



## Trial Protocol

# The C\*STEROID Trial: Corticosteroids before planned caesarean section from 35<sup>+0</sup> to 39<sup>+6</sup> weeks of pregnancy

**Full title:** The C\*STEROID Trial. Antenatal corticosteroids prior to planned caesarean section delivery from 35<sup>+0</sup> to 39<sup>+6</sup> weeks gestation; a randomised controlled trial assessing the effects on neonatal respiratory morbidity and glycaemic control.

**Short title:** The C\*STEROID Trial: Corticosteroids before planned caesarean section from 35<sup>+0</sup> to 39<sup>+6</sup> weeks of pregnancy.

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# The C\*STEROID Trial: Corticosteroids before planned caesarean section from 35<sup>+0</sup> to 39<sup>+6</sup> weeks.

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## List of abbreviations

AE	Adverse Event
ALPS	Antenatal Betamethasone for Women at Risk for Late Preterm Delivery
BGC	Blood Glucose Concentration
CRF	Case Report Form
CS	Caesarean Section
DMC	Data Monitoring Committee
GA	Gestational Age
IQ	Intelligence Quotient
HRC	Health Research Council
MFM	Maternal Fetal Medicine
NICU	Neonatal Intensive Care Unit
NNU	Neonatal Unit
RCT	Randomised Controlled Trial
RDS	Respiratory Distress Syndrome
RR	Relative risk
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
TSC	Trial Steering Committee
TTN	Transient tachypnoea of the newborn

## **1. LAY SUMMARY**

In New Zealand and Australia, over 50 000 babies are born by planned caesarean section (CS) each year and rates continue to rise. Planned CS poses some risk to babies, in particular, the need for admission to the neonatal unit (NNU) for breathing support which means mothers are separated from their baby.

When given to mothers expecting a preterm birth, corticosteroid injections save babies' lives and improve neonatal and childhood health. This knowledge has led clinicians to prescribe corticosteroids before a planned CS at or near term. Limited research in this area has shown that as well as benefits on neonatal breathing corticosteroids may lower baby's blood sugar levels and so possibly cause harm.

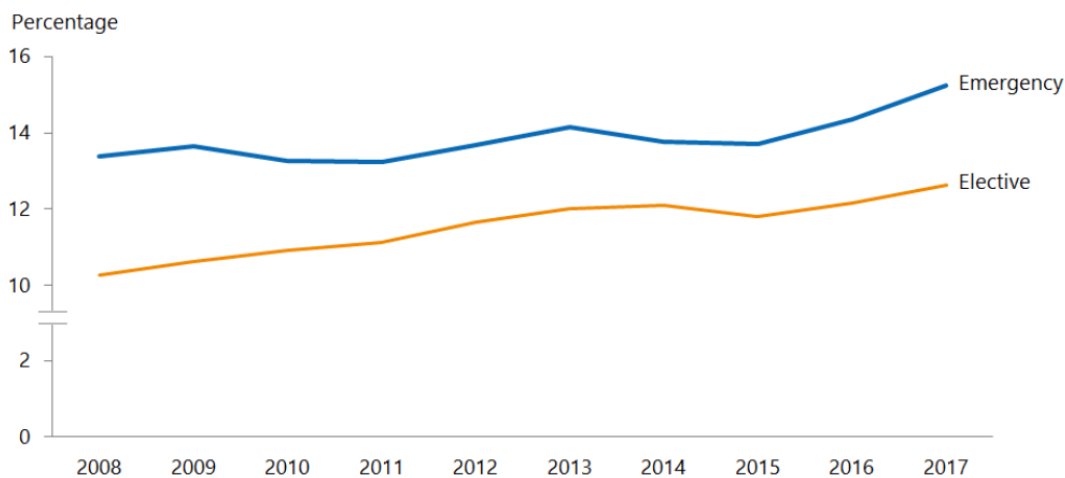
The C\*STEROID Trial is a multi-centre, placebo-controlled, randomised trial across New Zealand and Australia able to assess the effects of corticosteroids on newborn and childhood health when given to mothers prior to a planned CS at or near term. It will provide the first high-quality evidence on the balance between benefit and harm of corticosteroids in this setting. It will reliably inform clinical practice for more than one in ten of all future births in New Zealand and Australia.

## 2. BACKGROUND

### 2.1 Rationale

The rate of birth by planned, also referred to as elective and pre-labour, CS continues to rise each year and now accounts for more than one in ten births and over 50 000 babies born in New Zealand and Australia each year (Figure 1).<sup>1</sup> Compared to vaginal birth, CS poses additional risks to baby. Most specifically respiratory morbidity, often referred to as respiratory distress syndrome (RDS) and transient tachypnoea of the newborn (TTN). Term and late preterm babies rarely die from these conditions which are typically self-limiting, but often require neonatal unit (NNU) admission for monitoring and/or respiratory support. This separates mother and baby interfering with breastfeeding and bonding.

**Figure 1.** Rates of CS in New Zealand 2008-2017.<sup>1</sup>



Neonatal respiratory morbidity after birth by pre-labour planned CS is increased 7-fold compared with infants born vaginally and 3-fold compared with infants born by CS once labour has established.<sup>2,3</sup> Gestational age at birth also contributes to this increased risk (Figure 2);<sup>4,5</sup> hence, national practice guidelines recommend planned CS should occur  $\geq 39^{+0}$  weeks.<sup>6-8</sup> However, planned CS at late preterm or early term gestation may still be necessary on maternal and/or fetal grounds, and planned CS at  $39^{+0}$  to  $39^{+6}$  weeks still imposes a 2-fold increase in neonatal respiratory morbidity.<sup>5</sup>

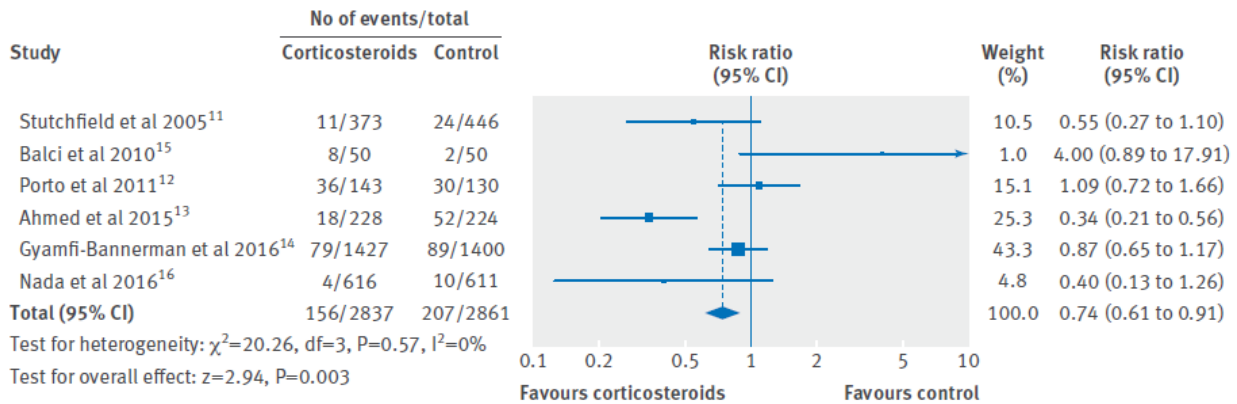
**Figure 2.** Neonatal respiratory morbidity after elective CS compared to intended vaginal birth (reference) by gestational age.<sup>5</sup>

