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Corticosteroids to safely reduce neonatal respiratory morbidity after late preterm and term planned caesarean section birth? A randomised placebo-controlled feasibility study

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ABSTRACT

Objectives To assess the feasibility of conducting a randomised placebo-controlled trial of corticosteroids prior to planned caesarean section from 35^{+0} to 39^{+6} weeks.

Design A triple-blind, placebo-controlled, parallel, trial randomised at the participant level (1:1 ratio). Additional feasibility data obtained by questionnaires from trial participants and women who declined trial participation, and focus groups with local site researchers and clinicians.

Setting Three obstetric units in New Zealand including tertiary and secondary care; public and private care, and research active and non-active units.

Participants Women undergoing a planned caesarean section from 35^{+0} to 39^{+6} weeks; local site researchers and clinicians.

Interventions Two doses of 11.4 mg betamethasone or saline placebo. Questionnaires and focus group meetings.

Primary and secondary outcome measures Primary outcome: trial recruitment rate of eligible women. Secondary outcomes: trial recruitment by gestational age, site and delivery indication; proportion of babies who completed measurements of blood glucose concentrations as per protocol; overall incidence neonatal respiratory distress requiring >60 min of respiratory support; overall incidence of neonatal hypoglycaemia, and barriers and enablers to trial participation by participants, researchers and clinicians.

Results The recruitment rate was 8.9% (88/987) overall and 11.2% (88/789) for those approached about the trial. Neonatal blood glucose concentrations were measured as per protocol in 87/92 (94.6%) babies. For potential participants, key enablers to participation were contributing to research, a feeling of relevance and a good understanding; key barriers were a lack of understanding and concerns over safety. For researchers and clinicians, themes representing enablers and barriers included relevance, communication and awareness, influences on women's decision-making, resource challenges and trial process practicalities.

Conclusions Some women are willing to participate in a randomised placebo-controlled trial of corticosteroids prior to a planned caesarean section birth at late preterm and term gestations. Participation in such a trial can be enhanced.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The multicentre nature and inclusion of three different types of hospitals as recruiting sites strengthen the generalisability and applicability of the results.
⇒ The inclusion of questionnaires for women who declined participation in the randomised trial strengthens the identification of barriers and enablers to participation in this trial as well as clinical trials research for pregnant women more broadly. However, this is limited as not all women who declined trial participation agreed to complete questionnaires.
⇒ The inclusion of researchers and clinicians, as well as potential participants, provides additional information on enablers and barriers, including practical trial processes.
⇒ The limited duration of this study means it was not able to explore the effect of the resources developed on recruitment rates within the randomised trial.

INTRODUCTION

The rate of birth by caesarean section (CS) has continued to increase globally with an average year-on-year increase of 3.7% from 2000 to 2015, by which time almost 30 million births per year were by CS.[1] Birth by a planned or elective CS is a planned procedure before or following the onset of labour where the decision to have a CS has been made before labour.[2] Planned CS birth may provide some protection to the newborn but also imposes additional risk compared with planned vaginal birth.[3] The major risk is neonatal respiratory morbidity which, although typically self-limiting in term and late-preterm

babies, often requires neonatal unit admission for monitoring and/or respiratory support, separating mother and baby and interfering with breastfeeding and bonding.

The risk of neonatal respiratory morbidity after planned CS increases with decreasing gestational age[4 5]; hence, national and international clinical practice guidelines recommend delaying planned CS until ≥39^{+0} weeks.[3 6 7] However, even at 39^{+0} to 39^{+6} weeks the risk of respiratory morbidity is increased twofold compared with infants whose mothers plan a vaginal birth[5] and planned CS may still be necessary on maternal and/or fetal grounds at late-preterm and early-term gestations. Beyond timing of birth, there are no other evidence-based interventions to protect the neonate from this adverse effect of birth by planned CS.

The administration of corticosteroids to mothers prior to early-preterm birth accelerates fetal lung maturation and reduces short-term respiratory morbidity without short-term or long-term harm[8] and is considered standard of care for births <35 weeks gestation.[7 9–11] Less is known about the benefits and potential harms of corticosteroids given from 35 weeks gestation and, specifically, prior to planned CS. Recent systematic and Cochrane reviews suggest significant neonatal respiratory benefit after both late-preterm birth, regardless of mode of birth,[12 13] and term planned CS birth.[13] However, for those trials included in the Cochrane review the risk of bias was moderate and the overall quality of evidence considered low indicating that the true effect of corticosteroids may be substantially different to the estimate of effect.[13] The quality of these trials has been questioned further[14] raising more concern over the validity of results. Furthermore, the unexpected finding of an increased rate of neonatal hypoglycaemia in the largest trial of corticosteroid use prior to late-preterm birth[15] requires further consideration. To date, none of the trials of corticosteroid use prior to planned CS have reported on rates of neonatal hypoglycaemia.

