BMJ Open

Caffeine prophylaxis to improve intermittent hypoxaemia in infants born late preterm: a randomised controlled dosage trial (Latte Dosage Trial)

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-038271
Article Type:	Protocol
Date Submitted by the Author:	05-Mar-2020
Complete List of Authors:	Oliphant, Elizabeth; The University of Auckland, Department of Paediatrics: Child and Youth Health; Starship Child Health, Auckland District Health Board McKinlay, Christopher; The University of Auckland, Liggins Institute; Kidz First Neonatal Care, Counties Manukau Health McNamara, David; Starship Child Health, Auckland District Health Board Alsweiler, Jane; University of Auckland, Paediatrics:Child and Youth Health
Keywords:	NEONATOLOGY, CLINICAL PHARMACOLOGY, Paediatric thoracic medicine < PAEDIATRICS

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Caffeine prophylaxis to improve intermittent hypoxaemia in infants born late preterm: a randomised controlled dosage trial (Latte Dosage Trial)

Elizabeth A Oliphant[1,2], Christopher JD McKinlay[3,4], David G McNamara[2], Jane M Alsweiler[1,2]

[1] Department of Paediatrics: Child and Youth Health, University of Auckland, Auckland, New Zealand

[2] Starship Child Health, Auckland District Health Board, Auckland, New Zealand

[3] Liggins Institute, University of Auckland, Auckland, New Zealand

[4] Kidz First Neonatal Care, Counties Manukau Health, Auckland, New Zealand

Correspondence to:

Elizabeth Anne Oliphant

Clinical Fellow, Department of Paediatrics: Child and Youth Health

University of Auckland

PO Box 92019

Auckland Mail Centre

Auckland

New Zealand

e.oliphant@auckland.ac.nz

Word Count: 3345

Key words: neonate, intermittent hypoxaemia, caffeine, late preterm

Abstract:

Introduction

Infants born late preterm (34^{+0} – 36^{+6} weeks' gestational age) have frequent episodes of intermittent hypoxaemia compared to term infants. Caffeine citrate reduces apnoea and intermittent hypoxaemia and improves long-term neurodevelopmental outcomes in infants born very preterm and may have similar effects in late preterm infants. Clearance of caffeine citrate increases with gestational age and late preterm infants are likely to need a higher dose than very preterm infants. Our aim is to determine the most effective and best tolerated dose of caffeine citrate to reduce intermittent hypoxaemia in late preterm infants.

Methods and analysis

A phase IIB, double-blind, five-arm, parallel, randomised controlled trial to compare the effect of four doses of oral caffeine citrate versus placebo on the frequency of intermittent hypoxaemia. Late preterm infants will be enrolled within 72 hours of birth and randomised to receive 5, 10, 15 or 20 mg/kg/day caffeine citrate or matching placebo daily until term corrected age. The frequency of intermittent hypoxaemia (events/hour where oxygen saturation concentration is ≥10% below baseline for ≤two minutes), will be assessed with overnight oximetry at baseline, two weeks after randomisation (primary outcome) and at term corrected age. Growth will be measured at these timepoints, and effects on feeding and sleeping will be assessed by parental report. Data will be analysed using generalised linear mixed models.

Ethics and dissemination

This trial has been approved by the Health and Disability Ethics Committees of New Zealand (reference 18/NTA/129) and the local institutional research review committees. Findings will be disseminated to peer-reviewed journals, to clinicians and researchers at local and international

conferences and to the public. The findings of the trial will inform the design of a large multi-centre trial of prophylactic caffeine in late preterm infants, by indicating the most appropriate dose to use and providing information on feasibility.

Registration

ACTRN12618001745235

Strengths and limitations of this study

- This study seeks to address the rates of neurodevelopmental impairment among late preterm infants by investigating the optimal dose of caffeine, as a potential primary neuroprotective strategy.
- This is the first randomised placebo-controlled trial of four different doses of caffeine for the prevention of intermittent hypoxaemia in late preterm infants.
- A strength of the trial is that both clinicians and parents will be blinded to treatment allocation with all groups receiving the same volume of an identical-appearing masked suspension.
- The success of the trial depends on high compliance of administration of study medication by caregivers, which will be monitored by intermittent measurement of study bottle contents and infant salivary caffeine concentrations.
- Future studies will be required to determine if caffeine reduces neurodevelopmental impairment in late preterm infants, based on the optimal dose determined by this trial.

Introduction:

Late preterm infants are those born between 34 weeks and 36 weeks and 6 days' gestation [1]. They form the largest group within the preterm population, accounting for 68% of all preterm births or 5% of all births in New Zealand[2] and 7% of all births in the United States of America[3]. Late preterm infants are physiologically and metabolically immature[1] and have a higher risk of morbidity and mortality in the neonatal period than full term infants[4]. They are more likely than full term infants to have delayed establishment of oral feeding, temperature instability, hypoglycaemia, jaundice and respiratory distress, and to undergo investigation for sepsis[5]. Despite these risks, their size and weight mean they are often managed in a similar manner to full term infants and cared for on postnatal wards rather than in neonatal units[6], 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 infants. Importantly, for population health outcomes, although the individual morbidity is generally lower in late preterm infants than those born more preterm, the much larger size of the late preterm population nevertheless means that they account for a significant portion of all neonatal morbidity. Late preterm birth thus has significant implications in terms of resource use both in the immediate care needed in the neonatal period, and in the longer term for health and education support[7].

Very preterm infants are at high risk of apnoea of prematurity and intermittent hypoxaemia[8,9]. 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[10] and neurodevelopmental impairment[11]. Late preterm infants experience apnoea of prematurity, although less frequently than in very preterm infants[8]. Recently, we have demonstrated that late preterm infants have frequent episodes of intermittent hypoxaemia,[12] brief repetitive decreases in oxygen saturation not associated with apnoea, but

potentially causing similar organ hypoxia. In late preterm infants, the frequency of intermittent hypoxaemia peaks at two weeks' postnatal age, before reducing to baseline levels at term corrected age (Fig 1)[12].

Figure 1: Rate of intermittent hypoxaemia in late preterm infants in the 9-11 weeks following birth (adapted)[12]

Studies in adults have consistently shown that even brief exposure to hypoxia, whether from high altitude[13] or carbon monoxide poisoning[14], 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 infants[15–17]. Intermittent hypoxaemia is associated with altered brain development in neonatal mice[18] and reduced cognition and behavioural deficits in neonatal rats[19]. In humans, intermittent hypoxaemia is associated with poor neurodevelopmental outcomes in extremely preterm infants[20] and in children with sleep disordered breathing[21] and congenital heart disease[22].

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 infants[23–25]. Follow-up to 11 years of age has recently shown that caffeine treatment reduces the risk of motor dysfunction by a third in infants born very preterm[26,27]. While some of the long term beneficial effects of caffeine may be due to its effect in reducing the incidence of bronchopulmonary dysplasia[28], there is also benefit from reducing the amount of time that infants are hypoxic, independent of the effect on bronchopulmonary dysplasia[29]. Thus, caffeine has become the standard of care for very preterm infants 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 to also be very well tolerated.

In the longer term, late preterm infants are more likely to be diagnosed with cerebral palsy [30,31], developmental delay [32,33], cognitive impairment [34–36] and behavioural disorders [37] compared to their term-born peers. However, few studies have investigated interventions to improve the neurodevelopmental outcomes of late preterm infants. As late preterm infants have an increase in hypoxaemic events compared to term infants, and hypoxaemic events are associated with poor neurodevelopmental outcomes, it is possible that caffeine, an intervention that reduces hypoxaemic events and has already been shown to improve long-term outcomes in extremely and very preterm infants, may be effective at improving outcomes in late preterm infants.

In adults, most caffeine metabolism is via cytochrome P450 1A2 in the liver[38]. However, in newborn preterm infants, hepatic metabolism of caffeine is almost absent, and most caffeine is eliminated via the kidneys, which are also immature. Therefore, caffeine elimination is slow in extremely preterm infants, and the half-life of caffeine is long. With increasing postconceptial agethe elimination of of caffeine increases[39,40] , and larger doses may be needed to maintain a therapeutic effect. However, the pharmacokinetic studies of caffeine in preterm infants to date have been done to treat apnoea in very preterm infants, rather than to treat intermittent hypoxaemia in late preterm infants[41].

There is a wide range in the dose of caffeine citrate given to extremely preterm infants, from daily doses of 5 mg/kg[24] to 20 mg/kg[42]. The Caffeine for Apnoea of Prematurity (CAP) trial used a dose of 5 mg/kg, which could be increased to 10 mg/kg if necessary to control apnoea of prematurity[24]. The trial by Rhein et al found that in very preterm infants, 6 mg/kg of caffeine citrate reduced intermittent hypoxaemia at 35 and 36 weeks' post-menstrual age, but not after 36

weeks' post-menstrual age[9]. The authors hypothesised that this may have been due to an insufficient dose as the infants matured. Therefore, the most effective dose of caffeine to treat intermittent hypoxaemia in late preterm infants is unknown.

In very preterm infants, caffeine is usually well tolerated, but occasionally infants on caffeine develop tachycardia and feed intolerance[42]. Caffeine also causes reduced neonatal weight gain compared to placebo[24], and in ventilated preterm infants a higher dose of caffeine citrate (20 mg/kg) leads to reduced weight gain compared with a low dose (5 mg/kg)[42]. As in adults, infants on caffeine can develop irritability, sleeplessness and gastrointestinal disturbance. For caffeine to be used as a prophylactic medication in a large number of late preterm infants, it will need to be prescribed at a dose that has a low risk of significant side effects.

We are therefore undertaking the Latte Dosage Trial, a randomised, placebo-controlled dosage trial, to determine the most effective and best tolerated dose of oral caffeine citrate to reduce intermittent hypoxaemia in late preterm infants.

Aim: To determine the most effective and best tolerated dose of caffeine citrate to reduce intermittent hypoxaemia in late preterm infants.

Hypothesis: Caffeine citrate will reduce the frequency of intermittent hypoxaemia in late preterm infants in a dose dependant manner.