Gestational Age	Adjusted Odds Ratio	95% CI
37 weeks	3.7	2.2-6.1
38 weeks	3.0	2.1-4.4
39 weeks	1.9	1.2-3.0
40 weeks	0.9	0.2-3.7

Corticosteroids accelerate fetal lung maturation by enhancing alveolar type II pneumocyte cell maturation and surfactant production; improve anti-oxidant activity and reduce pro-inflammatory cytokine production,<sup>9</sup> thereby reducing short-term neonatal respiratory morbidity. A large body of evidence from over 30 randomised trials supports the administration of corticosteroids prior to preterm birth at <35<sup>+0</sup> weeks gestation, regardless of mode of birth, to reduce perinatal death, RDS and other measures of neonatal adverse outcome with no evidence of later harm.<sup>8,10</sup> What is less clear is if their use at gestational ages ≥35 weeks, and specifically prior to planned CS, provides benefit without harm.

A 2016 systematic review has identified six randomised trials for all modes of birth, planned or expected, ≥35 weeks gestation of antenatal corticosteroids compared to placebo (n=3 trials) or no treatment (n=3 trials).<sup>11</sup> Three trials were specific to planned CS at term, ≥37<sup>+0</sup> weeks,<sup>12-14</sup> and three included women at risk of late preterm birth for all modes of birth at 34<sup>+0</sup> to 36<sup>+6</sup> weeks.<sup>15-17</sup> Meta-analysis of all trials demonstrates that corticosteroid use reduces the incidence of RDS (5.5% vs 7.2%, RR 0.74 95%CI 0.61-0.91) and TTN (5.9% vs 9.1%, RR 0.56 95%CI 0.37-0.86) (Figure 3).<sup>11</sup> A 2018 Cochrane Review of four randomised trials of corticosteroid use prior to planned CS at ≥37<sup>+0</sup> weeks<sup>18</sup> (three trials were also included in the 2016 review) found lower overall rates of respiratory morbidity, consistent with later gestation, but greater benefit than for late preterm births appearing to halve the risk of respiratory morbidity (RDS 0.8% vs 1.7%, RR 0.48 95%CI 0.27-0.87 and TTN 2.3% vs 5.3%, RR 0.43 95% CI 0.29-0.65).<sup>18</sup> Consequently leading to fewer admissions to neonatal special care overall (3.0% vs 5.3% RR 0.62; 95% CI 0.43- 0.89) and for respiratory complications (2.4% vs 5.0%, RR 0.45 95% CI 0.22-0.90).<sup>18</sup>

**Figure 3.** Effect of maternal corticosteroid use after 34<sup>+0</sup> weeks gestation on RDS (all trials).<sup>11</sup>



These systematic reviews suggest benefit, at least in the short term.<sup>11,18</sup> However, for all trials specific to planned CS, the risk of bias was moderate and the GRADE quality of evidence was low indicating that the true effect of corticosteroids may be substantially different than the estimate of effect given.<sup>18</sup> Furthermore, recent commentaries and reviews highlight the potential for harm,<sup>19-22</sup> supported by an unanticipated finding of the Antenatal Betamethasone for Women at Risk for Late Preterm Delivery (ALPS) trial. This is the largest trial to date, including 2827 women at high risk of imminent birth at 34<sup>+0</sup>-36<sup>+6</sup> weeks<sup>16</sup>, and although respiratory morbidity was significantly reduced, the rates of neonatal hypoglycaemia were significantly higher in babies exposed to corticosteroids (22.8% vs 14.2%, RR 1.6 95% CI 1.4-1.9). Blood glucose was not

systematically measured in all babies in the ALPS trial and only recorded as an outcome in babies requiring NNU admission; thus, it is possible that this outcome is confounded. Nevertheless, it is physiologically plausible that maternal corticosteroid use may cause neonatal hypoglycaemia.

Neonatal hypoglycaemia has been associated with a variety of brain abnormalities<sup>23</sup> seen on ultrasound and MRI, and recent but accumulating evidence suggests that even transient and treated neonatal hypoglycaemia is associated with adverse childhood outcomes.<sup>24-27</sup> A 2019 systematic review has identified nine cohort studies exploring the later effects of hypoglycaemia in children who were born 'at-risk'.<sup>28</sup> Although the quality of these studies was deemed low, significant effects on early childhood visual-motor and executive function and mid-childhood neurodevelopment, literacy and numeracy<sup>28</sup> are evident, making the finding in the ALPS trial a major concern which requires further consideration and evaluation.

The risk of neonatal hypoglycaemia after corticosteroids prior to planned CS birth  $\geq 37^{+0}$  weeks is unknown as none of the randomised trials to date have reported rates of hypoglycaemia.<sup>11</sup> There are no high quality data on later benefit or harm associated with term and late preterm use of corticosteroids. Only one trial with limited follow-up (37%) has reported childhood outcomes after corticosteroids prior to planned CS  $\geq 37^{+0}$  weeks, with a suggestion of poorer academic performance at 8-15 years of age after maternal corticosteroid use.<sup>29</sup>

Advice from national and international guidelines in this area is limited and conflicting.<sup>6-8,30-34</sup> Until recently the UK RCOG guideline recommended their use for planned CS  $\leq 38^{+6}$  weeks. This guideline now has been archived and its replacements give no guidance on this common clinical dilemma.<sup>6,30</sup> The ACOG recommends use for all births at  $34^{+0}$  to  $36^{+6}$  weeks but again no advice is given for planned CS  $> 36^{+6}$  weeks.<sup>31</sup> Data from our own work show significant variation in practice across New Zealand with some units routinely offering corticosteroids prior to all planned CS birth  $\leq 38^{+6}$  weeks,<sup>34</sup> despite the 2015 guidelines from Australia and New Zealand concluding there is insufficient evidence to make a recommendation for planned CS  $> 34^{+6}$  weeks.<sup>8</sup> However, these guidelines do include a research recommendation calling for randomised trials to investigate the neonatal effects and childhood disability rates when corticosteroids are administered to women prior to planned CS at term.<sup>8</sup>

**There is insufficient evidence to guide practice on corticosteroid use prior to planned CS at late preterm and term gestational ages. There is low quality evidence on neonatal respiratory morbidity, minimal evidence on long-term effects and no evidence on neonatal hypoglycaemia.**

**The C\*STEROID Trial is a large multicentre randomised placebo controlled trial with sufficient power to assess both potential beneficial (respiratory) and harmful (hypoglycaemia) effects of corticosteroids prior to planned CS at  $35^{+0}$  to  $39^{+6}$  weeks and from this, to establish a randomised cohort able to assess the childhood benefits and/or harm of this intervention.**

## **2.2 Feasibility to undertake the C\*STEROID Trial**

The C\*STEROID Trial concept was developed by a multi-disciplinary group facilitated by experts in the field, clinicians, biostatisticians, consumers and a Māori research advisor at the annual ON TRACK Network Concept Development Workshop in 2017.