It is physiologically plausible that maternal corticosteroid use prior to birth may cause neonatal hypoglycaemia. Neonatal hypoglycaemia in the setting of other conditions has been associated with later effects on neurodevelopment in early childhood, including executive function and visual-motor skills, and numeracy and language skills in mid-childhood.[16] There is no randomised evidence regarding longer term safety of corticosteroids after late-preterm birth and only very limited randomised evidence after planned CS which suggests an association between maternal corticosteroid use and poorer academic ability at school age.[17]

High-quality evidence on the benefits and harms of corticosteroid use prior to planned CS at late-preterm and term gestations is needed to guide best practice for this common obstetric intervention. In planning a randomised controlled trial to generate this high-quality evidence, we identified the need for a trial able to assess both newborn benefit (neonatal respiratory morbidity) and potential harm (neonatal hypoglycaemia), as well as to create a cohort to assess the longer term effects of this intervention. We estimated that 2548 babies and their mothers will need to be included to achieve these goals. Undertaking a trial of this nature and size requires thoughtful consideration and planning to ensure that it is fundable, implementable, acceptable, efficient and ultimately, achievable. We undertook the C*STEROID Feasibility Study to support the development of the C*STEROID Trial.

The aims of the C*STEROID Feasibility Study were to identify women's willingness to participate in a randomised placebo-controlled trial of corticosteroids prior to planned CS from 35^{+0} to 39^{+6} weeks; explore the reasons they were willing or not willing to participate; explore the barriers and enablers to participation for women, clinicians and local site researchers, and to establish and optimise trial processes to enable effective and efficient conduct of a multicentre trial.

METHODS

We conducted the C*STEROID Feasibility Study in three New Zealand obstetric units. The study included a triple-blind, placebo-controlled, parallel, trial randomised at the participant level (1:1 ratio) with additional feasibility data obtained by questionnaires to trial participants (at recruitment and 6 weeks after birth) and to women who declined randomised trial participation, and via focus groups including local site researchers and clinicians. The study was planned for a 12-month period. National ethics approval was provided by Southern Health and Disability Ethics Committee (18/STH/227) with governance approval obtained at each site. The trial was prospectively registered with the Australian New Zealand Clinical Trials Registry ACTRN=12618002028280 registered 18/12/2018 (trial protocol online supplemental appendix 1) and sponsored by The University of Auckland.

Women were recruited from National Women's Health, Auckland City Hospital (research active tertiary unit including private obstetric practice), Tauranga Hospital (research active secondary obstetric unit with no private obstetric practice) and, for the last 3 months of the study, Waikato Hospital (tertiary unit with no private obstetric practice and limited research activity). Inclusion criteria were: a planned prelabour CS at 35^{+0} to 39^{+6} weeks gestation; >24 hours and <7 days to planned birth and; singleton or twin pregnancy. Exclusion criteria were: diabetes (pre-existing or gestational); major fetal abnormality; and prior intramuscular corticosteroid use in current pregnancy. Local site research staff and clinicians identified eligible women through antenatal clinics and booked CS lists and invited them to participate in the randomised trial; those who were eligible but declined participation were invited to complete a questionnaire to identify the reasons for declining. All participants provided written informed consent.

Randomised trial

Women participating in the randomised trial provided baseline data regarding demographics, medical and

obstetric history, and pregnancy details. At recruitment, participants completed the Short Form Health Survey (SF-36)[18] and the Edinburgh Postnatal Depression Scale[19] to assess baseline quality of life and mental well-being, respectively, and a questionnaire exploring their knowledge of risks and benefits of planned CS birth and use of corticosteroids, along with reasons for consenting to participate in the trial and factors that encouraged or discouraged participation.

The trial statistician prepared the computer-generated randomisation sequence balanced in mixed block sizes with stratification according to gestational age at planned CS (35^{+0} to 36^{+6}, 37^{+0} to 38^{+6} and 39^{+0} to 39^{+6} weeks), recruiting site and singleton or twin pregnancy. A central web-based randomisation service assigned participants to receive betamethasone or placebo via a unique study identifying number and an allocated treatment pack number. Participants, care providers and investigators were blind to treatment allocation. Participants received two doses of 11.4 mg betamethasone (Celestone Chronodose) or saline placebo in visually matching syringes by intramuscular injection into the buttock/thigh 24 (±4) hours apart, administered by research staff within 7 days of planned CS birth. Betamethasone and placebo syringes were prepared by Baxter Healthcare New Zealand, for which drug stability was confirmed by independent laboratory testing. An investigator independent to trial participant activity packaged two syringes per allocation into sealed treatment packs with the allocated treatment pack number. Participants were supplied with a safety Subject Alert Card and asked to report any potential adverse effects.

Care of the woman at CS and during the antenatal and postnatal periods was determined by the local responsible obstetric and midwifery teams; care of the neonate was the responsibility of the local paediatric and midwifery teams. Neonatal blood glucose concentrations were measured using a glucose oxidase method point-of-care device, following an 'at-risk' infants protocol (after first-feed at 1–2 hours of age, then prefeed 3 to 4 hourly until 12 hours of age).[20] If hypoglycaemia (blood glucose concentration <2.6 mmol/L) occurred, treatment following a standardised protocol[21] was recommended and testing continued until at least 12 hours after last low blood glucose. Data on treatment provided for hypoglycaemia and any additional clinically indicated blood glucose concentrations measured in the neonatal period were collected.

