STUDY PROTOCOL

NEO GLU CO
Neonatal Glucose Care Optimisation Study

Oral diazoxide versus placebo to reduce time to successful treatment of hypoglycaemia in neonates with severe or recurrent hypoglycaemic episodes

The Neonatal Glucose Care Optimisation (NeoGluCO) Study (I)
STUDY PROTOCOL

ADMINISTRATIVE INFORMATION

Oral diazoxide versus placebo to reduce time to successful treatment of hypoglycaemia in neonates with severe or recurrent hypoglycaemic episodes: The Neonatal Glucose Care Optimisation (NeoGluCO) Study (I).

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This study protocol follows the SPIRIT checklist.1,2
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1 INTRODUCTION

1.1 Background and Rationale

**Neonatal hypoglycaemia is a significant clinical problem with the potential for long-term sequelae**

At least 30% of all newborn babies or 20,000 per annum in New Zealand (NZ) are at risk of transitional hypoglycaemia (low blood glucose concentration, BGC) due to being born small, large, preterm or the infant of a diabetic mother. They require regular testing of BGC in the first 24 to 48 hours after birth and approximately 50% develop hypoglycaemia and require further testing and intervention.³ Optimal management of transitional neonatal hypoglycaemia is important not only because of its impact on breastfeeding⁴,⁵ and use of health care resources,⁶ ⁷ but also because of the potential for permanent brain injury. The immature brain is dependent on a continuous supply of glucose for energy, as other brain fuels such as ketones are low after birth.⁸,⁹ We have shown that babies with asymptomatic hypoglycaemia have a two- to three-fold increased likelihood of later neurocognitive difficulties by 4 to 5 years of age, especially of executive function and visual-motor integration.¹⁰ ¹² These functions are critical for learning, and even brief transitional neonatal hypoglycaemia has been associated with a two-fold increased likelihood of poor school achievement.¹³ In moderately preterm infants, transitional hypoglycaemia is the main modifiable risk factor for developmental delay at preschool age.¹⁴

**Better treatment is needed for babies with severe or recurrent neonatal hypoglycaemia**

If oral dextrose gel and additional feeding do not correct hypoglycaemia, babies are typically admitted to the neonatal unit for frequent or continuous feeding by gastric tube or intravenous glucose, with the aim of correcting glucose concentrations as rapidly as possible to a high normal level.³,¹⁵ Approximately 20% of babies with neonatal hypoglycaemia require neonatal admission for severe or recurrent hypoglycaemia (1,800 per annum in NZ).¹⁵ These babies often have prolonged neonatal admission, ongoing hypoglycaemia despite the provision of intravenous fluids, and can be difficult to establish on enteral feeds due to glucose instability. Even with standard management, babies with severe or recurrent transitional hypoglycaemia continue to have substantially higher rates (approximately four-fold) of adverse neurological outcome.¹¹ This may be due, at least in part, to additional oxidative injury from too rapid correction of hypoglycaemia,¹⁶ ¹⁷ and the fact that episodes of clinically undetected hypoglycaemia are common in these babies, further increasing the risk of brain injury.¹¹ Thus, the current treatment of babies with severe or recurrent transitional hypoglycaemia remains sub-optimal and better management strategies are needed that address the underlying pathophysiology.

**Effective management strategies are needed that target the underlying pathophysiology**

The primary cause of severe or recurrent transitional neonatal hypoglycaemia is dysregulated insulin secretion, especially the inability to suppress insulin secretion at low BGCs and with fasting. During fetal life, insulin is a key growth hormone that is secreted by the fetal pancreas in response to placental uptake of glucose and free fatty acids, with a low set-point for insulin release.⁹ Fetal glucose synthesis is negligible because the continuous supply of glucose via the placenta stimulates fetal insulin secretion. Hepatic expression of enzymes for gluconeogenesis and glycogenolysis is also low until late gestation. At birth, placental glucose supply ceases and the neonate must adapt to bolus feeding and intermittent fasting. Successful neonatal metabolic transition requires the initiation of glycogenolysis (release of glucose from hepatic glycogen), gluconeogenesis (synthesis of glucose in the liver) and lipolysis (release of fuels from fat, including glycerol for glucose synthesis), all of which are inhibited by insulin. If insulin secretion remains inappropriately high during this transition period, hepatic glucose output is inadequate for metabolic requirements, and hypoglycaemia ensues. Increasing delivery of exogenous glucose, either with formula or intravenous dextrose, may result in a vicious cycle of further insulin secretion and ongoing hypoglycaemia, despite the escalating provision of glucose. Further, the counter-regulatory mechanisms of glucagon, cortisol and growth hormone,
which promote glycogenolysis (release of hepatic glucose stores) and gluconeogenesis, may be less effective in neonates with hyperinsulinaemic hypoglycaemia,\textsuperscript{18,19} and coupling of cerebral blood flow and metabolic demand may also be perturbed.\textsuperscript{20,21}

Under normal conditions, the brain accounts for the majority neonatal glucose utilisation,\textsuperscript{22,23} and uptake is by facilitated diffusion, independent of insulin.\textsuperscript{24} Thus, higher circulating concentrations of insulin during neonatal transition, rather than facilitating cerebral energy uptake, increase the risk of neuroglycopenia by limiting hepatic glucose output. Further, the capacity for cerebral glucose uptake after birth may be rate-limited as the maximal expression of glucose transporter proteins at the blood-brain barrier (GLUT1 and GLUT3) does not occur for several days to weeks.\textsuperscript{24} Ketone bodies are an important cerebral alternative fuel, but higher circulating insulin concentrations also suppress lipolysis (releases free fatty acids) and hepatic beta-oxidation, such that ketones are largely absent in babies with hypoglycaemia.\textsuperscript{8,25}