Through ON TRACK Network, we have engaged with district health boards (DHBs) around New Zealand, undertaking a survey 'Opinions & Current Practice in Antenatal Corticosteroid Administration Prior to Planned Caesarean Section Delivery from 35<sup>+0</sup> Weeks Gestation'.<sup>35</sup> We received responses from 15/18 DHBs which have 40 000 births annually with planned CS rates varying from 7.9% to 18.0% (over 4500 births each year). Thirteen units reported experience of participation in multi-centre trials and seven units currently employ research staff. Betamethasone is the corticosteroid of choice in all units. Thirteen units have a guideline for newborn blood glucose monitoring and all 15 units have a guideline for the management of hypoglycaemia. At that time 11 units expressed willingness to participate in the C\*STEROID Trial and a further five units expressed interest in participation; no units were unwilling to consider participation. Subsequently 14 New Zealand maternity units have provided letters of intent to participate to support Health Research Council funding applications.

We have also completed a local consumer feasibility survey of women booked for a planned CS at 35<sup>+0</sup> to 39<sup>+6</sup> weeks at Auckland District Health Board (ADHB)<sup>36</sup> to explore attitudes to corticosteroid use prior to planned CS and to assess engagement in our research. ADHB guidelines follow bi-national guidelines<sup>8</sup> that do not support the use of corticosteroids prior to planned CS  $\geq 35$  weeks.<sup>37</sup> Women were provided with written information about corticosteroids and planned CS and an anonymous questionnaire. Of 63 responses, 48 (76%) had planned CS  $\geq 39^{+0}$  weeks. The majority of women (53/63, 84%) reported that the risks of CS had been explained to them by their maternity care provider but the use of corticosteroids had only been discussed with five women and offered to two. After provision of information regarding corticosteroids and planned CS, 11 (17%) women identified that, if offered, they would definitely or probably accept corticosteroids in their current pregnancy, 28 (44%) were unsure and 23 (37%) identified maybe or not at all as their response. In keeping with our previous work exploring consumer attitudes to corticosteroids at preterm gestations,<sup>38</sup> women identified lack of information about risks and benefits as an important factor determining their decision. Of all respondents, 51% of women undergoing planned CS  $\geq 35^{+0}$  weeks would consider participating in a trial. Of these, the vast majority would be willing for their baby to undergo blood sugar testing in the first few days after birth (26/30, 87%).

From July 2019 to March 2020 we have completed a nine-month randomised C\*STEROID Feasibility Study.<sup>39</sup> This was originally planned as a 12-month study but recruitment closed at the start of New Zealand's Level 4 COVID-19 lockdown with all objectives achieved. The study was funded by Cure Kids, Lottery Health Research New Zealand, the Hugo Charitable Trust and the University of Auckland Faculty Research Development Fund. Recruitment occurred at three sites (Auckland City, Tauranga and Waikato hospitals). With the same eligibility criteria as for the C\*STEROID Trial, the primary outcome was recruitment rate. Women were invited to participate and/or complete a questionnaire exploring the reasons women chose to, or not to, participate in the trial. Focus groups for clinicians and site researchers explored barriers and enablers to trial participation and completion allowing trial systems to be as efficient and effective as possible for a wider roll-out. The randomisation service, drug allocation and data collection system, trial drug production and packaging, standard operating procedures, and clinician and participant engagement resources were funded and successfully established for C\*STEROID Trial during the Feasibility Study. As planned *a priori*, we have remained blinded to outcome data by treatment



group for the C\*STEROID Feasibility Study allowing data to contribute to the main C\*STEROID Trial (n = 88 mothers and 92 babies).

A further practitioner survey including all Fellows of the Royal Australian and New Zealand College of Obstetricians and Gynaecologists has been undertaken in 2020. This provides up-to-date information on practitioner's views of corticosteroid use prior to planned CS at late preterm and term gestations, as well as attitudes towards the C\*STEROID Trial and expressions of interest to participate from Australian sites. There were 253 responses from Australian obstetricians including those working in all states; metropolitan, regional and rural areas; and across both public and private practice. A total of 107 Australian respondents expressed interest in participation in the C\*STEROID Trial and this is expected to cover at least 30 different maternity units.

### **3. TRIAL HYPOTHESIS & AIMS**

#### **3.1 Hypothesis**

The maternal administration of betamethasone compared to placebo prior to planned CS at 35<sup>+0</sup> to 39<sup>+6</sup> weeks gestation will reduce the risk of neonatal respiratory distress without increasing the risk of neonatal hypoglycaemia.

#### **3.2 Aims**

**Primary Aim:** To measure the effect of maternal betamethasone compared to placebo on the incidence of neonatal respiratory distress and on neonatal hypoglycaemia.

**Secondary Aims:** To measure the effect of maternal betamethasone compared to placebo therapy on:

- (i) the neonate: NNU admission, NNU duration of stay and breastfeeding at six weeks of age;
- (ii) the mother: postnatal infection and maternal wellbeing; and
- (iii) to establish a cohort of sufficient size to assess benefit and/or harm at 6-7 years of age in a later childhood outcome study exploring executive function, body size, and respiratory, cardiovascular and metabolic wellbeing.

### **4. TRIAL & DRUG SAFETY**

#### **4.1 Potential Risks to the Baby**

Antenatal corticosteroids including betamethasone are used as standard practice for mothers at high risk of preterm birth at <35<sup>+0</sup> weeks gestation to provide protection against RDS, perinatal death and other measures of neonatal adverse outcome with little or no evidence of later harm.<sup>10,11</sup> Previous research suggests that it may provide protection against respiratory conditions at later gestational ages and specifically when given before planned CS. This trial will assess other risks to the baby, in particular, neonatal hypoglycaemia. To date, no trials of corticosteroids prior

to planned CS at term or near term gestational ages have included data on rates of neonatal hypoglycaemia or included its measurement as a standard of the protocol.

#### **4.2 Potential Risks to the Mother**

The use of maternal corticosteroids may impose risk relating to infection morbidity. This has not been seen in previous trials.<sup>10,11</sup> However, to date no trials of corticosteroids prior to planned CS only at term or near term gestational ages have included data on maternal outcomes including any infection. This trial will assess and quantify maternal infection risk.