Methods and analysis:

Study Design: The Latte Dosage Trial is a phase IIB, double-blind, five-arm, parallel, randomised controlled trial to compare the effect of four different doses of oral caffeine citrate versus placebo on the frequency of intermittent hypoxaemia in late preterm infants.

Recruitment and randomisation

Participants will be recruited by trial investigators or study nurses / midwives within 72 hours of birth from the neonatal unit and postnatal wards at Auckland City and Middlemore Hospitals in Auckland, New Zealand. Following written informed consent and enrolment, trial participation may occur in hospital, at a primary maternity unit or at home, as the patient's clinical care dictates. Eligible participants are those infants born between 34 weeks and 36 weeks' and six days gestation without contradiction to caffeine treatment, with the following exclusions:

- 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
- Residing outside of the Auckland region

Infants will be assigned randomly via an internet randomisation service (Clinical Data Research Hub, Liggins Institute, University of Auckland) to receive either daily caffeine citrate 5 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg or placebo. The allocation sequence will be generated by the study statistician, with 1:1:1:1:1 allocation stratified by study site and gestational age at birth (34, 35 or 36 weeks) (Figure 2) using variable block sizes, with infants from multiple births being randomised to the same treatment group.

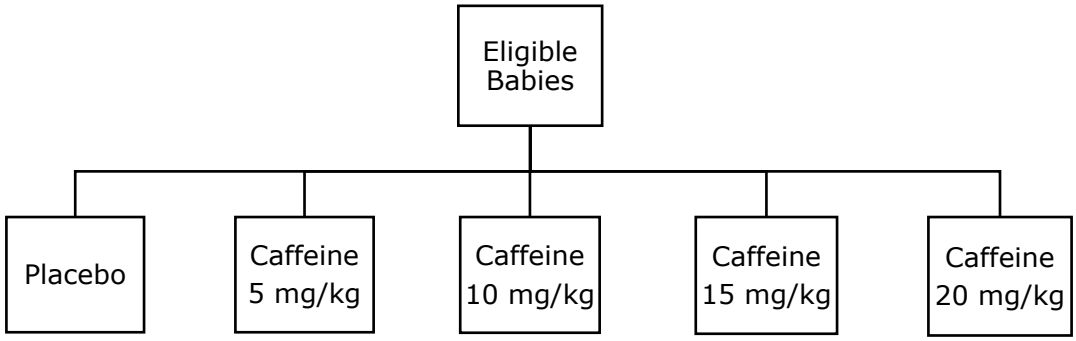


Figure 2: Flow diagram of randomisation schedule

Different concentrations of the caffeine citrate (5 mg/ml, 10 mg/ml, 15 mg/ml and 20 mg/ml) will be prepared in identical bottles to the placebo so that all infants receive the same dose volume (2 ml/kg loading dose followed by 1 ml/kg, once daily). Bottles will be labelled in randomisation blocks using a lettering system which will change halfway through the study in order to maintain concealment.

Study Intervention

The infant will be given an enteral loading dose of the study drug (10 mg/kg, 20 mg/kg, 30 mg/kg or 40 mg/kg of caffeine citrate or water) in the morning after baseline oximetry (i.e. prior to the infant reaching 96 hours of age), followed by a daily dose each morning (5 mg/kg, 10mg/kg, 15 mg/kg or 20 mg/kg of caffeine citrate or placebo) until term equivalent age (40 weeks' post-menstrual age). The dose will be recalculated weekly for weight after the infant has regained birth weight using the weight recorded by study staff at two weeks after randomisation and those recorded by usual care providers between two weeks' and term corrected age. The study drug will be given via a nasogastric tube for infants with a tube *in situ*, and orally for infants who do not require a nasogastric tube. Infants who are not able to tolerate enteral medications will have the study drug withheld until they are able to tolerate enteral intake.

Compliance will be assessed by measurement of study medication remaining in the bottle. At the two-week visit, study staff will collect the initial bottle(s) issued at the start of the study and replace it with a new bottle(s), which will in turn be collected at the final visit. Liquid remaining in the bottle on each occasion will be measured and compared with the expected volume to assess compliance. Good compliance will be defined as ≥80% of the expected volume having been removed from the bottle. At the final visit, parents will be asked which treatment they think their infant received to assess the adequacy of blinding.

Apart from the study intervention and associated assessments, all other clinical care will continue to be provided by the local clinical team, in accordance with usual guidelines and practices. Should an infant participating in the study require treatment for apnoea or intermittent hypoxaemia, clinicians will be encouraged to use oxygen or positive pressure ventilation as first line treatments. If necessary, a loading dose of caffeine citrate may be given. If ongoing treatment with caffeine is necessary in the opinion of the treating clinician, they can discuss the option of partially unblinding the infant (caffeine or placebo) with the Site Principal Investigator. Clinical open-label use of caffeine will be recorded, with infants analysed on an intention-to-treat basis.

Outcomes

The primary outcome for this study is the frequency of intermittent hypoxaemia (events/hour, defined as a brief fall in oxygen saturation concentration ≥10% below baseline for not more than 2 minutes) on overnight oximetry, two weeks after randomisation.

Secondary outcomes include:

- Respiratory: frequency of intermittent hypoxaemia on overnight oximetry at term equivalent age; mean overnight oxygen saturation at 2 weeks and term equivalent age; use of respiratory support, including oxygen, until term equivalent age)

- Growth: growth velocity for weight gain, length and head circumference; failure to regain birthweight by 2 weeks of age
- Side effects: Feed intolerance as reported by parents[43]; duration of tube feeding; sleep and arousal as reported by parents (measured by subscale nine on the Infant Behaviour Questionnaire-Revised, modified for neonates[44]); tachycardia; study drug stopped due to presumed side effects
- Infant salivary caffeine concentration at two weeks after randomisation[45]
- Readmission to hospital until 44 weeks post-menstrual age or open label caffeine use
- Maternal mental health (Edinburgh postnatal depression score)[46]

The timing of the study intervention and assessments is summarised in Table 1.

Table 1: Study intervention and assessment

	Baseline	**Morning following baseline oximetry**	**1 week**	**2 weeks**	**3-5 weeks**	**Term equivalent age**
Pulse oximetry	X			X		X
Randomisation	X					
Loading dose		X				
Demographics, contacts	X					
Dose adjustment for weight				X	X	
Neonatal salivary caffeine concentration				X		
Maternal salivary caffeine concentration				X		
Drug Diary		X	X	X	X	X
Compliance assessment				X		X
Parental Questionnaires:						
Maternal smoking in pregnancy & household smoke exposure questionnaire	X					
Sleep questionnaire				X		X
Feed tolerance questionnaire				X		X

Maternal caffeine intake questionnaire	X			X		X
Edinburgh Postnatal Depression Scale	X					X

Data collection methods

Online data management services will be provided by the Clinical Data Research Hub (Liggins Institute, University of Auckland). Data collection will utilise the REDCap platform (Vanderbilt University) for clinical report forms, with password-protected secure servers used to store data.

Pulse oximetry: Overnight pulse oximetry (Rad 8, Masimo Corp., Irvine, CA) will be recorded for a period of 12 hours from either foot at baseline, two weeks after randomisation (range 12-21 days) and at term corrected age (range 40 to 41 weeks postmenstrual age) using a 2-second averaging time and 2-second resolution. Unless clinically required, oximeters will be operated in sleep mode, with no displays or alarms. The oximetry recording will be downloaded with PROFOX oximetry software (version Masimo 2011.27D, PROFOX Associates Inc, Esconditso, CA) and edited to remove readings with poor signal or aberrant data. Only recordings with more than six hours will be included in the analysis, recordings with less than six hours of edited data will be repeated the following night.

Anthropometry: Weight, length and head circumference will be measured at study entry and at the two-week and term visits, with birthweight and neonatal centiles calculated using Fenton-WHO growth charts for preterm infants[47], and growth velocity calculated between birth and term equivalent using an exponential model[48].

Salivary caffeine concentrations: Two weeks after randomisation, a saliva sample will be collected from infants for assessment of caffeine concentration. Samples will be taken using a mouth swab prior to administration of the morning dose of trial medication. In the 24 hours preceding this,

mothers will be asked to collect three saliva samples by spitting into collection tubes at three pre-determined timepoints during the day, with the mean of these three samples used to determine average daytime maternal salivary caffeine concentration. Collection of these samples will allow us to compare maternal and infant salivary caffeine concentrations to establish if maternal caffeine intake contributes significantly to infant caffeine levels via breastfeeding or not, and to help assess compliance with the study intervention.

Questionnaires: Mothers will complete questionnaires to provide demographic and contact details at enrolment, and to assess smoking, infant feeding and sleeping, maternal caffeine intake and maternal mental health as detailed in Table 1.

Neonatal morbidity: Information on neonatal morbidity, including supplemental oxygen, respiratory support and apnoea requiring stimulation, will be recorded from the neonatal record. Exposure to antenatal corticosteroids will be recorded.

Discontinuation of intervention / withdrawal

The allocated treatment may be stopped at any time by the parents or the clinician caring for the infant if they feel that this is in the best interests of the infant, without formally withdrawing, in which case data collection will continue and results will be analysed on an intention-to-treat basis.

Should a parent wish to withdraw from the study, they will have the option of:

1. Discontinuation of study drug, with continuation of collection of minimum outcome data
2. Withdrawal from the study and discontinuation of further data collection, with data collected prior to withdrawal used
3. Complete withdrawal from the study, with removal of previously collected data

Patient and Public Involvement

The Latte Dosage Study methodology was discussed, developed and refined as part of the 2017 On-Track Network clinical trial development workshop which included consumer and Maori cultural advisor input. Perinatal consumer representatives provided advice and input into the development of the clinical trial protocol.

Sample size

Based on our previous study[12] we estimate a background mean (SD) frequency of 6.9 (3.4) episodes of intermittent hypoxaemia per hour at two weeks' post randomisation. To detect a 50% reduction of 3.5 episodes per hour with 90% power, allowing for a 10% drop out rate and clustering of multiples with an ICC of 0.05, we will require 24 infants in each of the five arms (total 120 infants), with two-sided alpha of 0.05.