Both large and small babies are at risk of dysregulated insulin secretion. Babies who are large for gestation are typically born to mothers with obesity or diabetes (pre-existing or gestational), which can lead to excess fetal supply of glucose and free fatty acids. This increases fetal insulin secretion, which in turn increases fetal pancreatic beta cell mass (hypertrophy and hyperplasia), adaptations that persist for a period after birth.\textsuperscript{26,27} Conversely, in growth restriction and placental insufficiency, fetal supply of oxygen and nutrients is reduced. Fetal hypoxaemia raises plasma catecholamine concentrations, especially noradrenaline, which acts on beta cells to suppress in utero insulin secretion.\textsuperscript{28,29} At birth, loss of the sustained adrenergic signalling exposes beta cell hyperresponsiveness, resulting in increased insulin secretion. Thus, both fetal over- and under-nutrition can result in transient neonatal hyperinsulinism and associated hypoglycaemia.

Achieving glucose stability in neonates with severe or recurrent hypoglycaemia is challenging not only because of an exaggerated glucose-stimulated insulin response but also because with escalating treatment, episodes of hyperglycaemia also occur. This risk is greatest in fetal growth restriction and with the use of intravenous dextrose.\textsuperscript{16} The reasons for this instability are not fully known, but it may be due to periodic impairment of peripheral glucose disposal due to variations in insulin sensitivity or temporary depletion of beta cell insulin vesicles. Importantly, we have shown that higher glucose concentrations after hypoglycaemia or correction that is too rapid may exacerbate brain injury,\textsuperscript{12,16} as has been demonstrated in animals.\textsuperscript{30,31} This suggests that the goal of management should be glucose stability rather than simply correction of hypoglycaemia per se. To achieve optimal glycaemic control in neonates with severe or recurrent transitional hypoglycaemia new treatment approaches are needed that target the underlying pathophysiology, namely, dysregulation of insulin secretion.

**Diazoxide is a potential new management strategy to improve treatment of neonatal hypoglycaemia**

Diazoxide acts on the pancreatic beta cell in a dose-dependent manner to decrease insulin secretion by interacting with the sulfonylurea receptor (SUR1). Binding of diazoxide to the SUR1 subunit inhibits closure of the ATP-sensitive potassium (K) channel, which in turn diminishes first and second phase glucose-stimulated insulin secretion.\textsuperscript{32-34} Advantages of diazoxide include rapid onset of action, oral formulation and low cost. Diazoxide has been used for many decades as first-line treatment for certain forms of congenital (genetic) hyperinsulinism, with a good efficacy and safety profile.\textsuperscript{35}

It has also been used selectively in babies with transient hyperinsulinism. Hoe et al. described 21 hyperinsulinaemic babies without known genetic defect, 20 (95%) of whom were responsive to diazoxide (5 to 10 mg/kg/day), when commenced at a median age of 13 days. In a retrospective case series, we identified eight late preterm or term neonates with severe or recurrent transitional hypoglycaemia who were commenced on diazoxide in the first week (unpublished data). Diazoxide was effective in facilitating weaning of intravenous dextrose and transition to enteral feeds, although six neonates had episodes of hyperglycaemia ≥7 mmol/L, most likely due to use of maintenance doses that were potentially too high (5 to 10 mg/kg/day) and not adequately weaned.

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In a small randomised trial of 30 small-for-gestational age neonates with transient hyperinsulinism in the first five days, diazoxide at 6 to 12 mg/kg/day reduced the median time to achieve hypoglycaemic control (40 vs 72 hours, \( P=0.02 \)), the total duration of intravenous fluids (114 vs 164 hours, \( P=0.04 \)) and time to achieve full feeds (74 vs 124 hours, \( P=0.02 \)). There were no apparent adverse events, although episodes of hyperglycaemia were not reported.

In babies with congenital hyperinsulinism on regular diazoxide, cardiac complications have been rarely reported, including congestive heart failure, patent ductus arteriosus and pulmonary hypertension. In all cases, there was full resolution of symptoms on stopping diazoxide. Similarly, in children recently diagnosed with type 1 diabetes and treated with regular diazoxide at 5-7.5 mg/kg/day, 5% experienced reversible oedema, but no serious adverse effects were reported.

Together these data suggest that diazoxide may have a role in early management of severe neonatal hypoglycaemia to reduce the need for intravenous glucose, shorten neonatal unit admissions and facilitate earlier introduction of enteral feeds, and that low dose that treatment is likely to be well tolerated.

The NeoGluCO Study (I)

We propose the Neonatal Glucose Care Optimisation (NeoGluCO) Study (I) to investigate if early use of oral diazoxide in severe or recurrent neonatal hypoglycaemia results in the earlier establishment of enteral bolus feeding and normal glucose concentrations without intravenous fluids. If effective, such a treatment could have major benefits for neonates with severe or recurrent hypoglycaemia, including reduced length of admission and separation of mother and baby, reduced use of formula and facilitation of the earlier establishment of breastfeeding, reduced number of heel pricks for BG testing, and better long-term neurodevelopmental outcomes.

1.2 Objectives and Hypotheses

Primary objective: To determine if early use of diazoxide in severe or recurrent neonatal hypoglycaemia reduces time to successful hypoglycaemia treatment, defined as achieving enteral bolus feeding and normal glucose concentrations without intravenous fluids (see below).

Primary hypothesis: Early diazoxide therapy will improve glycaemic stability, allowing earlier weaning of intravenous fluids and establishment of enteral feeds.