### **5. STUDY DESIGN**

The C\*STEROID Trial is a multi-centre, triple-blind, placebo controlled, parallel, phase III trial with randomisation at participant level (1:1 allocation ratio).

#### **5.1 Trial Setting**

This trial will be conducted at maternity units across New Zealand and Australia. 14 of 20 district health boards in New Zealand have expressed interest in participation and provided support for the Health Research Council funding application. A request for expressions of interest for Australian sites has been made via a survey distributed to all fellows of the Royal Australian and New Zealand College of Obstetricians and Gynaecologists and obstetricians from at least 30 maternity units have expressed willingness to participate.

#### **5.2 Trial Co-ordination**

The trial will be coordinated by staff at The University of Auckland including the C\*STEROID Trial Principal Investigator and Lead Investigators, Clinical Research Coordinator(s), research midwives, PhD student(s) and any other staff required to support clinical trial activities or analysis.

### **6. STUDY POPULATION – Inclusion & Exclusion Criteria**

Women for whom CS is planned pre-labour at 35<sup>+0</sup> to 39<sup>+6</sup> weeks gestation will be identified from antenatal clinics and booked CS operating lists at each recruiting site.

#### **6.1 Inclusion Criteria:**

- Planned pre-labour CS  $\geq 35^{+0}$  - 39<sup>+6</sup> weeks gestation
- $\geq 24$  hours\* and  $< 7$  days until planned birth
- Singleton or twin pregnancy with a live fetus

\*At the point of randomisation it must be  $\geq 24$  hours until the planned CS date and time for the participant to be eligible. This is to allow two doses of study drug to be administered, at 24 hours

(+/- 4 hours) apart, prior to the planned CS date and time (refer to section [10.3 Drug Administration](#)).

## **6.2 Exclusion Criteria:**

- Diabetes (pre-existing or gestational)\*
- Major fetal abnormality
- Prior corticosteroid use in this pregnancy (intramuscular corticosteroid use for fetal lung maturity)
- Prior enrolment in the C\*STEROID Feasibility Study or C\*STEROID Trial, in a previous pregnancy

\*Women with pre-existing or gestational diabetes will not be included in this trial as risks for neonatal respiratory morbidity and hypoglycaemia are significantly different in these populations. Corticosteroid use may also significantly disrupt glycaemic control in women with diabetes, with potential to ‘unblind’ treatment allocation and pose risk to these women. The effect of corticosteroids prior to planned CS in women with diabetes will be examined in other studies.

## **6.3 Withdrawal of Participants**

All study participants are free to discontinue the study drug and/or withdraw their consent at any point during treatment without prejudice. Participants who elect to discontinue the study drug early (receive no or one dose only) will continue with all other trial involvement unless they specify that they wish to withdraw from the study.

If a participant indicates that they wish to withdraw their consent for further participation data collected to the point of withdrawal will be retained and used. The investigator will be encouraged to ask a participant who is withdrawing which level of continued participation they agree to, if any, and to document this in the CRF. If a participant specifically requests complete withdrawal of consent, publicly available information only such as from the Birth Register may still be accessed to collect survival status. All participants will receive on-going medical care according to clinical need.

## **7. STUDY NUMBERS & POWER CALCULATION**

### **7.1 C\*STEROID Trial**

We hypothesise that corticosteroid use will reduce neonatal respiratory distress without increasing neonatal hypoglycaemia and therefore have selected co-primary outcomes of a superiority endpoint for benefit and non-inferiority endpoint for harm. The efficacy of corticosteroids is based on the success of both co-primary endpoints; therefore, no multiplicity adjustment is necessary.<sup>40</sup>

Published literature only provides surrogate estimates for the incidence of respiratory distress requiring  $\geq 60$  minutes of support which varies by gestation and mode of birth. The rate of mask

and/or mechanical ventilation use is 4.4% (21/475) after planned CS  $\geq 37^{+0}$  weeks<sup>14</sup> but 16.3% (258/1580) for all births at  $34^{+0}$  to  $36^{+6}$  weeks.<sup>15-17</sup> To best estimate the incidence of this outcome we have used ADHB 2018 data for planned CS at  $35^{+0}$  to  $39^{+6}$  weeks; from a total of 1259 planned CS, 63 infants required  $>60$  minutes respiratory support (5.0%).

Using a conservative relative risk reduction of 0.5<sup>11-14</sup> and 5.0% event rate, **a sample size of 2424 infants (1212 per group) will have 90% power, with  $\alpha$  0.05, to detect a reduction from 5.0% to 2.5%. We will recruit 2548 infants (1274 per group) to allow for 3% drop out and design effect 1.02** (clustering of babies within mothers estimated 1.02 babies per mother with ICC of 0.8, based on the incidence of multiples at this gestation in the ADHB dataset).

There are no reliable data on rates of hypoglycaemia after planned CS  $\geq 35$  weeks in any published trials or cohort studies. Using New Zealand specific data for those within our cohort who are preterm, small- or large-for- gestational age (rates of hypoglycaemia 53%, 39% and 56% respectively<sup>41</sup>) and for appropriately grown term babies (20% background rate of hypoglycaemia) and ADHB 2018 data for the proportion of babies born after planned CS at  $35^{+0}$  to  $39^{+6}$  weeks who fell into each of these four groups, we estimate an overall rate of hypoglycaemia of 28.2% (355/1259). To demonstrate the non-inferiority of corticosteroid use we have set a 10% non-inferiority margin (clinically relevant difference). **With an event rate of 28%, a sample size of 728 infants (364 per group) will have 90% power, with  $\alpha$  0.05, to reject inferiority (up to 38% hypoglycaemia in corticosteroid group), allowing for 3% drop out and design effect 1.02.**

As planned *a priori*, we have remained blinded to outcome data by treatment group for the C\*STEROID Feasibility Study allowing data to contribute to the main C\*STEROID Trial. Data from 88 mothers and 92 babies in the feasibility Study will contribute to the C\*STEROID Trial.

## **8. PARTICIPANT SELECTION & RECRUITMENT**

All women booked for a planned pre-labour CS at  $35^{+0}$  to  $39^{+6}$  weeks gestation at the recruiting sites will be assessed for eligibility. Once women have been identified as eligible by meeting all of the inclusion criteria, and none of the exclusion criteria, they will be provided with information regarding the trial. This will include a parent trial summary flyer; email or telephone introduction; a participant information video; verbal information and a written participant information sheet and consent form provided by clinicians and/or site trial investigators and research staff. All women will be given time for full consideration and consultation as required. Contact telephone numbers will be provided. Clinical and/or research staff will make contact with the potential recruit and if women wish to join the study the informed consent process will be completed and written, informed consent will be obtained.

For women who decline to take part in the C\*STEROID Trial antenatal care will continue to the same standard as for all women undergoing planned CS at  $35^{+0}$  to  $39^{+6}$  weeks gestation. It will be recommended to clinicians that corticosteroids should not be available as part of this standard of care.