Data analysis

The primary analysis will compare primary and secondary outcomes between groups using generalised linear mixed models with adjustment for gestational age at birth and site (fixed effects), non-independence of multiples (random effect) and pairwise comparisons between the different caffeine groups and between the caffeine groups and the placebo group using Dunnett's multiple comparison test. The selection of the optimal dose will be based on a combination of the dose with the greatest reduction of intermittent hypoxaemia with a minimum number of side effects and a pragmatic consideration of the ease of administration. Linear trends, such as growth, will be tested using orthogonal contrasts. Baseline imbalance between babies in the randomised groups will not be formally tested. Edinburgh Postnatal Depression Scale scores will be adjusted for baseline values. 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. Treatment effects will be presented as odds ratio, count ratio, mean difference or

ratio of geometric means (positively skewed data), as appropriate, with 95% confidence intervals. All tests will be two-tailed, with P<0.05 considered significant. The data will be analysed on an intention-to-treat basis.

The following secondary analyses will be performed:

- *Compliance*: A per-protocol analysis will be performed for the primary outcome that includes only those infants who were compliant with the study drug.
- *Open-label caffeine treatment:* A sensitivity analysis will be performed for the primary outcome that includes only those infants who did not receive additional open-label caffeine treatment.
- *Maternal caffeine:* An exploratory analysis will be performed on the effect of maternal caffeine intake on the primary outcome by performing additional adjustments for maternal caffeine intake from the questionnaire and maternal salivary caffeine concentration. For infants that are fully formula fed, infant caffeine exposure to maternal caffeine intake will be assumed to be zero.

An independent data monitoring committee will review trial data after enrolment of 60 infants to the trial. The data monitoring committee provide advice to the trial steering group on any modifications that may be required. There are no formal stopping guidelines.

Ethics and dissemination:

Ethical approval has been obtained from the Health and Disability Ethics Committees of New Zealand (reference 18/NTA/129) and by the local institutional research review committees for each centre. The trial is registered with the Australian New Zealand Clinical Trials Registry (Registration number: ACTRN12618001745235) from 24 October 2018.

The results of the trial will be published in an international peer-reviewed journal and disseminated via presentations at local and international conferences to researchers and clinicians. A lay summary of the research findings will be made available to those parents who indicated a wish to receive these on their consent forms.

Discussion

Late preterm infants experience higher rates of intermittent hypoxaemia than their term-born peers, and have poorer long-term neurodevelopmental outcomes[30–37]. Caffeine is well established as a treatment for apnoea of prematurity in very and extremely preterm infants, and improves long term neurodevelopmental outcomes in these infants[23,49,50]. Caffeine use in late preterm infants may also reduce episodes of intermittent hypoxaemia and improve long term outcomes for these infants. As late preterm infants make up the majority of preterm infants, interventions that improve long term outcomes in this population are likely to have the greatest public health impact in terms of interventions for preterm infants[7].

The Latte Dosage Trial seeks to establish the most effective and best tolerated dose of caffeine citrate for the prevention of intermittent hypoxaemia in late preterm infants. It is the first trial to investigate the use of caffeine, an inexpensive medication already widely used in neonatal care, for this indication. Data from the Latte Dosage Trial will be used to inform the development of a large-scale, multicentre trial investigating the efficacy of caffeine treatment in late preterm infants in preventing neurodevelopmental impairment by indicating the most appropriate dose to use and providing information on feasibility.

References

1 Engle WA, Tomashek KM, Wallman C. “Late-preterm” infants: a population at risk. *Pediatrics* 2007;**120**:1390–401. doi:10.1542/peds.2007-2952

2 Ministry of Health. Report on Maternity 2017 - tables. Wellington: 2019. https://www.health.govt.nz/publication/report-maternity-2017 (accessed 8 Jul 2019).

3 Martin JA, Hamilton BE, Osterman MJK, *et al.* Births: final data for 2017. 2017. https://www.cdc.gov/nchs/data_access/Vitalstatsonline.htm

4 McIntire DD, Leveno KJ. Neonatal mortality and morbidity rates in late preterm births compared with births at term. *Obstet Gynecol* 2008;**111**:35–41. doi:10.1097/01.AOG.0000297311.33046.73

5 Wang ML, Dorer DJ, Fleming MP, *et al.* Clinical outcomes of near-term infants. *Pediatrics* 2004;**114**:372–6. doi:10.1542/peds.114.2.372

6 Boyle EM, Johnson S, Manktelow B, *et al.* Neonatal outcomes and delivery of care for infants born late preterm or moderately preterm: a prospective population-based study. *Arch Dis Child Fetal Neonatal Ed* 2015;**100**:F479–F485. doi:10.1136/fetalneonatal-2014-308136

7 March of Dimes, The Partnership for Maternal Newborn and Child Health, Save the Children, *et al.* Born too soon: the global action report on preterm birth. Geneva: 2012. doi:http://whqlibdoc.who.int/publications/2012/9789241503433_eng.pdf

8 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. doi:10.1111/j.1440-1754.1981.tb01957.x

9 Rhein LM, Dobson NR, Darnall RA, *et al.* Effects of Caffeine on Intermittent Hypoxia in Infants Born Prematurely. *JAMA Pediatr* 2014;**168**:250. doi:10.1001/jamapediatrics.2013.4371

10 Butcher-Puech MC, Henderson-Smart DJ, Holley D, *et al.* Relation between apnoea duration and type and neurological status of preterm infants. *Arch Dis Child* 1985;**60**:953–8. doi:10.1136/adc.60.10.953

11 Janvier A, Khairy M, Kokkotis A, *et al.* Apnea is associated with neurodevelopmental impairment in very low birth weight infants. *J Perinatol* 2004;**24**:763–8. doi:10.1038/sj.jp.7211182

12 Williams LZJ, Mcnamara D, Alsweiler JM. Intermittent hypoxemia in infants born late preterm: a prospective cohort observational study. *J Pediatr* 2018;**204**:89-95.e1. doi:10.1016/j.jpeds

13 Bahrke MS, Shukitt-Hale B. Effects of altitude on mood, behaviour and cognitive functioning. A review. *Sports Med* 1993;**16**:97–125. doi:10.2165/00007256-199316020-00003

14 Weaver LK, Hopkins RO, Chan KJ, *et al.* Hyperbaric oxygen for acute carbon monoxide poisoning. *N Engl J Med* 2002;**347**:1057–67. doi:10.1056/NEJMoa013121

15 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. 2013;**105**:55–63. doi:10.1159/000356561

16 Carlo WA, Finer NN, Walsh MC, *et al.* Target ranges of oxygen saturation in extremely preterm infants. *N Engl J Med* 2010;**362**:1959–69. doi:10.1056/NEJMoa0911781

17 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**:1680–2. doi:10.1056/NEJMc1101319

18 Kanaan A, Farahani R, Douglas RM, *et al.* Effect of chronic continuous or intermittent hypoxia and reoxygenation on cerebral capillary density and myelination. *Am J Physiol - Regul Integr Comp Physiol* 2006;**290**:R1105-14. doi:10.1152/ajpregu.00535.2005

19 Row BW, Kheirandish L, Neville JJ, *et al.* Impaired spatial learning and hyperactivity in developing rats exposed to intermittent hypoxia. *Pediatr Res* 2002;**52**:449–53. doi:10.1203/00006450-200209000-00024

20 Poets CF, Roberts RS, Schmidt B, *et al.* Association between intermittent hypoxemia or bradycardia and late death or disability in extremely preterm infants. *J Am Med Assoc* 2015;**314**:595–603. doi:10.1001/jama.2015.8841

21 Ali NJ, Pitson D, Stradling JR. Sleep disordered breathing: effects of adenotonsillectomy on behaviour and psychological functioning. *Eur J Pediatr* 1996;**155**:56–62. doi:10.1007/bf02115629

22 Bass JL, Corwin M, Gozal D, *et al.* The effect of chronic or intermittent hypoxia on cognition in childhood: A review of the evidence. Pediatrics. 2004;**114**:805–16. doi:10.1542/peds.2004-0227

23 Schmidt B, Roberts RS, Davis P, *et al.* Long-term effects of caffeine therapy for apnea of prematurity. *N Engl J Med* 2007;**357**:1893–902.www.nejm.org (accessed 18 Apr 2019).

24 Schmidt B, Roberts RS, Davis P, *et al.* Caffeine therapy for apnea of prematurity. *N Engl J Med* 2006;**354**:2112–21.www.nejm.org (accessed 5 Dec 2018).

25 McNamara DG, Nixon GM, Anderson BJ. Methylxanthines for the treatment of apnea associated with bronchiolitis and anesthesia. Paediatr. Anaesth. 2004;**14**:541–50. doi:10.1111/j.1460-9592.2004.01351.x

26 Schmidt B, Roberts RS, Anderson PJ, *et al.* Academic performance, motor function, and behavior 11 years after neonatal caffeine citrate therapy for apnea of prematurity. *JAMA Pediatr* 2017;**171**:564. doi:10.1001/jamapediatrics.2017.0238

27 Doyle LW, Ranganathan S, Cheong JLY. Neonatal caffeine treatment and respiratory function at 11 years in children under 1,251 g at birth. *Am J Respir Crit Care Med* 2017;**196**:1318–24. doi:10.1164/rccm.201704-0767OC

28 Davis PG, Schmidt B, Roberts RS, *et al.* Caffeine for apnea of prematurity trial: benefits may vary in subgroups. *J Pediatr* 2010;**156**:382–7. doi:10.1016/j.jpeds.2009.09.069

29 Doyle LW, Cheong J, Hunt RW, *et al.* Caffeine and brain development in very preterm infants. *Ann Neurol* 2010;**68**:734–42. doi:10.1002/ana.22098

30 Moster D, Lie RT, Markestad T. Long-term medical and social consequences of preterm birth. *N Engl J Med* 2008;**359**:262–73.www.nejm.org (accessed 12 Jul 2019).