1.3 Study Design and Synopsis

Phase 2, Double-blinded, randomised controlled, two-arm, parallel trial of diazoxide versus placebo in neonates born at \( \geq 35 \) weeks’ gestation admitted to neonatal care with severe or recurrent hypoglycaemia in the first week (Table 1). Severe hypoglycaemia is defined as any BG <1.2 mmol/L or BG 1.2 to <2.0 mmol/L despite two doses of dextrose gel and feeding in a single episode; recurrent hypoglycaemia is defined as \( \geq 3 \) episodes (one or more consecutive BGs) of hypoglycaemia <2.6 mmol/L in 48 h. Babies will be randomised to either oral diazoxide 5 mg/kg load, then 1.5 mg/kg 12 hourly or an equivalent volume of placebo. Management of feeds, fluid and hypoglycaemic episodes will occur according to local practice. Once glycaemic stability is achieved, the study drug will be weaned by protocol. If hyperglycaemia occurs (\( \geq 7.0 \) mmol/L), the study drug will be discontinued. The primary outcome is time to successful treatment of hypoglycaemia, defined as achieving enteral bolus feeding and normal glucose concentrations without intravenous fluids (see below).
Table 1: PICOT Summary

<table>
<thead>
<tr>
<th>Participants</th>
<th>Neonates ≥35 weeks admitted to the neonatal unit with severe or recurrent hypoglycaemia in the first week.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>Oral diazoxide 5 mg/kg loading dose, then 1.5 mg/kg 12 hourly maintenance dose, weaning by protocol.</td>
</tr>
<tr>
<td>Control</td>
<td>An equivalent volume of identical placebo.</td>
</tr>
<tr>
<td>Primary outcome</td>
<td>Time to successful hypoglycaemia treatment, defined as achieving enteral bolus feeding and normal glucose concentrations without intravenous fluids.</td>
</tr>
<tr>
<td>Planned sample size</td>
<td>74 babies will be randomised in 1:1 ratio, giving 80% power to detect a relative hazard of 2.0 (2-tailed alpha 0.05).</td>
</tr>
<tr>
<td>Timing of assessment</td>
<td>Assessment for the primary outcome will continue for up to 4 weeks, after which the primary outcome will be censored.</td>
</tr>
</tbody>
</table>

2 METHODS

2.1 Participants, Interventions and Outcomes

2.1.1 Study Setting

Counties and Auckland DHB Neonatal Care Units.

2.1.2 Eligibility Criteria

Babies are eligible for this study if they are born at ≥35 weeks and are admitted to a neonatal unit in the first week after birth with recurrent or severe hypoglycaemia, defined by one or more of the following:

- Any episode of hypoglycaemia <1.2 mmol/L
- BGC of 1.2 to <2.0 mmol/L persisting after 2 doses of dextrose gel and feeding in a single episode
- ≥3 episodes of hypoglycaemia <2.6 mmol/L in 48 h

Babies must also be receiving ongoing management for hypoglycaemia at the time of randomisation, e.g., intravenous dextrose, carbohydrate supplements, continuous or frequent feeding (≤2 hourly), or inability to wean off formula due to hypoglycaemia.

The following babies will be excluded from randomisation:

- Confirmed major congenital malformation or chromosomal disorder
- Suspected genetic syndrome associated with hypoglycaemia, e.g., Beckwith Wiedemann Syndrome
- Gastrointestinal disorder likely to affect feed tolerance
- Planned or likely neonatal surgery
- Confirmed sepsis (culture of pathogenic organism from blood, CSF or urine)
- Hypoxic ischaemic encephalopathy
- Family history of congenital hyperinsulinism
- Suspected inborn error of metabolism
- Triplets

Exclusions are expected to be uncommon.

Twins may be included and will be individually randomised. If more than 10% of the sample involves twins, sample size assumptions will be reviewed.

Eligibility will be based only on true BGC, either by gas analyser (portable or laboratory) or laboratory chemical analyser.
2.1.3 Interventions

Following written, informed parental consent, babies will be allocated via the online randomisation system to one of the following two interventions:

**Diazoxide**

The active intervention will be compounded by the hospital trial pharmacist by adding five 100 mg diazoxide capsules to 50 ml of Ora Blend (standard paediatric compounding solution), giving a concentration of 10 mg/ml. Babies will be loaded with 5 mg/kg (0.5 ml/kg) orally or by gastric tube and then commenced on a maintenance dose of 1.5 mg/kg (0.15 ml/kg) every 12 h. These doses are at the lower end of the range recommended in the NZ Formulary for Children. Although infants with congenital hyperinsulinism usually receive higher maintenance doses of 5-10 mg/kg/day, our clinical experience has shown that this is often too high for babies with transitional hypoglycaemia and may cause hyperglycaemia, whereas lower doses are similarly efficacious but avoid high BGC. Weekly dose adjustment for weight will be made, if required, once the baby returns to birthweight.

**Placebo**

The control intervention will consist of an equal volume of Ora Blend (0.5 ml/kg load, 0.15 ml/kg maintenance), combined with a small amount of corn-starch. Our bench studies have shown that this placebo is identical in appearance to the diazoxide solution and both maintain similar physical characteristics at room temperature for at least 2 weeks. The glucose load from the corn-starch is trivial and will not affect BGC. Weekly dose adjustment for weight will be made, if required, once the baby returns to birthweight.

**Titration of the intervention**

A bedside algorithm will be used to titrate the study drug according to BGC, commencing before the third maintenance dose, with the aim of maintaining BGC at 2.6-5.4 mmol/L (Table 2). This target range is based on normative BGC data from the GLOW Study.