## **9. RANDOMISATION**

Eligible women who have provided written, informed consent to participate will be enrolled by clinicians and research staff using a web-based randomisation service operating at the Clinical Data Research Hub Research Hub (CDRH) hosted by the Liggins Institute, The University of Auckland.

Randomisation will be stratified for;

1. Gestational age at planned caesarean section 35<sup>+0</sup>-36<sup>+6</sup>, 37<sup>+0</sup>-38<sup>+6</sup>, 39<sup>+0</sup>-39<sup>+9</sup> weeks
2. Recruiting site
3. Singleton or twin pregnancy

Women will be randomised in a 1:1 ratio to betamethasone:placebo.

The randomisation process will assign each participant with a unique study ID number. This study ID number will be required when allocating study drug treatment pack and for recording data on the CRF. The randomisation service provides 24 hour access, 7 days per week. If a woman is found not to be eligible for the trial when her details are entered into the randomisation program the program will return a screen failure notification.

## **10. TREATMENT GROUPS & STUDY DRUG**

### **10.1 Treatment Groups**

Women will be randomised to one of two groups:

1. *Corticosteroid Group*

Two doses of 11.4 mg betamethasone (Celestone Chronodose) by intramuscular injection 24 hours (+/- 4 hours) apart given within seven days of planned CS.

OR

2. *Placebo Group*

Two doses of visually matching placebo by intramuscular injection 24 hours (+/- 4 hours) apart given within seven days of planned CS.

Participants, medical professionals caring for women and trial investigators will remain blinded to treatment allocation until the trial is completed.

### **10.2 Drug Supply and Storage**

Betamethasone and visually matching placebo injections (containing no betamethasone) will be prepared by Baxter Healthcare and packaged in identical sterile syringes, for which drug stability has been confirmed by independent laboratory testing. Syringes will be labelled as C\*STEROID trial drug by staff not involved in participant recruitment and drug administration. Two syringes per allocation will be packaged into sealed treatment packs with an allocated treatment pack

number. Drugs will be stored at each recruiting site according to local hospital pharmacy procedure and under appropriate conditions (<25°C, ampoules protected from light).<sup>42</sup> The Investigator at each site is responsible for study drug inventory and accountability throughout the trial.

### **10.3 Drug Administration and Assessment of Compliance**

The study drug will be administered by intramuscular injection, to the thigh, arm or buttock, by appropriately qualified clinical or research staff at the study site within seven days prior to planned CS. Two doses of study drug should be administered 24 hours apart +/- 4 hours (i.e. 20-28 hours). If the date/time of the participant's CS is brought forward and/or labour commences spontaneously before the second dose has been administered it should still be given as long as it is ≥20 hours following the first dose. If birth is planned (CS) or inevitable (spontaneous labour) and it is <20 hours since the first dose the second dose should not be given. There is no minimum timeframe between the second dose and the planned CS (or expected birth). The timing of each dose and compliance will be recorded on the CRF.

### **10.4 Emergency Unblinding**

In the event that there is an immediate need for the treating doctor to know a participant's treatment allocation to ensure patient safety it will be possible to break the randomisation code. The facility to perform emergency unblinding will be available 24 hours per day. Participant unblinding can be completed by contacting the Auckland coordinating centre (contact details page one).

## **11. TREATMENT DURATION/INDICATIONS TO STOP TREATMENT**

### **11.1 Treatment Duration**

Randomised participants will be given the first dose of study drug within seven days of their planned CS and a second dose 24 hours (+/- 4 hours) later. The first dose of study drug should be scheduled to allow for the administration of two doses 24 hours (+/- 4 hours) apart prior to the participants planned CS. No further doses of study drug or antenatal corticosteroids will be given, even in the event of a delayed planned CS date.

### **11.2 Indications to Stop Treatment**

1. Significant maternal reaction to the first injection as determined by the clinician.
2. Birth required on clinical grounds prior to scheduled second dose of study drug.
3. Maternal request.

## **12. DATA COLLECTION**

### **12.1 Participant Schedule**

The study procedures for randomised participants are summarised in the flow chart below.

#### **Individual Participant Trial Flow Chart**



### **12.1.1 Baseline Data Collection**

Data will be collected on current and past medical history and demographics including date of birth, ethnicity, height and weight, past obstetric history, past medical history, complications to date in current pregnancy, medication use in pregnancy, indication(s) for CS and indication for timing of CS.

### **12.1.2 Baseline Questionnaires**

All participants will complete the following questionnaires at the first study visit:

- The SF-36 quality of life questionnaire to assess overall health and wellbeing.
- The Edinburgh Postnatal Depression Scale (EPDS) to assess mental wellbeing.

The EPDS will be reviewed by the local site once questionnaires are completed. Where the overall EPDS score  $\geq 13$  or item 10 is marked as yes, appropriate follow up will be made by the local site investigator or research midwife/coordinator.

### **12.1.3 Randomisation and Study Drug Allocation**

The randomisation process will assign each participant with a study drug treatment pack number. The system will only allocate treatment packs assigned to and available at the individual recruiting site. Each treatment pack contains two syringes containing 11.4 mg betamethasone or visually matching placebo. The second dose syringe will be kept securely at the recruiting site prior to second dose.

### **12.1.4 Study Drug Treatment**

First and second doses of study drug will be administered by clinical and qualified research staff within seven days of planned CS and 24 hours (+/- 4 hours) apart. Timing and compliance will be recorded in the CRF.

At the time of the first dose women will be provided with a Clinical Trial Participant Alert Card which will include space to record any adverse effects. At the second dose visit and on admission for planned CS, the Participant Alert Card will be reviewed and women will be asked to report any adverse reactions (local or systemic). These will be recorded in the CRF.

### **12.1.5 Consent for the child/children**

Written confirmation of consent for the child/children to be part of the research will be obtained for New Zealand participants as soon as possible after birth has occurred, this is required pursuant to section 36 of the Care of Children Act (NZ). In circumstances where the mother is unable to provide consent other parent or guardian consent should be obtained. If this consent is delayed neonatal blood glucose monitoring must be performed for safety reasons and consent should be sought as soon as this is appropriate.



#### **12.1.6. Neonatal blood glucose monitoring**

Neonatal blood glucose concentrations (BGC) will be measured after first feed at 1-2 hours of age and then pre-feed 3-4 hourly until 12 hours of age unless hypoglycaemia has occurred (continue monitoring until three consecutive blood glucose concentrations have been  $\geq 2.6$  mM). BGC should be measured using a glucose oxidase method, e.g. i-STAT analyser or blood gas analyser; if this is not available alternatives such as Accucheck should be used. Method of analysis will be noted with BGC recordings. If it is not possible to complete one or more of the recommended BGC this will be recorded in the CRF along with the reason why it was not carried out. Any additional clinically indicated blood glucose levels  $< 2.6$  mM recorded in the neonatal period will be collected. We will recommend that hypoglycaemia is treated following the ADHB Hypoglycaemia in the neonate guideline<sup>43</sup> and the national Oral Dextrose Gel guideline.<sup>44</sup> Surveillance and treatment algorithms will be supplied to sites (Appendix).