31 Odd DE, Lingam R, Emond A, *et al.* Movement outcomes of infants born moderate and late preterm. *Acta Paediatr* 2013;**102**:876–82. doi:10.1111/apa.12320

32 Darlow BA, Horwood LJ, Wynn-Williams MB, *et al.* Admissions of all gestations to a regional neonatal unit versus controls: 2-year outcome. *J Paediatr Child Health* 2009;**45**:187–93. doi:10.1111/j.1440-1754.2008.01457.x

33 Woythaler MA, McCormick MC, Smith VC. Late preterm infants have worse 24 month neurodevelopmental outcomes than term infants. *Pediatrics* 2011;**127**:e622-9. doi:10.1542/peds.2009-3598

34 Talge NM, Holzman C, Wang J, *et al.* Late-preterm birth and its association with cognitive and socioemotional outcomes at 6 years of age. *Pediatrics* 2010;**126**:1124–31. doi:10.1542/peds.2010-1536

35 Quigley MA, Poulsen G, Boyle E, *et al.* Early term and late preterm birth are associated with poorer school performance at age 5 years: a cohort study. *Arch Dis Child Fetal Neonatal Ed* 2012;**97**:F167-73. doi:10.1136/archdischild-2011-300888

36 Heinonen K, Eriksson JG, Lahti J, *et al.* Late preterm birth and neurocognitive performance in late adulthood: a birth cohort study. *Pediatrics* 2015;**135**:e818-25. doi:10.1542/peds.2014-3556

37 Huddy CLJ, Johnson A, Hope PL. Educational and behavioural problems in babies of 32-35 weeks gestation. *Arch Dis Child Fetal Neonatal Ed* 2001;**85**:F23–8. doi:10.1136/fn.85.1.F23

38 Anderson BJ, Gunn TR, Holford NHG, *et al.* Caffeine overdose in a premature infant: clinical course and pharmacokinetics. *Anaesth Intensive Care* 1999;**27**:307–11.https://search-proquest-

com.ezproxy.auckland.ac.nz/docview/224844582/fulltextPDF/363FABA09B4649A6PQ/1?accountid=8424 (accessed 12 Nov 2018).

39 Le Guennec J-C, Billon B, Pare C. Maturational Changes of Caffeine Concentrations and Disposition in Infancy During Maintenance Therapy for Apnea of Prematurity: Influence of Gestational Age, Hepatic Disease, and Breast-Feeding. 1985. www.aappublications.org/news (accessed 12 Nov 2018).

40 Falcão AC, de Gatta MMF, Iribarnegaray MFD, *et al.* Population pharmacokinetics of caffeine in premature neonates. *Eur J Clin Pharmacol* 1997;**52**:211–7. doi:10.1007/s002280050276

41 Thomson AH, Kerr S, Wright S. Population pharmacokinetics of caffeine in neonates and young infants. *Ther Drug Monit* 1996;**18**:245–53.https://oce-ovid-com.ezproxy.auckland.ac.nz/article/00007691-199606000-00005/HTML (accessed 12 Dec 2018).

42 Steer P, Flenady V, Shearman A, *et al.* High dose caffeine citrate for extubation of preterm infants: a randomised controlled trial. *Arch Dis Child Fetal Neonatal Ed* 2004;**89**:F499-503. doi:10.1136/adc.2002.023432

43 Kleinman L, Rothman M, Strauss R, *et al.* The infant gastroesophageal reflux questionnaire revised: development and validation as an evaluative instrument. *Clin Gastroenterol Hepatol* 2006;**4**:588–96. doi:10.1016/j.cgh.2006.02.016

44 Gartstein MA, Rothbart MK. Studying infant temperament via the Revised Infant Behavior Questionnaire. *Infant Behav Dev* 2003;**26**:64–86. doi:10.1016/S0163-6383(02)00169-8

45 Dobson NR, Liu X, Rhein LM, *et al.* Salivary caffeine concentrations are comparable to plasma concentrations in preterm infants receiving extended caffeine therapy. *Br J Clin Pharmacol* 2016;**82**:754–61. doi:10.1111/bcp.13001

46 Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression: development of the 10-item Edinburgh postnatal depression scale. *Br J Psychiatry* 1987;**150**:782–6. doi:10.1192/bjp.150.6.782

47 Fenton TR, Kim JH. A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants. *BMC Pediatr* 2013;**13**:59. doi:10.1186/1471-2431-13-59

48 Patel A, Engstrom J, Meier P, *et al.* Calculating postnatal growth velocity in very low birth weight (VLBW) premature infants. *J Perinatol* 2009;**29**:618–22.

49 Schmidt B, Anderson PJ, Doyle LW, *et al.* Survival without disability to age 5 years after neonatal caffeine therapy for apnea of prematurity. *JAMA* 2012;**307**:275. doi:10.1001/jama.2011.2024

50 Mürner-Lavanchy IM, Doyle LW, Schmidt B, *et al.* Neurobehavioral outcomes 11 years after neonatal caffeine therapy for apnea of prematurity. *Pediatrics* 2018;**141**:e20174047.www.aappublications.org/news (accessed 13 May 2019).

Authors' contributions:

JMA conceived and developed the study design, drafted the original study protocol, approved the final study protocol and reviewed the article for publication.

EAO contributed to the study design, approved the final version of the study protocol, and drafted the article for publication.

CM contributed to the study design, approved the final version of the study protocol, and reviewed the article for publication.

DM contributed to the study design, approved the final version of the study protocol, and reviewed the article for publication.

Funding statement: This work is supported by the Health Research Council of New Zealand: grant number 18/613. The funder had no role in the study design and will have no role in collection, management, analysis and interpretation of the data; writing the report or the decision to submit a report for publication.

Competing interests' statement.

The authors have no competing interests to declare

Acknowledgements

Brian Darlow and Members of the ON TRACK network for assistance in developing and refining the study design.

Sarah Phillipsen, Sabine Huth, Lisa Mravicich and Florella Keen for assistance in setting up the trial.

Sara Hanning and Trusha Purohit for advice on caffeine testing and development of the caffeine assay.

Alana Cavadino for statistical advice.

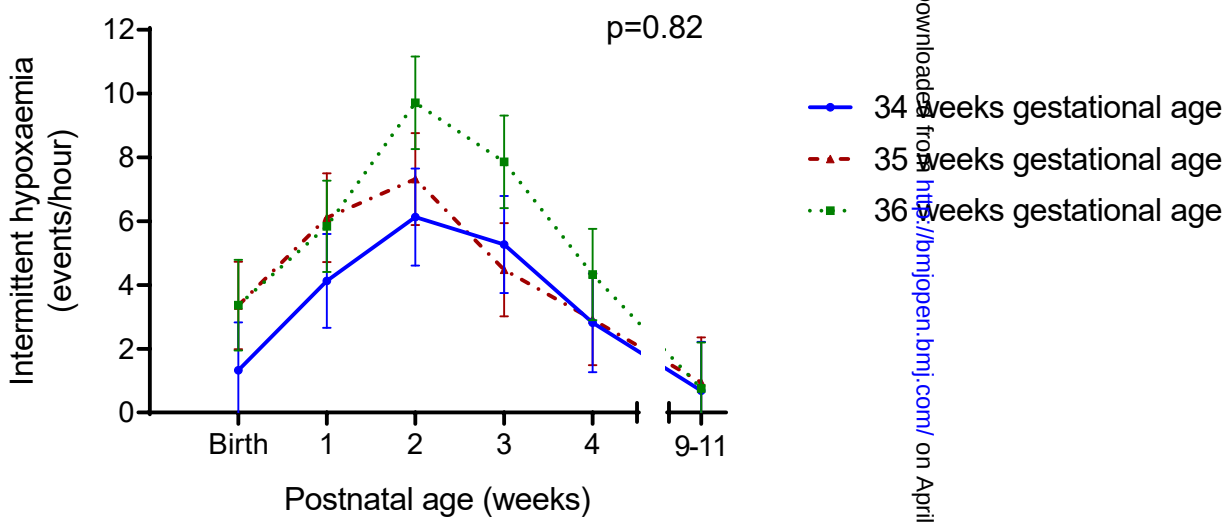


Figure 1: Rate of intermittent hypoxaemia in late preterm infants in the 9-11 weeks following birth (adapted)[12]

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	
Protocol version	3	Date and version identifier	On publication
Funding	4	Sources and types of financial, material, and other support	21
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 21
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	21
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	NA

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4 - 7
	6b	Explanation for choice of comparators	7, 9
Objectives	7	Specific objectives or hypotheses	8
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	8
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-10
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	10, 13-14
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	10
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	11-13
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Table 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	14
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	8
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	9
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	3, 8, 10
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	10
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11-13
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	14

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	12
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	14-15
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14-15
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	14-15
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	16
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	16
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	14
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	15-16
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	NA

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	14
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	22
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Submission documentation
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	10
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	16
	31b	Authorship eligibility guidelines and any intended use of professional writers	21
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	NA
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	13

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Caffeine prophylaxis to improve intermittent hypoxaemia in infants born late preterm: a randomised controlled dosage trial (Latte Dosage Trial)

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-038271.R1
Article Type:	Protocol
Date Submitted by the Author:	16-Jul-2020
Complete List of Authors:	Oliphant, Elizabeth; The University of Auckland, Department of Paediatrics: Child and Youth Health; Starship Child Health, Auckland District Health Board McKinlay, Chris ; The University of Auckland, Liggins Institute; Kidz First Neonatal Care, Counties Manukau Health McNamara, David; Starship Child Health, Auckland District Health Board Alsweiler, Jane; University of Auckland, Paediatrics:Child and Youth Health
Primary Subject Heading:	Paediatrics
Secondary Subject Heading:	Respiratory medicine, Pharmacology and therapeutics
Keywords:	NEONATOLOGY, CLINICAL PHARMACOLOGY, Paediatric thoracic medicine < PAEDIATRICS

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Caffeine prophylaxis to improve intermittent hypoxaemia in infants born late preterm: a randomised controlled dosage trial (Latte Dosage Trial)

Elizabeth A Oliphant[1,2], Christopher JD McKinlay[3,4], David G McNamara[2], Jane M Alsweiler[1,2]

[1] Department of Paediatrics: Child and Youth Health, University of Auckland, Auckland, New Zealand

[2] Starship Child Health, Auckland District Health Board, Auckland, New Zealand

[3] Liggins Institute, University of Auckland, Auckland, New Zealand

[4] Kidz First Neonatal Care, Counties Manukau Health, Auckland, New Zealand

Correspondence to:

Elizabeth Anne Oliphant

Clinical Fellow, Department of Paediatrics: Child and Youth Health

University of Auckland

PO Box 92019

Auckland Mail Centre

Auckland

New Zealand

e.oliphant@auckland.ac.nz

Word Count: 3345

Key words: neonate, intermittent hypoxaemia, caffeine, late preterm

Abstract:

Introduction

Infants born late preterm (34^{+0} – 36^{+6} weeks' gestational age) have frequent episodes of intermittent hypoxaemia compared to term infants. Caffeine citrate reduces apnoea and intermittent hypoxaemia and improves long-term neurodevelopmental outcomes in infants born very preterm and may have similar effects in late preterm infants. Clearance of caffeine citrate increases with gestational age and late preterm infants are likely to need a higher dose than very preterm infants. Our aim is to determine the most effective and best tolerated dose of caffeine citrate to reduce transient intermittent hypoxaemia events in late preterm infants.