**Table 2: Intervention beside algorithm**

<table>
<thead>
<tr>
<th>BGC</th>
<th>Action (commencing before 3rd maintenance dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤2.5 mmol/L</td>
<td>• If episodes of hypoglycaemia occur &gt;24 h after commencing the intervention (loading plus two maintenance doses), increase maintenance dose to 0.25 ml/kg (diazoxide 2.5 mg/kg) every 12 h</td>
</tr>
<tr>
<td></td>
<td>• If hypoglycaemia persists after two doses of study drug at 0.25 ml/kg, increase maintenance dose to 0.5 ml/kg (diazoxide 5.0 mg/kg) every 12 h</td>
</tr>
<tr>
<td></td>
<td>• If further hypoglycaemia occurs after 2 doses of study drug at 0.5 ml/kg, discuss with the Site Principal Investigator and a paediatric endocrinologist; congenital hyperinsulinism should be considered in refractory cases and unblinding may be appropriate</td>
</tr>
<tr>
<td>2.6-5.4 mmol/L</td>
<td>• Continue maintenance dose every 12 h while weaning intravenous fluids and grading up feeds</td>
</tr>
<tr>
<td></td>
<td>• Stop intervention 12 h after the primary outcome point is reached*</td>
</tr>
<tr>
<td>5.5-6.9 mmol/L</td>
<td>• If on intravenous dextrose, stop or wean fluids more rapidly</td>
</tr>
<tr>
<td></td>
<td>• If repeat glucose still elevated, stop any remaining intravenous fluids and withhold the next study drug dose; if glucose remains elevated for ≥12 h, discontinue the intervention</td>
</tr>
<tr>
<td></td>
<td>• If glucose returns to the target range (2.6-5.4 mmol/L), recommence maintenance at 0.1 ml/kg (diazoxide 1 mg/kg) every 12 h; if a further episode of elevated glucose occurs, stop any remaining intravenous dextrose and discontinue the intervention</td>
</tr>
<tr>
<td>≥7 mmol/L</td>
<td>• Discontinue intervention; wean any intravenous dextrose</td>
</tr>
</tbody>
</table>
*Give any doses scheduled in this 12-hour period.

**Supply of the intervention**

Study interventions will be prepared by the hospital trial pharmacist every 2 weeks, but once formal stability test data are available, it is likely this can be extended to every 3-4 weeks.

2.1.4 Concomitant care and co-interventions

**Fluids and feeds**

Fluids and feeds will be managed according to local practice but with the aim of weaning intravenous fluids and introducing enteral feeds and as soon as possible once glucose is stabilised.

**Hypoglycaemia after randomisation**

Episodes of hypoglycaemia after randomisation (<2.6 mmol/L on blood gas or laboratory chemical analyser) will be managed according to local practice, which could include starting or increasing intravenous dextrose fluids or increasing enteral feed volume or frequency. If hypoglycaemia occurs >24 h after commencing the study drug, the maintenance dose may be increased (section 2.1.3).

Glucagon injections should only be used in emergencies where intravenous access cannot be obtained and BGC persists <1.2 mmol/L. Glucagon infusions are not permitted.

Glucocorticoids are not permitted for treatment of hypoglycaemia but may be used if deemed essential for management of other conditions, e.g., adrenal insufficiency.

Open label diazoxide may be considered in refractory cases once other management strategies have been maximised and after discussion with the attending neonatologist, Site Principal Investigator and a paediatric endocrinologist. This will require unblinding of treatment allocation, which should generally not occur before 2 weeks of age.

**Glucose monitoring**

Management decisions will be based only on true BGC, either by gas analyser (portable or laboratory) or laboratory chemical analyser. Because gas analysers provide plasma-equivalent glucose concentration, whole blood gas analyser and laboratory plasma measurements will be used interchangeably without adjustment.\(^{41}\) Capillary, arterial or venous blood samples are acceptable. During weaning and stabilisation, BGC should be measured at least every 6 hours (pre-feed if on enteral bolus feeding). Once glucose stability has occurred, as defined by the primary outcome, BGC measurement frequency will be at clinical discretion but should be at least 12-hourly while on diazoxide or continuous glucose monitoring (CGM).

**Continuous glucose monitoring**

Babies enrolled in the trial will have a subcutaneous real-time CGM sensor inserted in the lateral thigh (Medtronic Guardian 3). It will be calibrated four times in the first 24 h, then every 12 h using BGC in the target range (2.6-5.4 mmol/L). Calibration will be avoided when sensory glucose concentration (SGC) is changing rapidly (Rise or Fall Alert).\(^{41}\) Using Bluetooth transmission to a bedside tablet computer and remote cloud monitoring with text alerts, research staff will use pre-defined Trend Alert criteria to inform the bedside nurse that a BGC measurement is indicated, i.e., glucose is trending out of range (Table 3).
Table 3: Trend Alarms

<table>
<thead>
<tr>
<th>Trend Alert</th>
<th>Medtronic Guardian setting</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>Low Alert SGC=3.1 mmol/L AND Fall Alert ≥1 for 10 min*</td>
<td>BGC expected to be 2.5 mmol/L</td>
</tr>
<tr>
<td></td>
<td>Low Alert SGC=3.1 AND ≤2.5 mmol/L after 20 min**</td>
<td>BGC falling by 0.03 mmol/L/min</td>
</tr>
<tr>
<td>High</td>
<td>High Alert SGC=5.6 mmol/L AND Rise Alert ≥1 for 10 min*</td>
<td>BGC expected to be 6.2 mmol/L</td>
</tr>
<tr>
<td></td>
<td>High Alert SGC=5.6 mmol/L AND ≥6.1 mmol/L after 20 min***</td>
<td>BGC rising by 0.03 mmol/L/min</td>
</tr>
</tbody>
</table>

Medtronic Guardian provides an SGC reading every 5 min. SGC/BGC, sensor/blood glucose concentration. *Fall/Rise Alert 1 indicates SGC is changing by 0.06 mmol/L/min; Fall/Rise Alert 2 indicates SGC is changing by 0.11 mmol/L/min; Fall/Rise Alert 3 indicates SGC is changing by 0.17 mmol/L/min. **If the SGC is ≥2.6 after 20 min, no Trend Alert is signaled. Snooze time for device Low Alert set to 20 min. ***The BGC 97th percentile for healthy breastfed babies >72 h is 6.0 mmol/L.

