. American Journal of Physiology - Regulatory, Integrative and Comparative Physiology. 2006;290(4):R1105-R14.
31. Row BW, Kheirandish L, Neville JJ, Gozal D. Impaired spatial learning and hyperactivity in developing rats exposed to intermittent hypoxia. Pediatr Res. 2002;52(3):449-53.
32. Poets CF, Roberts RS, Schmidt B, Whyte RK, Asztalos EV, Bader D, et al. Association between intermittent hypoxemia or bradycardia and late death or disability in extremely preterm infants. JAMA. 2015;314(6):595-603.
33. Ali NJ, Pitson D, Stradling JR. Sleep disordered breathing: Effects of adenotonsillectomy on behaviour and psychological functioning. Eur J Pediatr. 1996;155(1):56-62.
34. Bass JL, Corwin M, Gozal D, Moore C, Nishida H, Parker S, et al. The effect of chronic or intermittent hypoxia on cognition in childhood: a review of the evidence. Pediatrics. 2004;114:805-16.
35. Schmidt B, Roberts RS, Davis P, Doyle LW, Barrington KJ, Ohlsson A, et al. Long-term effects of caffeine therapy for apnea of prematurity. N Engl J Med. 2007;357(19):1893-902.
36. McNamara DG, Nixon GM, Anderson BJ. Methylxanthines for the treatment of apnea associated with bronchiolitis and anesthesia. Pediatric Anesthesia. 2004;14(7):541-50.
37. Schmidt B, Roberts RS, Anderson PJ, Asztalos EV, Costantini L, Davis PG, et al. Academic performance, motor function, and behavior 11 years after neonatal caffeine citrate therapy for apnea of prematurity: an 11-year follow-up of the CAP randomized clinical trial. JAMA Peds. 2017;171(6):564-72.
38. Doyle LW, Ranganathan S, Cheong JLY. Neonatal caffeine treatment and respiratory function at 11 years in children <1251 g birth weight. Am J Respir Crit Care Med. 2017;Online, ahead of print.
39. Davis PG, Schmidt B, Roberts RS, Doyle LW, Asztalos E, Haslam R, et al. Caffeine for Apnea of Prematurity trial: benefits may vary in subgroups. J Pediatr. 2010;156(3):382-7.

40. Doyle LW, Cheong J, Hunt RW, Lee KJ, Thompson DK, Davis PG, et al. Caffeine and brain development in very preterm infants. Ann Neurol. 2010;68(5):734-42.
41. Atik A, Harding R, De Matteo R, Kondos-Devcic R, Cheong J, Doyle L, et al. Caffeine for apnea of prematurity: Effects on the developing brain. Neurotoxicology. 2017;58:94-102.
42. Oliphant EA, McKinlay CJD, McNamara DG, Alsweiler JM. Caffeine prophylaxis to improve intermittent hypoxaemia in infants born late preterm: a randomised controlled dosage trial (Latte Dosage Trial). BMJ Open. 2020;10(10):e038271.
43. Paine S-J, Cormack D, Reid P, Harris R, Robson B. 13 Kaupapa Maori informed approaches to support data rights and self-determination. In: Walters M., Kukutai T, Russo Carroll S, Rodriquez-Lonebear D, editors. Indigenous Data Sovereignty and Policy. Oxon, New York. : Routledge. ; 2021.
44. Månsson J, Stjernqvist K, Serenius F, Ådén U, Källén K. Agreement between Bayley-III measurements and WISC-IV measurements in typically developing dhildren. Journal of Psychoeducational Assessment. 2018;37:603-16.
45. Flynn RS, Huber MD, DeMauro SB. Predictive value of the BSID-II and the Bayley-III for early school age cognitive function in very preterm infants. Glob Ped Heal. 2020;7:2333794X20973146-2333794X.
46. Cheong JL, Doyle LW, Burnett AC, Lee KJ, Walsh JM, Potter CR, et al. Association between moderate and late preterm birth and neurodevelopment and social-emotional development at age 2 years. JAMA Peds. 2017;171(4):e164805-e.
47. Cans C, Dolk H, Platt MJ, Colver A, Prasauskiene A, Krageloh-Mann I, et al. Recommendations from the SCPE collaborative group for defining and classifying cerebral palsy. Dev Med Child Neurol. 2007;109:35-8.
48. Palisano RJ, Hanna SE, Rosenbaum PL, Russell DJ, Walter SD, Wood EP, et al. Validation of a model of gross motor function for children with cerebral palsy. Phys Ther. 2000;80(10):974-85.
49. Pedersen ESL, Spycher BD, de Jong CCM, Halbeisen F, Ramette A, Gaillard EA, et al. The simple 10-item predicting asthma risk in children tool to predict childhood asthma-an external validation. J Allergy Clin Immunol Pract. 2019;7(3):943-53 e4.
50. Fenton TR, Kim JH. A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants. BMC Pediatrics. 2013;13(1):59.
51. Johnson W. Analytical strategies in human growth research. Am J Hum Biol. 2015;27(1):69-83.