#### **12.1.7 Concomitant Clinical Management and Co-interventions**

Management of care and any additional therapies required will be provided at the discretion of the clinician/study site. Care of the woman during the antenatal period, labour and postnatal stay will be managed by the responsible obstetric and midwifery teams and care of the neonate will be the responsibility of the neonatology and midwifery teams. Relevant data regarding co-interventions and care will be recorded in the CRF.

#### **12.1.8 Outcome data collection**

Detailed data will be collected regarding delivery, maternal and neonatal outcomes from the maternal and neonatal records. Maternal outcome data will be collected until six weeks after birth. Neonatal outcome data will be collected until six weeks after birth.

To allow for later economic analyses, cost weight scores; clinical codes; and diagnostic sequences from the New Zealand National Minimum Dataset (NMDS) for mother and baby will be collected from health records and/or the Ministry of Health. In Australia Medicare data will be obtained from the federal government via the Health Insurance Commission. The Medicare system provides reimbursement for pharmaceutical benefits schedule (PBS) and medical benefits schedule (MBS) health care costs incurred by individuals within Australia.

#### **12.1.9 Post-partum questionnaires**

Participants will be sent the following questionnaires six weeks after delivery via email (or postal hard copy if requested):

- The SF-36 quality of life questionnaire to assess overall health and wellbeing.
- The Edinburgh Postnatal Depression Scale (EPDS) to assess mental wellbeing.
- C\*STEROID Trial 6 week follow up questionnaire.

The EPDS will be reviewed centrally once questionnaires are returned. Questionnaires completed electronically by the participant will be scored automatically. The REDCap database

will send an immediate notification to the Auckland coordinator for any questionnaires where the overall EPDS score  $\geq 13$  or item 10 is marked as yes; the local site investigator, research midwife, participant's LMC or GP will then be contacted to ensure that follow up with the participant takes place.

## **13. SAFETY ASSESSMENT & MONITORING**

### **13.1 Assessment of Adverse Events**

Information will be collected regarding all adverse events (AE) that occur from the time of randomisation until maternal and neonatal primary hospital discharge after delivery. Any events reported in the six week post-partum questionnaire will be reviewed for their potential to fulfil adverse event criteria and reported if necessary.

The general definition of an AE is any unfavourable and unintended change in structure, function, or chemistry of the body temporally associated with the study drug whether or not considered related to the use of the study medication. Worsening of a pre-existing condition which is temporally associated with the use of the study medication may also be considered an AE.

### **13.2 Serious Adverse Events**

In this trial the following will be considered serious adverse events:

- Maternal death
- Fetal death
- Neonatal death
- Maternal life threatening event
- Maternal persistent or significant disability or incapacity
- Major antepartum or postpartum haemorrhage (>1500 mL)
- Other medically important event considered to be an SAE by Investigator

Important medical events that may not result in death, threat to life, or not require hospitalisation may be also considered an SAE when, based upon appropriate medical judgment, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above. The term life threatening here refers to an event in which the patient is at risk of death at the time of the event; it does not refer to an event that might hypothetically cause death if it was more severe.

In the event of maternal SAE that may impact on the mother's ability to provide consent after birth other parent or guardian consent should be obtained for the baby/babies. If this consent is delayed neonatal blood glucose monitoring must be performed for safety reasons and consent should be sought as soon as this is appropriate.

### **13.3 Investigator Review of AEs/SAEs:**

The maximum intensity of adverse and serious adverse events must be assessed by an investigator. The following are the minimum parameters to be collected for each event:

- Maximum intensity: mild, moderate, severe, life threatening, death. Severity criteria based on the Common Terminology Criteria for Adverse Events (CTCAE), and adapted for the neonatal population should be used in this assessment<sup>45</sup>, as per table 1 below.
- Duration. The start and stop dates will be identified and recorded.
- Action taken in regards to the study drug. Does the event cause the study medication to be temporarily or permanently discontinued?
- Relationship to study medication. The investigator will determine if the study medication contributed to the AE/SAE. Factors to consider:

Exposure: Was participant exposed to the study medication?

Likely cause: Is the event reasonably explained by aetiology such as underlying disease or other environmental factors?

Re-challenge: Was the participant re-exposed to the study medication? If yes, did the event recur or worsen?

Consistency with the study medication: Is the clinical/pathology presentation of the event consistent with previous knowledge regarding the study medication?

- Details of any treatment given.

**Table 1:** Adverse event severity criteria.

	<b>Mild</b>	<b>Moderate</b>	<b>Severe</b>	<b>Life threatening</b>	<b>Death</b>
<b>Adult/ paediatric</b>	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.	Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living.	Severe or medically significant but not immediately life threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self care activities of daily living.	Life-threatening consequences; urgent intervention indicated.	Death related to AE.
<b>Neonate</b>	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; no change in baseline age-appropriate behaviour*; no change in baseline care or monitoring indicated.	Moderate; resulting in minor changes of baseline age appropriate behaviour*; requiring minor changes in baseline care or monitoring. †	Severe; resulting in major changes of baseline age-appropriate behaviour* or non-life-threatening changes in basal physiological processes‡; requiring major change in baseline care or monitoring. §	Life threatening; resulting in life-threatening changes in basal physiological processes‡; requiring urgent major change in baseline care. §	Death related to AE.

\*Age-appropriate behaviour refers to oral feeding behaviour, voluntary movements and activity, crying pattern, social interactions and perception of pain.

†Minor care changes constitute: brief, local, non-invasive or symptomatic treatments.

‡Basal physiological processes refer to oxygenation, ventilation, tissue perfusion, metabolic stability and organ functioning.

§Major care changes constitute: surgery, addition of long-term treatment, upscaling care level.

## **Expectedness of SAEs**

SAEs must also be assessed for expectedness in this clinical setting. The investigator is responsible for determining whether an SAE is expected or not based on the underlying pregnancy and CS delivery, the pre-existing condition of the fetus/neonate, and the published reference safety information for betamethasone (including this protocol and the summary of product characteristics, such as the MedSafe Data Sheet). An unexpected adverse event/reaction is one that is not reported in the reference safety information, is more severe than previously reported or is not reasonably explained by the underlying condition.

Review of all of the known information about the SAE should conclude one of the following:

Expected Events:

- Expected Unrelated Event: the SAE is expected based on the known information about the study drug or the underlying condition and is not considered to be related to the study drug. This is referred to as an Expected SAE.
- Expected Related Event: an SAE which the Investigator considers possibly, probably or definitely related to the study drug. This is referred to as a SAR – Serious Adverse Reaction.