Actual SGC will not be reported to clinical staff, ensuring that management decisions are based solely on BGC. The CGM will remain in place for 24 h after discontinuation of the study drug or attainment of the primary outcome, whichever is longer, up to a maximum of 7 days. We have extensive experience with CGM, and have found these devices to be well tolerated in neonates (the subcutaneous filament is soft and <0.4 mm thick). CGM alert and SGC data will be recorded with all BGC measurements for later agreement analysis.

Other co-interventions

All other neonatal care will occur according to local practice.

2.1.5 Study Assessments

Baseline data

Demographic, obstetric and relevant family medical history will be collected at study entry. Participant ethnicity will be recorded according to Ministry of Health guidelines. For participants that identify as Māori, iwi and hāpu will be recorded.

Blood tests

As part of routine care, blood will be collected at baseline and sent to the hospital laboratory for measurement of metabolic markers, including plasma insulin, beta-hydroxybutyrate, free fatty acids, creatinine and blood gas. This is standard practice for babies admitted to neonatal intensive care with hypoglycaemia. All infants will have a standard metabolic screen by Guthrie card at ≥48 h as part of routine care.

Additional heparinised blood (~1.5 ml) will be collected before the third study maintenance dose (36 h after commencing the intervention) and plasma stored for measurement of insulin, creatinine and diazoxide concentrations (2x 150 μL aliquots). Where possible, this will be timed to coincide with other routine blood sampling.

Cardiac ultrasound

At Middlemore Hospital, a cardiac ultrasound will be performed ≥72 hours after commencing the study intervention to assess a) ductal patency, flow and shunt; b) pulmonary arterial pressure; and c) cardiac function. Images will be stored and measured off-line according to a standardised protocol. At other sites, cardiac ultrasound will be performed as clinically indicated.
Primary and secondary outcome data

BG results and fluid and feeding charts will be reviewed regularly and recorded on a flow sheet until primary hospital discharge to determine the primary and secondary outcomes. If the primary outcome has not occurred after four weeks, it will be censored.

2.1.6 Outcomes

Primary

The primary outcome is time to successful hypoglycaemia treatment, defined as achieving enteral bolus feeding and normal glucose concentrations without intravenous fluids. The primary outcome is the first time point at which all the following criteria are met concurrently (see appendix 5.6 for examples):

1) No intravenous fluids for ≥24 h (time recorded at the end of the 24-hour period).
2) Enteral bolus feeding for ≥24 h defined as a) breastfeeding without supplements; or b) breastfeeding with supplements at >2 hourly intervals, or c) if not breastfeeding, gastric tube or bottle feeds at 3-4 hourly intervals (time recorded at the end of the 24-hour period).
3) Glucose stabilisation for ≥24 h, defined as a minimum of four pre-feed BG in the target range of 2.6 to 5.4 mmol/L (last BG <4 h of primary outcome time point; four pre-feed BG spanning >20 h; no BG out of range for ≥24 h; time recorded at the end of the period).

Secondary

The following secondary outcomes will be assessed from the point of randomisation:

1) Time to glucose stabilisation (as per primary outcome)
2) Time to establish enteral bolus feeding (as per primary outcome)
3) Time to establish full sucking feeds defined as ≥five full (code E/F) breastfeeds in 24 hours or ≥120 ml/kg/d of expressed breast milk or formula by bottle (up to discharge to home)
4) Feeding at discharge from hospital and to home
5) Use of intravenous fluids and type
6) Duration of intravenous fluids (up to discharge from hospital)
7) Episodes of hypoglycaemia (<2.6 mmol/L), elevated glucose concentration (5.5 to 6.9 mmol/L) and hyperglycaemia (≥7 mmol/L), defined by BG measurement, including frequency, duration, timing and treatment before, during and after the episode (up to discharge from hospital)
8) Number of BG tests: during study intervention and hospital admission
9) Duration of admission: neonatal care, postnatal ward, community birthing unit
10) Duration of study intervention (up to discharge from hospital)
11) Plasma insulin, beta-hydroxybutyrate, free fatty acids, creatinine concentrations and blood gas (on admission to the neonatal unit)
12) Guthrie metabolic screen (≥48 hours from birth)
13) Plasma insulin, creatinine and diazoxide concentrations at ≥36 hours after commencing the intervention
14) Death (up to discharge from hospital)
15) Seizures (total; hypoglycaemic) (up to discharge from hospital)
16) Discontinuation of study intervention due to elevated BG concentration or hyperglycaemia (up to discharge from hospital)
17) Discontinuation of study intervention due to another adverse event (serious; non-serious) (up to discharge from hospital)
18) Congestive heart failure (respiratory distress as evidenced by tachypnoea, recession, or use of oxygen or positive pressure support with consistent CXR findings, including cardiomegaly, plethora, interstitial fluid or effusions) (up to discharge from hospital)
19) Commencement of low flow oxygen or positive pressure respiratory support (up to discharge from hospital)
20) Cardiac ultrasound (Middlemore Hospital) at (≥72 hours)
   a. Ductus arteriosus: closed; trivial (<1.5 mm 2D, a constricted pattern on Doppler); patent (≥1.5 mm, growing, pulsatile or bidirectional pattern on Doppler)
   b. Pulmonary hypertension: pulmonary artery pressure ≥systemic as estimated by tricuspid regurgitant jet (RV-RA gradient +5 mmHg) or ductal shunt right to the left (>20%) with characteristic pulmonary Doppler envelope (TPV/ RVET <20%)
   c. Cardiac impairment: left ventricular internal diameter diastole z-score >2 and reduced systolic function (FS% <25 or MPI >0.41)