Methods and analysis

A phase IIB, double-blind, five-arm, parallel, randomised controlled trial to compare the effect of four doses of oral caffeine citrate versus placebo on the frequency of intermittent hypoxaemia. Late preterm infants will be enrolled within 72 hours of birth and randomised to receive 5, 10, 15 or 20 mg/kg/day caffeine citrate or matching placebo daily until term corrected age. The frequency of intermittent hypoxaemia (events/hour where oxygen saturation concentration is ≥10% below baseline for ≤two minutes), will be assessed with overnight oximetry at baseline, two weeks after randomisation (primary outcome) and at term corrected age. Growth will be measured at these timepoints, and effects on feeding and sleeping will be assessed by parental report. Data will be analysed using generalised linear mixed models.

Ethics and dissemination

This trial has been approved by the Health and Disability Ethics Committees of New Zealand (reference 18/NTA/129) and the local institutional research review committees. Findings will be disseminated to peer-reviewed journals, to clinicians and researchers at local and international

conferences and to the public. The findings of the trial will inform the design of a large multi-centre trial of prophylactic caffeine in late preterm infants, by indicating the most appropriate dose to use and providing information on feasibility.

Registration

ACTRN12618001745235

Strengths and limitations of this study

- This study seeks to address the rates of neurodevelopmental impairment among late preterm infants by investigating the optimal dose of caffeine, as a potential primary neuroprotective strategy.
- This is the first randomised placebo-controlled trial of four different doses of caffeine for the prevention of intermittent hypoxaemia in late preterm infants.
- A strength of the trial is that both clinicians and parents will be blinded to treatment allocation with all groups receiving the same volume of an identical-appearing masked suspension.
- The success of the trial depends on high compliance of administration of study medication by caregivers, which will be monitored by intermittent measurement of study bottle contents and infant salivary caffeine concentrations.
- Future studies will be required to determine if caffeine reduces neurodevelopmental impairment in late preterm infants, based on the optimal dose determined by this trial.

Introduction:

Late preterm infants are those born between 34 weeks and 36 weeks and 6 days' gestation [1]. They form the largest group within the preterm population, accounting for 68% of all preterm births or 5% of all births in New Zealand[2] and 7% of all births in the United States of America[3]. Late preterm infants are physiologically and metabolically immature[1] and have a higher risk of morbidity and mortality in the neonatal period than full term infants[4]. They are more likely than full term infants to have delayed establishment of oral feeding, temperature instability, hypoglycaemia, jaundice and respiratory distress, and to undergo investigation for sepsis[5]. Despite these risks, their size and weight mean they are often managed in a similar manner to full term infants and cared for on postnatal wards rather than in neonatal units[6], 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 infants.

. Apnoea of prematurity are prolonged pauses in breathing, of 20 seconds or more, which may cause a reduction in the oxygen saturation and bradycardia, and are associated with an increased incidence of brain injury[7] and neurodevelopmental impairment[8]. Late preterm infants experience apnoea of prematurity, although less frequently than in very preterm infants[9]. Recently, we have demonstrated that late preterm infants have frequent episodes of intermittent hypoxaemia,[10] transient repetitive decreases in oxygen saturation not associated with apnoea, but potentially causing similar organ hypoxia. In late preterm infants, the frequency of intermittent hypoxaemia peaks at two weeks' postnatal age, before reducing to baseline levels at term corrected age (Fig 1)[10].

Figure 1: Rate of intermittent hypoxaemia in late preterm infants in the 9-11 weeks following birth (adapted)[10]

Studies in adults have consistently shown that even brief exposure to hypoxia, whether from high altitude[11] or carbon monoxide poisoning[12], 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 infants[13–15]. Intermittent hypoxaemia is associated with altered brain development in neonatal mice[16] and reduced cognition and behavioural deficits in neonatal rats[17]. In humans, transient intermittent hypoxaemic events are associated with poor neurodevelopmental outcomes in extremely preterm infants[18] and in children with sleep disordered breathing[19] and congenital heart disease[20].

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 infants[21–23]. Follow-up to 11 years of age has recently shown that caffeine treatment reduces the risk of motor dysfunction by a third in infants born very preterm[24,25]. While some of the long term beneficial effects of caffeine may be due to its effect in reducing the incidence of bronchopulmonary dysplasia[26], there is also benefit from reducing the amount of time that infants are hypoxic, independent of the effect on bronchopulmonary dysplasia[27]. Thus, caffeine has become the standard of care for very preterm infants 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 to also be very well tolerated.

In the longer term, late preterm infants are more likely to be diagnosed with cerebral palsy [28,29], developmental delay [30,31], cognitive impairment [32–34] and behavioural disorders [35]

compared to their term-born peers. However, few studies have investigated interventions to improve the neurodevelopmental outcomes of late preterm infants. As late preterm infants have an increase in hypoxaemic events compared to term infants, and hypoxaemic events are associated with poor neurodevelopmental outcomes, it is possible that caffeine, an intervention that reduces hypoxaemic events and has already been shown to improve long-term outcomes in extremely and very preterm infants, may be effective at improving outcomes in late preterm infants.

In adults, most caffeine metabolism is via cytochrome P450 1A2 in the liver[36]. However, in newborn preterm infants, hepatic metabolism of caffeine is almost absent, and most caffeine is eliminated via the kidneys, which are also immature. Therefore, caffeine elimination is slow in extremely preterm infants, and the half-life of caffeine is long. With increasing postconceptial agethe elimination of of caffeine increases[37,38] , and larger doses may be needed to maintain a therapeutic effect. However, the pharmacokinetic studies of caffeine in preterm infants to date have been done to treat apnoea in very preterm infants, rather than to treat intermittent hypoxaemia in late preterm infants[39].

There is a wide range in the dose of caffeine citrate given to extremely preterm infants, from daily doses of 5 mg/kg[22] to 20 mg/kg[40]. The Caffeine for Apnoea of Prematurity (CAP) trial used a dose of 5 mg/kg, which could be increased to 10 mg/kg if necessary to control apnoea of prematurity[22]. The trial by Rhein et al found that in very preterm infants, 6 mg/kg of caffeine citrate reduced intermittent hypoxaemia at 35 and 36 weeks' post-menstrual age, but not after 36 weeks' post-menstrual age[41]. The authors hypothesised that this may have been due to an insufficient dose as the infants matured. Therefore, the most effective dose of caffeine to treat intermittent hypoxaemia in late preterm infants is unknown.

In very preterm infants, caffeine is usually well tolerated, but occasionally infants on caffeine develop tachycardia and feed intolerance[40]. Caffeine also causes reduced neonatal weight gain compared to placebo[22], and in ventilated preterm infants a higher dose of caffeine citrate (20 mg/kg) leads to reduced weight gain compared with a low dose (5 mg/kg)[40]. As in adults, infants on caffeine can develop irritability, sleeplessness and gastrointestinal disturbance. For caffeine to be used as a prophylactic medication in a large number of late preterm infants, it will need to be prescribed at a dose that has a low risk of significant side effects.

We are therefore undertaking the Latte Dosage Trial, a randomised, placebo-controlled dosage trial, to determine the most effective and best tolerated dose of oral caffeine citrate to reduce intermittent hypoxaemia in late preterm infants.

Aim: To determine the most effective and best tolerated dose of caffeine citrate to reduce intermittent hypoxaemia in late preterm infants.

Hypothesis: Caffeine citrate will reduce the frequency of intermittent hypoxaemia in late preterm infants in a dose dependant manner.

Methods and analysis:

Study Design: The Latte Dosage Trial is a phase IIB, double-blind, five-arm, parallel, randomised controlled trial to compare the effect of four different doses of oral caffeine citrate versus placebo on the frequency of intermittent hypoxaemia in late preterm infants.

Recruitment and randomisation

Participants will be recruited by trial investigators or study nurses / midwives within 72 hours of birth from the neonatal unit and postnatal wards at Auckland City and Middlemore Hospitals in Auckland, New Zealand. Following written informed consent and enrolment, trial participation may occur in hospital, at a primary maternity unit or at home, as the patient's clinical care dictates. Eligible participants are those infants born between 34 weeks and 36 weeks' and six days gestation without contradiction to caffeine treatment, with the following exclusions:

- 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
- Residing outside of the Auckland region

Infants will be assigned randomly via an internet randomisation service (Clinical Data Research Hub, Liggins Institute, University of Auckland) to receive either daily caffeine citrate 5 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg or placebo. The allocation sequence will be generated by the study statistician, with 1:1:1:1:1 allocation stratified by study site and gestational age at birth (34, 35 or 36 weeks) (Figure 2) using variable block sizes, with infants from multiple births being randomised to the same treatment group.

Figure 2: Flow diagram of randomisation schedule

Different concentrations of the caffeine citrate (5 mg/ml, 10 mg/ml, 15 mg/ml and 20 mg/ml) will be prepared in identical bottles to the placebo so that all infants receive the same dose volume (2 ml/kg loading dose followed by 1 ml/kg, once daily). Bottles will be labelled in randomisation blocks using a lettering system which will change halfway through the study in order to maintain concealment from study personnel.