Unexpected Events:

- Unexpected Unrelated Event: the SAE is unexpected based on the known information about the drug or the underlying condition and is not considered related to the study drug. This is referred to as an Unexpected SAE.
- Unexpected Related Event: the SAE is unexpected based on the known information about the drug or the underlying condition and is considered possibly, probably or definitely related to the study drug. This is referred to as a SUSAR – Suspected Unexpected Serious Adverse Reaction.

Fetal or neonatal death and maternal death and maternal life-threatening complications should always be considered unexpected events in this population and require immediate reporting.

### **13.4 Procedure for AE and SAE Reporting**

All AEs and SAEs must be documented in the participant's CRF. SAEs may also require immediate reporting by the site, as below:

Actions for SAEs:

1. Report immediately, within 24 hours of becoming aware of the event:
  - SAR – suspected adverse reaction.
  - Unexpected SAE.

- SUSAR – Suspected Unexpected Serious Adverse Reaction.
2. Documented in the CRF only (do not require immediate reporting):
- Expected SAE.

Unexpected SAEs, SUSARs and SARs will be reported to the C\*STEROID DMC, regulatory authorities and ethics committees, as required.

### **13.5 Data and Safety Monitoring**

A Safety Monitoring Committee (SMC) will review all serious adverse events. This committee will include a senior obstetrician and a senior neonatologist, as a minimum. The SMC will report to the Trial Steering Committee (TSC). The TSC will report any safety issues to an independent Data Monitoring Committee (DMC).

The C\*STEROID DMC has established terms of reference and will include a senior obstetrician, a senior neonatologist and a biostatistician, as a minimum. The DMC will review trial safety, efficacy and conduct and report to the TSC.

### **13.6 Interim Analysis**

There are no planned interim analyses. The DMC will review adverse and serious adverse events and have the ability to recommend early termination if a clear and significant unfavourable benefit-to-risk profile is demonstrated.

## **14. CONFIDENTIALITY & DATA MANAGEMENT**

### **14.1 Confidentiality**

Participants will be assigned a study ID number and data will be recorded against this. Data will be entered onto hard copy CRFs and/or directly into an electronic eCRF database stored on secure servers. Access to the eCRF database will be controlled by unique user ID and password, with full electronic tracking log.

Completed hard copy CRFs and a copy of the signed consent form will be securely transmitted to the Auckland coordinating centre, including contact details with identifying information for the purpose of enabling longer term follow up. Electronic and hard copy data will be securely stored in the Liggins Institute, The University of Auckland for a minimum of 10 years (maternal) and for a minimum of 10 years after the age of majority (child). Study reports will contain only summary data. Identifiable data will not be reported or released to any third party.

We will utilise social media to raise awareness of the C\*STEROID Trial. This will allow participants to potentially identify themselves. The participant information sheet and consent form will include reference to this.

All investigators, clinicians and participants will remain blinded to treatment allocations throughout the study. If a participant is un-blinded due to an urgent clinical need to reveal the

study allocation the investigator is advised to limit the distribution of this information to other site staff or study personnel.

#### **14.2 Access to Data and Data Sharing**

The Trial Steering Committee will have access to the full dataset and oversee analysis, interpretation and reporting of results. The de-identified data that support the findings of this study will be made available upon request to researchers who provide a methodologically sound proposal and whose proposed use of the data has been approved by an independent review committee identified for this purpose following publication of the primary C\*STEROID Trial results.

#### **14.3 Data Management Plan**

Further detail regarding data management is documented in the Data Management Plan.

### **15. OUTCOME MEASURES**

#### **15.1 Primary Outcome**

We have selected co-primary outcomes to accurately assess benefit *and* harm. These are:

- **Co-primary outcome (neonatal benefit):** incidence of respiratory distress requiring >60 minutes\* of respiratory support. Includes mechanical and non-invasive ventilation where sum of both is >60 minutes (e.g. intermittent positive pressure via endotracheal tube, nasal continuous positive airway pressure, Hi- or Lo-flow oxygen/air mix or increased ambient oxygen delivered into an incubator). *\*>60 minutes selected to eliminate short-term support which may be subject to variation by clinician.*
- **Co-primary outcome (neonatal harm):** incidence of hypoglycaemia (blood glucose level <2.6 mmol/L) prior to primary hospital discharge.

We hypothesise that corticosteroid use will reduce neonatal respiratory distress without increasing neonatal hypoglycaemia and therefore have selected co-primary outcomes of a superiority endpoint for benefit and non-inferiority endpoint for harm. The efficacy of corticosteroids is based on the success of both co-primary endpoints; therefore, no multiplicity adjustment is necessary.<sup>40</sup>

#### **15.2 Secondary Outcomes**

The following clinically relevant, reproducible and easily defined neonatal and maternal outcomes that reflect potential benefit and/or harm will be collected:

- NNU admission
- Duration of NNU stay
- Duration of neonatal hospital stay (to primary hospital discharge)

- Duration of neonatal respiratory support (sum of mechanical and non-invasive)
- Severe respiratory distress defined as any mechanical ventilation and/or need for surfactant therapy; moderate respiratory distress defined as respiratory support (sum of mechanical and non-invasive) for >24 hours
- Severe neonatal hypoglycaemia defined as blood glucose level <1.2 mmol/L
- Early onset infection and/or late onset infection as defined by ANZNN<sup>46</sup>
- Maternal self-reported adverse effects of injections including gastrointestinal upset; insomnia; pain, bruising or infection at injection site;
- Maternal perinatal infectious morbidity requiring postpartum antibiotic therapy;
- Duration of maternal postnatal stay (to primary hospital discharge);
- Breastfeeding (exclusive and full) at six weeks postpartum, and
- Maternal wellbeing and psychological status measured at six weeks postpartum.

### 15.3 Childhood Outcomes

Assessment in childhood is beyond the scope of current funding cycles. However, plans to assess childhood benefits and harms is an important and unique feature of the trial. Trial consent will include a request to maintain contact with families for later invitation to follow-up studies, and for Australian sites, we will include an option to consent for later linkage to maternal and child health records and child educational records.

We anticipate C\*STEROID children will undergo a multi-dimensional assessment at 6-7 years of age co-ordinated through the Liggins Institute Follow-up Programme. This assessment has been designed to be portable for school or office use; completed within a typical school timetable block; and conducted and analysed using a tablet computer. Tests can be administered by trained assessors and do not require the presence of a paediatrician or psychologist. Parent surveys with high readability can be completed online or in hard copy. Using this method we will be able to assess accurately neurocognition (language, memory, executive function, sensory processing, motor function) health and wellbeing (emotion, behaviour, physical health, growth) and cardiometabolic function (body composition, musculoskeletal and vascular development).