2.1.7 Participant Timeline

The study schedule is as follows:

<table>
<thead>
<tr>
<th>TIMEPOINT</th>
<th>Enrolment</th>
<th>Allocation</th>
<th>Week 1</th>
<th>Week 2-4</th>
<th>Discharge</th>
</tr>
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<tbody>
<tr>
<td>ENROLMENT:</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Eligibility screen</td>
<td>X</td>
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<tr>
<td>Informed consent</td>
<td>X</td>
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<tr>
<td>Baseline data</td>
<td>X</td>
<td></td>
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<tr>
<td>Demographics and contacts</td>
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<td>Baseline metabolic bloods</td>
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<td></td>
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<tr>
<td>Allocation</td>
<td></td>
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<tr>
<td>INTERVENTIONS:</td>
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<tr>
<td>Study drug</td>
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<td>±</td>
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<td></td>
<td></td>
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<tr>
<td>ASSESSMENTS:</td>
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<tr>
<td>Continuous glucose monitor</td>
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<td></td>
</tr>
<tr>
<td>Primary outcome assessment</td>
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<td>±</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood collection (≥36 hours)</td>
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<td></td>
</tr>
<tr>
<td>Echocardiogram (≥72 hours)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary outcome assessment</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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</tr>
</tbody>
</table>

2.1.8 Sample Size and Feasibility

A trial of 74 babies randomised in 1:1 ratio (37 per group), will give 80% power to detect a relative hazard of 2.0 (2-tailed alpha 0.05), assuming 90% of infants in each group have a primary outcome event within the study period (PAS v.16). A hazard ratio of 2.0 indicates that the diazoxide group reaches the primary outcome at twice the rate (events per unit of time) of the control group.

Approximately 50 babies ≥35 weeks’ gestation are admitted with hypoglycaemia each to the Middlemore and Auckland City Hospital neonatal units annually; thus, recruitment is feasible over 2 years at 40% recruitment rate or 18 months with the addition of a third site.

2.1.9 Recruitment

Recruitment will be face to face. It is anticipated that parental informed consent will be obtained after birth. Randomisation will only occur once a neonate is admitted to neonatal care and meets the
inclusion criteria. The study will be promoted in hospital posters, flyers and the BABBLE phone application.

2.2 Assignment of Interventions

2.2.1 Allocation Sequence Generation

A computer-generated randomisation sequence with random permuted blocks of 4 and 6, stratified by centre and SGA status (<10th customised centile)\(^4\) will be used to assign study interventions.

2.2.2 Allocation Concealment Mechanism

Participants will be assigned to study interventions using a web-based computer randomisation system (Central Coordinating Research Hub [CDRH], Liggins Institute). The randomisation system will assign a study drug bottle identified by a random number, containing either diazoxide or placebo. Only the study statistician and data manager will have access to the allocation sequence during the trial, and only the data manager and trial pharmacists will know the contents of the bottles.

2.2.3 Implementation

Participants will be enrolled and randomised by study personnel or neonatal unit staff.

2.2.4 Blinding (Masking)

Study personnel, clinical staff and parents will be blinded to the study interventions until all participants have completed the assessment period. Blinding will be achieved by using an identical medication bottle and identical inert placebo.

2.2.5 Emergency Unblinding

The attending neonatologist may request unblinding if this is deemed essential for the participant’s ongoing clinical care. The Site Principal Investigator will decide to unblind after discussion with the attending neonatologist and a paediatric endocrinologist (if relevant). If unblinding occurs, the data manager will inform the attending neonatologist directly of the study intervention status; where possible, study personnel will remain blinded until the trial is completed. Unblinding should generally not be considered until at least two weeks of age.

2.3 Data Collection, Management and Analysis

2.3.1 Data Collection Methods

Data will be collected directly into eCRFs using the REDCap system. Branching logic and range checks will be used to reduce data entry errors. CGM data will be captured in a secure cloud account and subsequently uploaded to the REDCap system.

2.3.2 Retention

If a participant is withdrawn, consent will be sought to use data collected up to the point of withdrawal. Where possible, reduced participation (stopping the intervention or not performing certain assessments) will be sought rather than withdrawal. Participants who withdraw but give consent for the use of collected data will be included in the intention to treat analysis, censored at the point of withdrawal.

2.3.3 Data Management

The CDRH, Liggins Institute will provide web-based data management. All eCRFs will be manually checked for completeness and logic errors by a data monitor, after which eCRFs will be locked. If the data monitor identifies potential errors, an electronic query will be raised and referred to the site for checking.
2.3.4 Statistical Methods

Statistical analysis will be performed with JMP v14 and SAS v9.4 (SAS Institute).

Derived variables

Customised birthweight centiles will be calculated using GROW software (Perinatal Institute, United Kingdom). Population z-scores for weight, length and head circumference at birth will be calculated using UK-WHO centiles.\(^45\)

Descriptive statistics

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

Primary analysis

Intervention groups will be compared for the primary outcome using Cox’s proportional hazards regression analysis, with treatment effect expressed as hazards ratio with a 95% confidence interval (CI). The analysis will be left-censored for 24 hours and right-censored at four weeks. Secondary outcomes will be compared between groups using generalised linear models with treatment effect presented as odds ratio, count ratio, mean difference or ratio of geometric means (positively skewed data), as appropriate, with 95% CI. Regression models will be adjusted for gestation length and birthweight z-score (fixed effects), and non-independence of multiples (random effect). For significance tests, the alpha level will be set at 0.05 (two-tailed).