Study Intervention

The infant will be given an enteral loading dose of the study drug (10 mg/kg, 20 mg/kg, 30 mg/kg or 40 mg/kg of caffeine citrate or water) in the morning after baseline oximetry (i.e. prior to the infant reaching 96 hours of age), followed by a daily dose each morning (5 mg/kg, 10mg/kg, 15 mg/kg or 20 mg/kg of caffeine citrate or placebo) until term equivalent age (40 weeks' post-menstrual age). The dose will be recalculated weekly for weight after the infant has regained birth weight using the weight recorded by study staff at two weeks after randomisation and those recorded by usual care providers between two weeks' and term corrected age. The study drug will be given via a nasogastric tube for infants with a tube *in situ*, and orally for infants who do not require a nasogastric tube. Infants who are not able to tolerate enteral medications will have the study drug withheld until they are able to tolerate enteral intake**.**

Compliance will be assessed by measurement of study medication remaining in the bottle. At the two-week visit, study staff will collect the initial bottle(s) issued at the start of the study and replace it with a new bottle(s), which will in turn be collected at the final visit. Liquid remaining in the bottle on each occasion will be measured and compared with the expected volume to assess compliance. Good compliance will be defined as ≥80% of the expected volume having been removed from the bottle. At the final visit, parents will be asked which treatment they think their infant received to assess the adequacy of blinding.

Apart from the study intervention and associated assessments, all other clinical care, including the decision on when to discharge participants from the hospital and/or primary birthing units, will continue to be provided by the local clinical team, in accordance with usual guidelines and practices. Should an infant participating in the study require treatment for apnoea or intermittent hypoxaemia, clinicians will be encouraged to use oxygen or positive pressure ventilation as first line treatments. If necessary, a loading dose of caffeine citrate may be given. If ongoing treatment with caffeine is necessary in the opinion of the treating clinician, they can discuss the option of partially unblinding the infant (caffeine or placebo) with the Site Principal Investigator. If unblinding is required, information on the allocation of the participant will be communicated by the data management team to the treating clinician or pharmacist (who may inform the parents if requested), with the research team remaining blinded. Clinical open-label use of caffeine will be recorded. Unblinded infants will remain in the study unless parents request withdrawal, with infants analysed on an intention-to-treat basis.

Outcomes

The primary outcome for this study is the frequency of intermittent hypoxaemia (events/hour, defined as a brief transient fall in oxygen saturation concentration ≥10% below baseline on overnight oximetry, two weeks after randomisation. Events longer than 2 minutes are considered a change in baseline rather than a transient desaturation event. Transient intermittent hypoxaemic events, if frequent or severe, are thought to have neurocognitive effects as significant as prolonged hypoxaemia [20,42]. Although a 3% threshold is used in polysomnography to define desaturation events, a definition of 10% is commonly used in the neonatal literature. In addition, due to the variability of events we considered a 10% threshold more repeatable and reliable than a 3% threshold for defining events.

Secondary outcomes include:

- Respiratory: frequency of intermittent hypoxaemia on overnight oximetry at term equivalent age; mean overnight oxygen saturation at 2 weeks and term equivalent age; use of respiratory support, including oxygen, until term equivalent age)
- Growth: growth velocity from birth to term equivalent age for weight gain, length and head circumference; failure to regain birthweight by 2 weeks of age
- Side effects: Feed intolerance as reported by parents[43]; duration of tube feeding; sleep and arousal as reported by parents (measured by subscale nine on the Infant Behaviour Questionnaire-Revised, modified for neonates[44]); tachycardia; study drug stopped due to presumed side effects; neonatal seizures requiring anticonvulsant treatment before 44 weeks postmenstrual age; neonatal or infant death
- Maternal and infant salivary caffeine concentration at two weeks after randomisation[45]
- Readmission to hospital until 44 weeks post-menstrual age or open label caffeine use
- Maternal caffeine intake at birth, two weeks and term corrected age and mental health (Edinburgh postnatal depression score)at birth and term corrected age[46]

The timing of the study intervention and assessments is summarised in Table 1.

Table 1: Study intervention and assessment

	Baseline	**Morning following baseline oximetry**	**1 week**	**2 weeks**	**3-5 weeks**	**Term equivalent age**
Pulse oximetry	X			X		X
Randomisation	X					
Loading dose		X				
Demographics, contacts	X					
Dose adjustment for weight				X	X	
Neonatal salivary caffeine concentration				X		

Maternal salivary caffeine concentration				X		
Drug Diary		X	X	X	X	X
Compliance assessment				X		X
Parental Questionnaires:						
Maternal smoking in pregnancy & household smoke exposure questionnaire	X					
Sleep questionnaire				X		X
Feed tolerance questionnaire				X		X
Maternal caffeine intake questionnaire	X			X		X
Edinburgh Postnatal Depression Scale	X					X

Data collection methods

Online data management services will be provided by the Clinical Data Research Hub (Liggins Institute, University of Auckland). Data collection will utilise the REDCap platform (Vanderbilt University) for clinical report forms, with password-protected secure servers used to store data.

Pulse oximetry: Overnight pulse oximetry (Rad 8, Masimo Corp., Irvine, CA) will be recorded for a period of 12 hours from either foot at baseline, two weeks after randomisation (range 12-21 days) and at term corrected age (range 40 to 41 weeks postmenstrual age) using a 2-second averaging time and 2-second resolution. Recordings will be conducted at home, in primary birthing units or at home as dictated by the clinical care requirements of the participants. Where recordings are conducted at home, parents will be visited the day that recording starts by a member of the research team. The oximeter will be set up, and the parents will receive instruction in attaching the probe to the baby's foot and be instructed to do this when placing the baby down to sleep in the evening. If necessary, the research team member may visit late in the day to apply the probe or provide support via a video call to ensure this is done correctly by parents. Unless clinically required, oximeters will be operated in sleep mode, with no displays or alarms. The oximetry recording will be

downloaded with PROFOX oximetry software (version Masimo 2011.27D, PROFOX Associates Inc, Esconditso, CA) and edited to remove readings with poor signal or aberrant data. Only recordings with more than six hours will be included in the analysis, recordings with less than six hours of edited data will be repeated the following night.

Anthropometry: Weight, length and head circumference will be measured at study entry and at the two-week and term visits, with birthweight and neonatal centiles calculated using Fenton-WHO growth charts for preterm infants[47], and growth velocity calculated between birth and term equivalent using an exponential model[48].

Salivary caffeine concentrations: Two weeks after randomisation, a saliva sample will be collected from infants for assessment of caffeine concentration. Samples will be taken using a mouth swab prior to administration of the morning dose of trial medication. In the 24 hours preceding this, mothers will be asked to collect three saliva samples by spitting into collection tubes at three pre-determined timepoints during the day, with the mean of these three samples used to determine average daytime maternal salivary caffeine concentration. Collection of these samples will allow us to compare maternal and infant salivary caffeine concentrations to establish if maternal caffeine intake contributes significantly to infant caffeine levels via breastfeeding or not, and to help assess compliance with the study intervention.

Questionnaires: Mothers will complete questionnaires to provide demographic and contact details at enrolment, and to assess smoking, infant feeding and sleeping, maternal caffeine intake and maternal mental health as detailed in Table 1.

Neonatal morbidity: Information on neonatal morbidity, including supplemental oxygen, respiratory support and apnoea requiring stimulation, will be recorded from the neonatal record. Exposure to antenatal corticosteroids will be recorded.

Discontinuation of intervention / withdrawal

The allocated treatment may be stopped at any time by the parents or the clinician caring for the infant if they feel that this is in the best interests of the infant, without formally withdrawing, in which case data collection will continue and results will be analysed on an intention-to-treat basis.

Should a parent wish to withdraw from the study, they will have the option of:

1. Discontinuation of study drug, with continuation of collection of minimum outcome data
2. Withdrawal from the study and discontinuation of further data collection, with data collected prior to withdrawal used
3. Complete withdrawal from the study, with removal of previously collected data

Patient and Public Involvement

The Latte Dosage Study methodology was discussed, developed and refined as part of the 2017 On-Track Network clinical trial development workshop which included consumer and Maori cultural advisor input. Perinatal consumer representatives provided advice and input into the development of the clinical trial protocol.

Sample size

Based on our previous study[10] we estimate a background mean (SD) frequency of 6.9 (3.4) episodes of intermittent hypoxaemia per hour at two weeks' post randomisation. To detect a 50% reduction of 3.5 episodes per hour with 90% power, allowing for a 10% drop out rate and clustering of multiples with an ICC of 0.05, we will require 24 infants in each of the five arms (total 120 infants),

with two-sided alpha of 0.05. Recruitment to the study started in February 2019 and is scheduled to conclude in December 2020.

Data analysis

The primary analysis will compare primary and secondary outcomes between groups using generalised linear mixed models with adjustment for gestational age at birth and site (fixed effects), non-independence of multiples (random effect) and pairwise comparisons between the different caffeine groups and between the caffeine groups and the placebo group using Dunnett's multiple comparison test. The selection of the optimal dose will be based on a combination of the dose with the greatest reduction of intermittent hypoxaemia with a minimum number of side effects and a pragmatic consideration of the ease of administration. Linear trends, such as growth, will be tested using orthogonal contrasts. In keeping with CONSORT recommendations[49], baseline imbalance between babies in the randomised groups will not be formally tested. Edinburgh Postnatal Depression Scale scores will be adjusted for baseline values. 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. Treatment effects will be presented as odds ratio, count ratio, mean difference or ratio of geometric means (positively skewed data), as appropriate, with 95% confidence intervals. All tests will be two-tailed, with $P<0.05$ considered significant. The data will be analysed on an intention-to-treat basis.

The following secondary analyses will be performed:

- *Compliance*: A per-protocol analysis will be performed for the primary outcome that includes only those infants who were compliant with the study drug.
- *Open-label caffeine treatment:* A sensitivity analysis will be performed for the primary outcome that includes only those infants who did not receive additional open-label caffeine treatment.

- *Maternal caffeine:* An exploratory analysis will be performed on the effect of maternal caffeine intake on the primary outcome by performing additional adjustments for maternal caffeine intake from the questionnaire and maternal salivary caffeine concentration. For infants that are fully formula fed, infant caffeine exposure to maternal caffeine intake will be assumed to be zero.