## 16. STATISTICAL ANALYSES

Data will be analysed on an intention-to-treat basis. To account for the correlation of twins, we will use marginal logistic regression model via generalised estimating equations to assess the treatment effect on respiratory distress adjusting for randomisation variables and other confounders which may influence the outcome of interest including by indication for CS. Two sided-p-values less than 0.05 will be used to determine statistical significance and confidence intervals will be reported at a two-sided 95% level. Farrington-Manning score test<sup>47</sup> will be used for assessing non-inferiority to compare hypoglycaemia rate between the two groups. Non-inferiority is established if the upper limit of the 90% confidence interval of the proportion difference between the two groups (steroid-placebo) is not greater than 10%. Descriptive summary statistics will be provided for continuous variables with mean, standard deviation, median, minimum and maximum and for categorical variables with frequency and percentage for each category.

## **17. STUDY TIMELINE**

### **2020**

Protocol preparation, New Zealand national ethics application, New Zealand site engagement/local governance

Commence recruitment to at least 50% of New Zealand sites

Applications for Australian site funding

Australian site engagement, commence Australian ethics and governance applications

### **2020 - 2023**

Recruitment, data collection and data cleaning

### **Mid 2024**

C\*STEROID Trial data analysis and results publication

*Children will be invited to participate in the later childhood outcome study at 6-7 years of age from 2025 (pending funding)*

## **18. ETHICS & REGULATORY**

The trial will be conducted in accordance with the internationally accepted standards set out in the CHMP guidance document EMA/CHMP/ICH/135/95 Guideline for Good Clinical Practice E6(R2) published by the European Medicines Agency (EMA) (the CHMP GCP guideline), as well as any addendum, amendment or regulation which applies in the region where the trial is being carried out.

All participating sites will have received ethics approval by an Institutional Review Board or Ethics Committee, local hospital governance approval and regulatory approval (if applicable) before commencing recruitment. Ethics approval for NZ sites has been granted by the NZ HDEC, ref: 20/NTB/166.

## **19. FUNDING**

The C\*STEROID Trial is funded by the Health Research Council of New Zealand (20/184). Additional funds that supported the C\*STEROID Feasibility Study have supported the set-up for the main trial including grants from Cure Kids, Lottery Health Research New Zealand, the Hugo Charitable Trust and the University of Auckland Faculty Research Development Fund.

Further funding applications will be made to support the participation of Australian sites.



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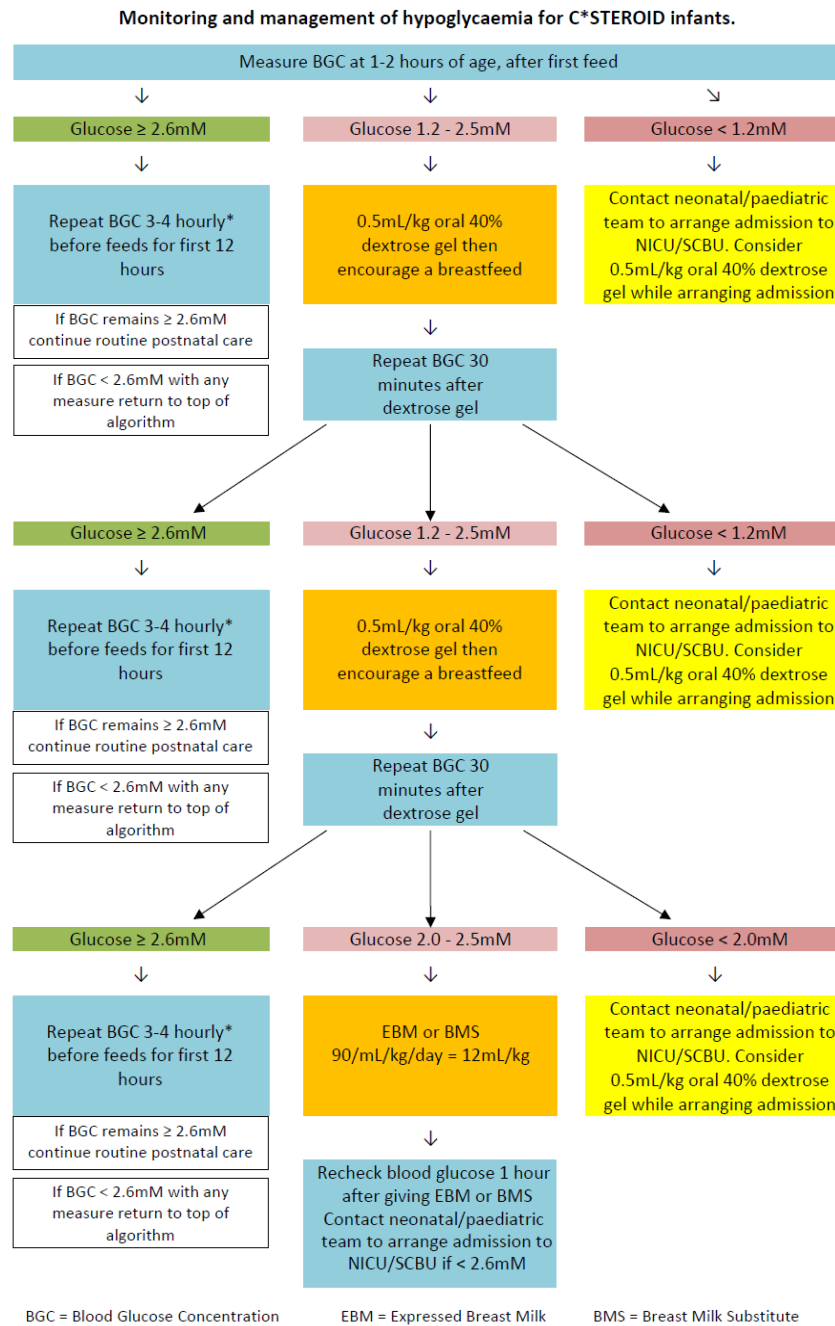
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## 21. APPENDIX

### Algorithm for the monitoring and management of hypoglycaemia for C\*STEROID infants.



This algorithm has been prepared using:

**ADHB guideline for the management of hypoglycaemia**

<https://www.starship.org.nz/for-health-professionals/newborn-services-clinical-guidelines/h/hypoglycaemia-in-the-neonate/>

**Oral Dextrose Gel to treat Neonatal Hypoglycaemia: Clinical Practice Guidelines**

[https://www.fmhs.auckland.ac.nz/assets/fmhs/som/paed/docs/Oral\\_dextrose%20gel\\_%20guideline2.pdf](https://www.fmhs.auckland.ac.nz/assets/fmhs/som/paed/docs/Oral_dextrose%20gel_%20guideline2.pdf)

\*For infants that meet criteria for routine BGC testing, e.g. small for gestational age, large for gestational age, preterm, the C\*STEROID algorithm can be applied, however, BGC testing should be done 3 hourly and it is recommended that the neonatal/paediatric service should be notified if BGC is < 2.0mM at any stage. For infants receiving BGC testing for C\*STEROID only it is appropriate to BGC at 3-4 hourly intervals.