CGM evaluation

All BGC will be paired with CGM Trend Alert status (Low, High, Unstable, None) over the preceding 20 min. For each Trend Alert status, descriptive statistics will be presented for BGC, including mean, SD, 95% range and the proportion of values within, below and above the target range (2.6-5.4 mmol/L). Agreement analysis, expressed as kappa value with 95% CI, will be performed overall comparing the binary variables Trend Alert (yes, no) and BGC out of range (yes, no), and separately for Trend Alert low (vs. BGC below range) and high (vs. BGC above range). Kappa values of 0.41 to 0.60 will be designated as indicating moderate agreement; 0.61 to 0.80 substantial agreement; and 0.81 to 1.00 as high agreement.\(^46\) Negative and positive predictive value for Trend Alarm will be calculated.

2.4 Monitoring

2.4.1 Data Monitoring and Safety Committee

A Data Monitoring and Safety Committee (DMSC) will monitor recruitment, completeness of data acquisition, and safety outcome measures (harms). The DMSC will advise the Steering Committee on trial continuation or protocol modification. DMSC Terms of Reference, including the content of DMSC reports, will be agreed prior to commencement of trial.

2.4.2 Interim Analysis

It is envisaged that the trial will be completed as planned with no interim efficacy analysis, but rates of adverse events will be monitored.

2.4.3 Harms

The following Serious Adverse Events (SAE) will be reported to the DMSC for immediate review:

- Death
- Seizure
- Congestive heart failure
Discontinuation of study intervention due to another serious adverse event, as judged by the Site Principal Investigator or attending neonatologist (an adverse event is considered serious if it is immediately life-threatening, requires prolongation of existing hospitalisation or substantial escalation in care, or results in persistent or significant disability or incapacity).

The serious adverse event review process will be specified in the DMSC Terms of Reference and agreed prior to commencement of the trial.

The DMSC will undertake an interim safety review when the primary outcome is known for 25% and 60% of participants, which will include rates of SAE and the following Adverse Events (AE) by masked treatment group:
- Hyperglycaemia (≥7 mmol/L)
- Discontinuation of study intervention due to elevated BG concentration or hyperglycaemia
- Discontinuation of study intervention due to another adverse event (non-serious)
- Commencement of low flow oxygen or positive pressure respiratory support

3 ETHICS AND DISSEMINATION

3.1 Research Ethics Approval
National ethics approval will be obtained from the Health and Disability Ethics Committee (HDEC) prior to commencement of randomisation. Annual reports will be submitted to HDEC during the course of the trial.

3.2 Locality Approval
Institutional approval will be obtained at each participating District Health Board (DHB) prior to commencement of randomisation at that site.

3.3 Protocol Amendments
All amendments to the final version of this protocol will require review and approval of the Steering Committee and will be submitted to HDEC and DHB Research Offices, as appropriate. All amendments, including an approval date, will be recorded with this protocol (Appendix 5.1).

3.4 Consent
Informed written parental consent will be obtained by study personnel and clinical staff prior to enrolment in the trial.

3.5 Withdrawal
Parents will retain the right to withdraw their baby from the study at any stage without the need to provide a reason. With parental permission, data collected up to the point of withdrawal will be used in the analysis.

3.6 Ancillary Studies
Participants may be invited to participate in a parallel study of patient-centred outcomes related to neonatal hypoglycaemia, including cultural perspectives.

3.7 Confidentiality
Electronic databases will be stored on secure servers at the University of Auckland and access will be controlled by unique user ID and password, with full electronic tracking log. The screening database
will record NHI, gestation length, birthweight, hypoglycaemic risk factor and eligibility criteria of participants considered for enrolment. This will enable the reporting of CONSORT data and assessment of external validity. Following randomisation, trial data will be stored in a separate database with eCRFs labelled by randomisation ID. NHI will be stored in the randomisation but not the trial database. Contact information will be stored in a separate database, independently of the trial database and will be accessible only to site coordinators and investigators. Data Access Groups will be employed so that site personnel can only see data for participants at their site. The download of data will be restricted to the data manager, study coordinator, site investigators and primary investigator, and only the data manager and primary investigator will be able to download identifiable data.

Electronic data files, e.g., CGM output, will be stored in the REDCap trial database file repository providing the same secure, protected access as above. Any hard copy CRFs will be stored in a locked cabinet until scanned into the file repository and then destroyed.

Study reports will contain only summary data and individual participant data will not be reported. Identifiable data will not be released to any third party. Research staff will be certified in best practice for clinical trials (ICH-GCP E6 and PHRP).

At the completion of the study, all electronic data will be permanently digitally archived with the CDRH, Liggins Institute, which has established processes for archiving and data sharing according to international best practice (https://wiki.auckland.ac.nz/display/ontrack/Data+Sharing).

3.8 Declaration of Interests

Investigators will declare any financial, intellectual or other potential conflicts of interest, as outlined by the ICMJE, to the Steering Committee. The Steering Committee will decide on how any conflicts of interest are to be managed. This will be recorded with the Steering Committee Terms of Reference.

3.9 Access to Data

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

3.10 Dissemination Policy

Results of the study will be presented at relevant conferences and hospital meetings and published in a peer-reviewed scientific journal.

3.11 Authorship policy

The Council of Science Editors standards for authorship will be applied (www.councilscienceeditors.org). The Steering Committee will be responsible for planning manuscripts and determining authorship. Investigators and study personnel who do meet the criteria for authorship will be acknowledged as non-author contributors.

3.12 Data Sharing Policy

For each main publication, the corresponding data set will be electronically archived with the CDRH. Anonymised data may be shared with external researchers upon request, according to the Data Sharing Protocol of the CDRH (https://wiki.auckland.ac.nz/display/ontrack/Data+Sharing).