An independent data monitoring committee will review trial data after enrolment of 60 infants to the trial. The data monitoring committee provide advice to the trial steering group on any modifications that may be required. There are no formal stopping guidelines.

Ethics and dissemination:

Ethical approval has been obtained from the Health and Disability Ethics Committees of New Zealand (reference 18/NTA/129) and by the local institutional research review committees for each centre. The trial is registered with the Australian New Zealand Clinical Trials Registry (Registration number: ACTRN12618001745235) from 24 October 2018.

The results of the trial will be published in an international peer-reviewed journal and disseminated via presentations at local and international conferences to researchers and clinicians. A lay summary of the research findings will be made available to those parents who indicated a wish to receive these on their consent forms.

Discussion

Late preterm infants experience higher rates of intermittent hypoxaemia than their term-born peers, and have poorer long-term neurodevelopmental outcomes[28–35]. Caffeine is well established as a treatment for apnoea of prematurity in very and extremely preterm infants, and improves long term neurodevelopmental outcomes in these infants[21,50,51]. Caffeine use in late preterm infants may

also reduce episodes of intermittent hypoxaemia and improve long term outcomes for these infants. As late preterm infants make up the majority of preterm infants, interventions that improve long term outcomes in this population are likely to have the greatest public health impact in terms of interventions for preterm infants[52].

The Latte Dosage Trial seeks to establish the most effective and best tolerated dose of caffeine citrate for the prevention of intermittent hypoxaemia in late preterm infants. It is the first trial to investigate the use of caffeine, an inexpensive medication already widely used in neonatal care, for this indication. Data from the Latte Dosage Trial will be used to inform the development of a large-scale, multicentre trial investigating the efficacy of caffeine treatment in late preterm infants in preventing neurodevelopmental impairment by indicating the most appropriate dose to use and providing information on feasibility.

References

1 Engle WA, Tomashek KM, Wallman C. "Late-preterm" infants: a population at risk. *Pediatrics* 2007;**120**:1390–401. doi:10.1542/peds.2007-2952

2 Ministry of Health. Report on Maternity 2017 - tables. Wellington: 2019. https://www.health.govt.nz/publication/report-maternity-2017 (accessed 8 Jul 2019).

3 Martin JA, Hamilton BE, Osterman MJK, *et al.* Births: final data for 2017. 2017. https://www.cdc.gov/nchs/data_access/Vitalstatsonline.htm

4 McIntire DD, Leveno KJ. Neonatal mortality and morbidity rates in late preterm births compared with births at term. *Obstet Gynecol* 2008;**111**:35–41. doi:10.1097/01.AOG.0000297311.33046.73

5 Wang ML, Dorer DJ, Fleming MP, *et al.* Clinical outcomes of near-term infants. *Pediatrics* 2004;**114**:372–6. doi:10.1542/peds.114.2.372

6 Boyle EM, Johnson S, Manktelow B, *et al.* Neonatal outcomes and delivery of care for infants born late preterm or moderately preterm: a prospective population-based study. *Arch Dis Child Fetal Neonatal Ed* 2015;**100**:F479–F485. doi:10.1136/fetalneonatal-2014-308136

7 Butcher-Puech MC, Henderson-Smart DJ, Holley D, *et al.* Relation between apnoea duration and type and neurological status of preterm infants. *Arch Dis Child* 1985;**60**:953–8. doi:10.1136/adc.60.10.953

8 Janvier A, Khairy M, Kokkotis A, *et al.* Apnea is associated with neurodevelopmental impairment in very low birth weight infants. *J Perinatol* 2004;**24**:763–8. doi:10.1038/sj.jp.7211182

9 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. doi:10.1111/j.1440-1754.1981.tb01957.x

10 Williams LZJ, Mcnamara D, Alsweiler JM. Intermittent hypoxemia in infants born late preterm: a prospective cohort observational study. *J Pediatr* 2018;**204**:89-95.e1. doi:10.1016/j.jpeds

11 Bahrke MS, Shukitt-Hale B. Effects of altitude on mood, behaviour and cognitive functioning. A review. *Sports Med* 1993;**16**:97–125. doi:10.2165/00007256-199316020-00003

12 Weaver LK, Hopkins RO, Chan KJ, *et al.* Hyperbaric oxygen for acute carbon monoxide poisoning. *N Engl J Med* 2002;**347**:1057–67. doi:10.1056/NEJMoa013121

13 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. 2013;**105**:55–63. doi:10.1159/000356561

14 Carlo WA, Finer NN, Walsh MC, *et al.* Target ranges of oxygen saturation in extremely preterm infants. *N Engl J Med* 2010;**362**:1959–69. doi:10.1056/NEJMoa0911781

15 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**:1680–2. doi:10.1056/NEJMc1101319

16 Kanaan A, Farahani R, Douglas RM, *et al.* Effect of chronic continuous or intermittent hypoxia and reoxygenation on cerebral capillary density and myelination. *Am J Physiol - Regul Integr Comp Physiol* 2006;**290**:R1105-14. doi:10.1152/ajpregu.00535.2005

17 Row BW, Kheirandish L, Neville JJ, *et al.* Impaired spatial learning and hyperactivity in developing rats exposed to intermittent hypoxia. *Pediatr Res* 2002;**52**:449–53. doi:10.1203/00006450-200209000-00024

18 Poets CF, Roberts RS, Schmidt B, *et al.* Association between intermittent hypoxemia or bradycardia and late death or disability in extremely preterm infants. *J Am Med Assoc* 2015;**314**:595–603. doi:10.1001/jama.2015.8841

19 Ali NJ, Pitson D, Stradling JR. Sleep disordered breathing: effects of adenotonsillectomy on behaviour

and psychological functioning. *Eur J Pediatr* 1996;**155**:56–62. doi:10.1007/bf02115629

20 Bass JL, Corwin M, Gozal D, *et al.* The effect of chronic or intermittent hypoxia on cognition in childhood: A review of the evidence. Pediatrics. 2004;**114**:805–16. doi:10.1542/peds.2004-0227

21 Schmidt B, Roberts RS, Davis P, *et al.* Long-term effects of caffeine therapy for apnea of prematurity. *N Engl J Med* 2007;**357**:1893–902.www.nejm.org (accessed 18 Apr 2019).

22 Schmidt B, Roberts RS, Davis P, *et al.* Caffeine therapy for apnea of prematurity. *N Engl J Med* 2006;**354**:2112–21.www.nejm.org (accessed 5 Dec 2018).

23 McNamara DG, Nixon GM, Anderson BJ. Methylxanthines for the treatment of apnea associated with bronchiolitis and anesthesia. Paediatr. Anaesth. 2004;**14**:541–50. doi:10.1111/j.1460-9592.2004.01351.x

24 Schmidt B, Roberts RS, Anderson PJ, *et al.* Academic performance, motor function, and behavior 11 years after neonatal caffeine citrate therapy for apnea of prematurity. *JAMA Pediatr* 2017;**171**:564. doi:10.1001/jamapediatrics.2017.0238

25 Doyle LW, Ranganathan S, Cheong JLY. Neonatal caffeine treatment and respiratory function at 11 years in children under 1,251 g at birth. *Am J Respir Crit Care Med* 2017;**196**:1318–24. doi:10.1164/rccm.201704-0767OC

26 Davis PG, Schmidt B, Roberts RS, *et al.* Caffeine for apnea of prematurity trial: benefits may vary in subgroups. *J Pediatr* 2010;**156**:382–7. doi:10.1016/j.jpeds.2009.09.069

27 Doyle LW, Cheong J, Hunt RW, *et al.* Caffeine and brain development in very preterm infants. *Ann Neurol* 2010;**68**:734–42. doi:10.1002/ana.22098

28 Moster D, Lie RT, Markestad T. Long-term medical and social consequences of preterm birth. *N Engl J Med* 2008;**359**:262–73.www.nejm.org (accessed 12 Jul 2019).

29 Odd DE, Lingam R, Emond A, *et al.* Movement outcomes of infants born moderate and late preterm. *Acta Paediatr* 2013;**102**:876–82. doi:10.1111/apa.12320

30 Darlow BA, Horwood LJ, Wynn-Williams MB, *et al.* Admissions of all gestations to a regional neonatal unit versus controls: 2-year outcome. *J Paediatr Child Health* 2009;**45**:187–93. doi:10.1111/j.1440-1754.2008.01457.x

31 Woythaler MA, McCormick MC, Smith VC. Late preterm infants have worse 24 month neurodevelopmental outcomes than term infants. *Pediatrics* 2011;**127**:e622-9. doi:10.1542/peds.2009-

3598

32 Talge NM, Holzman C, Wang J, *et al.* Late-preterm birth and its association with cognitive and socioemotional outcomes at 6 years of age. *Pediatrics* 2010;**126**:1124–31. doi:10.1542/peds.2010-1536

33 Quigley MA, Poulsen G, Boyle E, *et al.* Early term and late preterm birth are associated with poorer school performance at age 5 years: a cohort study. *Arch Dis Child Fetal Neonatal Ed* 2012;**97**:F167-73. doi:10.1136/archdischild-2011-300888

34 Heinonen K, Eriksson JG, Lahti J, *et al.* Late preterm birth and neurocognitive performance in late adulthood: a birth cohort study. *Pediatrics* 2015;**135**:e818-25. doi:10.1542/peds.2014-3556

35 Huddy CLJ, Johnson A, Hope PL. Educational and behavioural problems in babies of 32-35 weeks gestation. *Arch Dis Child Fetal Neonatal Ed* 2001;**85**:F23–8. doi:10.1136/fn.85.1.F23

36 Anderson BJ, Gunn TR, Holford NHG, *et al.* Caffeine overdose in a premature infant: clinical course and pharmacokinetics. *Anaesth Intensive Care* 1999;**27**:307–11.https://search-proquest-com.ezproxy.auckland.ac.nz/docview/224844582/fulltextPDF/363FABA09B4649A6PQ/1?accountid=8424 (accessed 12 Nov 2018).