3.13 Māori Responsiveness

This protocol was developed in consultation with the Liggins Institute Māori Advisory Group of (2019.08.14) and Te Teira Rawiri, Principal Kaumātua, Counties Manukau Health (2019.10.16). Our
investigator team includes a Māori paediatric researcher, Jenny Rogers (Ngāi Tahu), who will assist with Māori engagement, ensure that study processes are culturally appropriate and provide a Māori research perspective in analysis and dissemination of data.

4 STUDY MANAGEMENT

4.1 Steering Committee
The Steering Committee will take overall responsibility for all aspects of the study, meeting on a quarterly basis. Matters arising between meetings may be dealt with by email. The Principal Investigator will be responsible for maintaining a record of correspondence and minutes of meetings.

4.2 Management Committee
A Study Coordinator will be appointed to oversee the day-to-day running of the study. They will be supported by a Management Committee which will meet regularly.

4.3 Site Principal Investigator
A Principal / Lead Investigator will be appointed at each site, who will have overall responsibility for satisfying local governance requirements, recruitment, assessments, data collection and integrity. They will be supported by the Trial Coordinator and Management Committee.

4.4 Finance and Insurance
Funding has been provided from the University of Auckland and Health Research Council of New Zealand.
This is a non-commercial study; participants in New Zealand will be covered by provisions of ACC.
5 APPENDICES

5.1 Protocol Amendments

<table>
<thead>
<tr>
<th>Version, Date</th>
<th>Amendment(s)</th>
<th>Date accepted by Steering Group</th>
<th>Date ethics notified (or NA)</th>
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</thead>
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<tr>
<td>1.1, 2019.11.26</td>
<td>Addition of congestive heart failure and commencement of low flow oxygen or positive pressure respiratory support as secondary outcomes and serious adverse and adverse events, respectively.</td>
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<tr>
<td>1.2, 2019.12.22</td>
<td>Assessment time point updated for secondary outcomes.</td>
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<tr>
<td>1.3, 2020.2.5</td>
<td>Added &quot;phase 2&quot; to design; labelled as study number I; appendix 5.4 updated.</td>
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<tr>
<td>1.4, 2020.2.15</td>
<td>Definition of glucose stability corrected.</td>
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<tr>
<td>1.5, 2020.2.29</td>
<td>Updated with feedback from the ON TRACK Trials Workshop, including minor amendments to eligibility and definition of the primary outcome.</td>
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<tr>
<td>1.6, 2020.4.23</td>
<td>Michael Myer added as investigator. CGM methods updated.</td>
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<tr>
<td>1.7, 2020.5.1</td>
<td>Error in titration algorithm corrected.</td>
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<tr>
<td>1.8, 2020.5.13</td>
<td>Target range upper limit increased to 5.4 mmol/L based on new normative data. CGM methods.</td>
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5.2 Participant Documents

The following participant documents are to accompany this protocol:

<table>
<thead>
<tr>
<th>Title</th>
<th>Version</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participant Information Sheet and Consent</td>
<td>1.1</td>
<td>2019.11.26</td>
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</tbody>
</table>

5.3 Ethical and Locality Approval

The following letters of approval are to accompany this protocol:

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<thead>
<tr>
<th>Title</th>
<th>Reference</th>
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<tr>
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<tr>
<td>Liggins locality approval</td>
<td>Letter on file</td>
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<tr>
<td>Counties Manukau Health locality approval</td>
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<td>Auckland District Health Board locality approval (8745)</td>
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<td>HDEC approval 19CEN189 (corrected letter)</td>
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5.4 Study Committees

The following Terms of Reference are to accompany this protocol:

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<tr>
<th>Title</th>
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<th>Date</th>
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<tbody>
<tr>
<td>Data and Safety Monitoring Committee Terms of Reference</td>
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<td>2020.5.24</td>
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5.5 Standard Operating Procedures

The following Standard Operating Procedure documents are to accompany this protocol:

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<tbody>
<tr>
<td>Collection and handling of blood specimens</td>
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<tr>
<td>Echocardiography</td>
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<tr>
<td>Continuous glucose monitoring</td>
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<td>Study medication supply</td>
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<tr>
<td>Intervention management</td>
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<td></td>
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<tr>
<td>Recruitment and randomisation</td>
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<td>Study flow chart</td>
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<tr>
<td>Adverse event reporting</td>
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<tr>
<td>Data management</td>
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</tbody>
</table>

5.6 Primary Outcome Assessment

The following examples illustrate how the primary outcome is determined.

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<thead>
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<th>Day 1 12:00 tube feed</th>
<th>21:00 BF</th>
<th>Day 1 12:00</th>
<th>Day 3 0400</th>
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<td>02:00 BF</td>
<td>03:00 bottle</td>
<td>06:00 tube feed</td>
<td>06:00 BF</td>
<td>08:00 BF</td>
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<td>19:00 Bottle</td>
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<td>21:00 BF</td>
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<td>14:00 BF</td>
<td>20:00 BF</td>
<td>05:00 bottle*</td>
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<table>
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<th>Day 1 02:00 BF</th>
<th>04:00 BF</th>
<th>08:00 Bottle</th>
<th>11:00 BF</th>
<th>03:00 Bottle</th>
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<th>09:00 BF</th>
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*Earliest time that criterion can be met.
5.7 Funding

This study was funded through the following sources:

<table>
<thead>
<tr>
<th>Funder</th>
<th>Funding type</th>
<th>Named Investigators</th>
<th>Amount</th>
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<td>University of Auckland</td>
<td>Early Career Research Award</td>
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<tr>
<td>Hear Research Council</td>
<td>Feasibility Project</td>
<td>Chris McKinlay, Jane Alsweiler, Jane Harding, Wayne Cutfield, Jenny Rogers, Greg Gamble</td>
<td>$249,641</td>
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</table>
6 REFERENCES