37 Le Guennec J-C, Billon B, Pare C. Maturational Changes of Caffeine Concentrations and Disposition in Infancy During Maintenance Therapy for Apnea of Prematurity: Influence of Gestational Age, Hepatic Disease, and Breast-Feeding. 1985. www.aappublications.org/news (accessed 12 Nov 2018).

38 Falcão AC, de Gatta MMF, Iribarnegaray MFD, *et al.* Population pharmacokinetics of caffeine in premature neonates. *Eur J Clin Pharmacol* 1997;**52**:211–7. doi:10.1007/s002280050276

39 Thomson AH, Kerr S, Wright S. Population pharmacokinetics of caffeine in neonates and young infants. *Ther Drug Monit* 1996;**18**:245–53.https://oce-ovid-com.ezproxy.auckland.ac.nz/article/00007691-199606000-00005/HTML (accessed 12 Dec 2018).

40 Steer P, Flenady V, Shearman A, *et al.* High dose caffeine citrate for extubation of preterm infants: a randomised controlled trial. *Arch Dis Child Fetal Neonatal Ed* 2004;**89**:F499-503. doi:10.1136/adc.2002.023432

41 Rhein LM, Dobson NR, Darnall RA, *et al.* Effects of caffeine on intermittent hypoxia in infants born prematurely. *JAMA Pediatr* 2014;**168**:250–7. doi:10.1001/jamapediatrics.2013.4371

42 Blunden SL, Beebe DW. The contribution of intermittent hypoxia, sleep debt and sleep disruption to

daytime performance deficits in children: Consideration of respiratory and non-respiratory sleep disorders. doi:10.1016/j.smrv.2005.11.003

43 Kleinman L, Rothman M, Strauss R, *et al.* The infant gastroesophageal reflux questionnaire revised: development and validation as an evaluative instrument. *Clin Gastroenterol Hepatol* 2006;**4**:588–96. doi:10.1016/j.cgh.2006.02.016

44 Gartstein MA, Rothbart MK. Studying infant temperament via the Revised Infant Behavior Questionnaire. *Infant Behav Dev* 2003;**26**:64–86. doi:10.1016/S0163-6383(02)00169-8

45 Dobson NR, Liu X, Rhein LM, *et al.* Salivary caffeine concentrations are comparable to plasma concentrations in preterm infants receiving extended caffeine therapy. *Br J Clin Pharmacol* 2016;**82**:754–61. doi:10.1111/bcp.13001

46 Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression: development of the 10-item Edinburgh postnatal depression scale. *Br J Psychiatry* 1987;**150**:782–6. doi:10.1192/bjp.150.6.782

47 Fenton TR, Kim JH. A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants. *BMC Pediatr* 2013;**13**:59. doi:10.1186/1471-2431-13-59

48 Patel A, Engstrom J, Meier P, *et al.* Calculating postnatal growth velocity in very low birth weight (VLBW) premature infants. *J Perinatol* 2009;**29**:618–22.

49 Moher D, Hopewell S, Schulz KF, *et al.* CONSORT 2010 Explanation and Elaboration: updated guidelines for reporting parallel group randomised trials. *J Clin Epidemiol* 2010;**63**:e1–37. doi:10.1016/j.jclinepi.2010.03.004

50 Schmidt B, Anderson PJ, Doyle LW, *et al.* Survival without disability to age 5 years after neonatal caffeine therapy for apnea of prematurity. *JAMA* 2012;**307**:275. doi:10.1001/jama.2011.2024

51 Mürner-Lavanchy IM, Doyle LW, Schmidt B, *et al.* Neurobehavioral outcomes 11 years after neonatal caffeine therapy for apnea of prematurity. *Pediatrics* 2018;**141**:e20174047.www.aappublications.org/news (accessed 13 May 2019).

52 March of Dimes, The Partnership for Maternal Newborn and Child Health, Save the Children, *et al.* Born too soon: the global action report on preterm birth. Geneva: 2012. doi:http://whqlibdoc.who.int/publications/2012/9789241503433_eng.pdf

Figure Legends

Figure 1: Rate of intermittent hypoxaemia in late preterm infants in the 9-11 weeks following birth (adapted)[10]

Figure 2: Flow diagram of randomisation schedule

Authors' contributions:

JMA conceived and developed the study design, drafted the original study protocol, approved the final study protocol and reviewed the article for publication.

EAO contributed to the study design, approved the final version of the study protocol, and drafted the article for publication.

CM contributed to the study design, approved the final version of the study protocol, and reviewed the article for publication.

DM contributed to the study design, approved the final version of the study protocol, and reviewed the article for publication.

Funding statement: This work is supported by the Health Research Council of New Zealand: grant number 18/613. The funder had no role in the study design and will have no role in collection, management, analysis and interpretation of the data; writing the report or the decision to submit a report for publication.

Competing interests' statement.

The authors have no competing interests to declare

Acknowledgements

Brian Darlow and Members of the ON TRACK network for assistance in developing and refining the study design.

Sarah Phillipsen, Sabine Huth, Lisa Mravicich and Florella Keen for assistance in setting up the trial.

Sara Hanning and Trusha Purohit for advice on caffeine testing and development of the caffeine assay.

Alana Cavadino for statistical advice.

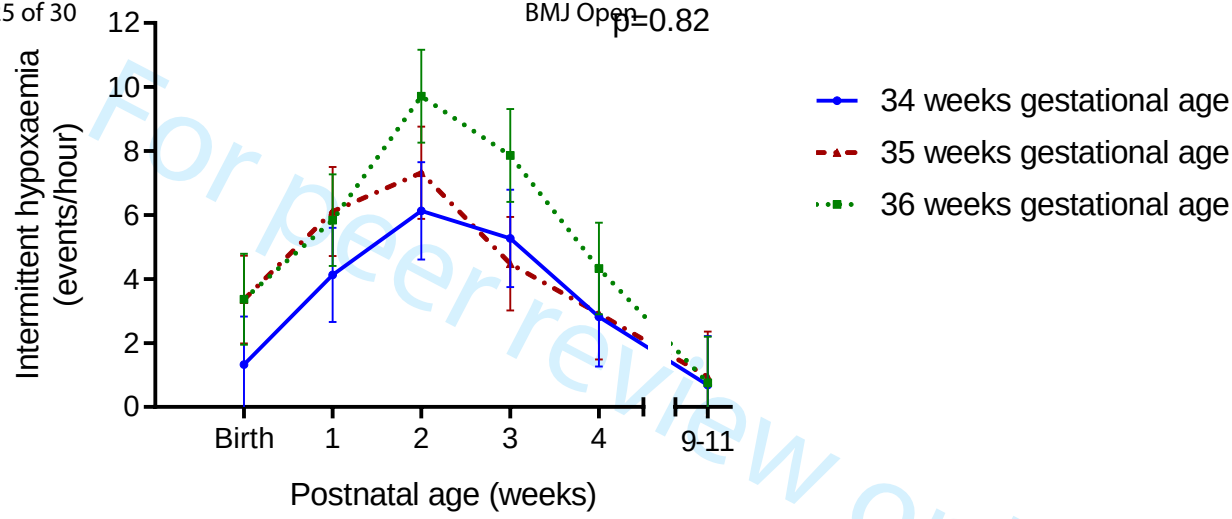
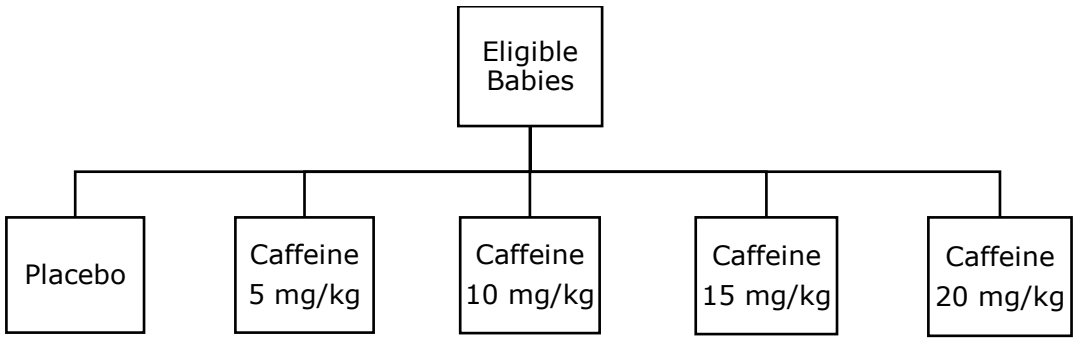


Figure 1: Rate of intermittent hypoxaemia in late preterm infants in the 9-11 weeks following birth (adapted)[10]



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	
Protocol version	3	Date and version identifier	On publication
Funding	4	Sources and types of financial, material, and other support	21
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 21
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	21
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	NA

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4 - 7
	6b	Explanation for choice of comparators	7, 9
Objectives	7	Specific objectives or hypotheses	8
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	8
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-10
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	10, 13-14
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	10
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	11-13
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Table 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	14
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	8
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	9
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	3, 8, 10
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	10
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11-13
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	14

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	12
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	14-15
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14-15
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	14-15
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	16
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	16
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	14
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	15-16
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	NA

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	14
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	22
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Submission documentation
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	10
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	16
	31b	Authorship eligibility guidelines and any intended use of professional writers	21
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	NA
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	13

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

Correction: *(Rad 8)Caffeine prophylaxis to improve intermittent hypoxaemia in infants born late preterm: a randomised controlled dosage trial (Latte Dosage Trial)*

Oliphant EA, McKinlay CJD, McNamara DG, *et al.* (Rad 8)Caffeine prophylaxis to improve intermittent hypoxaemia in infants born late preterm: a randomised controlled dosage trial (Latte Dosage Trial). *BMJ Open* 2020;10:e038271. doi: 10.1136/bmjopen-2020-038271.

This article was previously published with an error.

There was a typographical error in the title. The correct title is:

Caffeine prophylaxis to improve intermittent hypoxaemia in infants born late preterm: a randomised controlled dosage trial (Latte Dosage Trial)

BMJ Open 2020;**10**:e038271corr1. doi:10.1136/bmjopen-2020-038271corr1