Birth, maternal and neonatal outcome data were collected from clinical records until the time of primary hospital discharge. Six weeks after birth, participants were sent an electronic questionnaire to assess breastfeeding, any readmissions or new maternal infections, degree of satisfaction with pregnancy care and trial participation, and the SF-36 and Edinburgh Postnatal Depression Scale. All data were entered into electronic case records on a web-based data collection system (REDCap). Data quality was systematically and manually reviewed at regular intervals throughout the trial.

Declined randomisation participants

Women who declined to participate in the randomised trial were invited to complete a questionnaire including demographic and obstetric history information, indication for CS birth, knowledge of risks and benefits of planned CS birth and use of corticosteroids, reasons for deciding not to participate in the trial and factors that may have encouraged or discouraged their participation.

Patient and public involvement

The study design was informed by a 2-day multidisciplinary trial development workshop that included consumers and a survey of 63 women undergoing a planned CS birth at 35^{+0} to 39^{+6} weeks. This survey explored women's attitudes to corticosteroid use, interest in participation in a randomised trial and outcomes of importance for their infant/child.[22] Within this study women participating in the randomised trial and those that declined participation in the trial were asked to comment on the burden of the intervention and reasons for participating or not. Consenting participants will be provided with summary results once the study has been completed.

Clinician and researcher focus groups

A single investigator (JC) facilitated focus group meetings including local site researchers and clinicians at two sites (one tertiary and one secondary unit) after 5 months of active recruitment. Invitations to participate were sent via email to all trial researchers at each site and to interested individual clinicians. Participants provided written consent. Open-ended questions facilitated group discussion with additional prompting questions on trial progress being used as required. Each meeting was recorded and transcribed. Data were anonymised before qualitative reflexive thematic analysis[23] was undertaken to identify themes of barriers and enablers to recruitment and trial processes. Barriers were identified as modifiable or non-modifiable. For the non-modifiable barriers, the underlying issue cannot be changed but the barrier may be able to be ameliorated. Enablers were identified as positive and helpful underlying principles and values or as factors that need to be continued, emphasised or developed and reinforced or supported.

Trial outcomes

The primary outcome of this feasibility study was recruitment rate to the randomised trial calculated as the number of participants recruited/number of individuals identified as eligible. Secondary outcomes from the randomised trial were: recruitment rates by gestational age (35^{+0} to 36^{+6}, 37^{+0} to 38^{+6} and 39^{+0} to 39^{+6} weeks), indication for CS birth and site; proportion of babies who completed measurements of neonatal blood glucose concentrations as per protocol; overall incidence of each of the planned coprimary outcomes for the main C*STEROID trial (respiratory distress requiring >60 min of respiratory support and hypoglycaemia prior to primary hospital discharge). Further secondary outcomes

across the feasibility study were barriers and enablers to trial participation by participants, research staff and clinical staff.

Sample size calculation, analysis and trail monitoring

Since this was a feasibility study, a sample size calculation was not performed and sample size was determined by study duration. A 12-month period was selected as this deemed to be sufficient to allow for set-up and familiarisation with the study and to reach a steady recruitment state in the second half of the study to allow accurate assessment of recruitment rates (primary outcome) across three different recruiting sites. There was no prespecified criteria to determine whether or not to proceed with a definitive trial based on numbers recruited or recruitment rate as the main goal of the C*STEROID Feasibility Study was to enhance and understand challenges of recruitment and trial process to support a future definitive trial. Descriptive statistics were used for demographic and other baseline data. Data were analysed and reported as an overall group and not by study treatment group. Participants, care providers and investigators remain blind to treatment allocations to allow outcome data to contribute to the main C*STEROID Trial. A Safety Committee reviewed all adverse and serious adverse events. An independent Data Monitoring Committee monitored trial progress and all serious adverse events. The Consolidated Standards of Reporting Trials reporting guidelines have been used.[24]

RESULTS

The C*STEROID Feasibility Study was open for recruitment from 14 June 2019 until 23 March 2020. The study closed after 9 months due to New Zealand Level 4 COVID-19 restrictions; all study objectives had been met. A total of 88 women and 92 babies participated in the randomised trial, 127 women who declined trial participation completed a questionnaire and 4 focus groups included 13 clinicians and 8 local researchers.

Recruitment rates

A total of 1517 women had planned CS births during this time, 987 were eligible for participation in the randomised trial, 789 were approached, 88 agreed to participate and 127 declined but agreed to complete questionnaires (17.8% of those approached) (figure 1). The randomised trial recruitment rate was 8.9% (88/987) overall, 11.2% (88/789) of those approached. Recruitment rate did not vary by gestational age group, indication for planned CS birth or recruiting site (table 1).

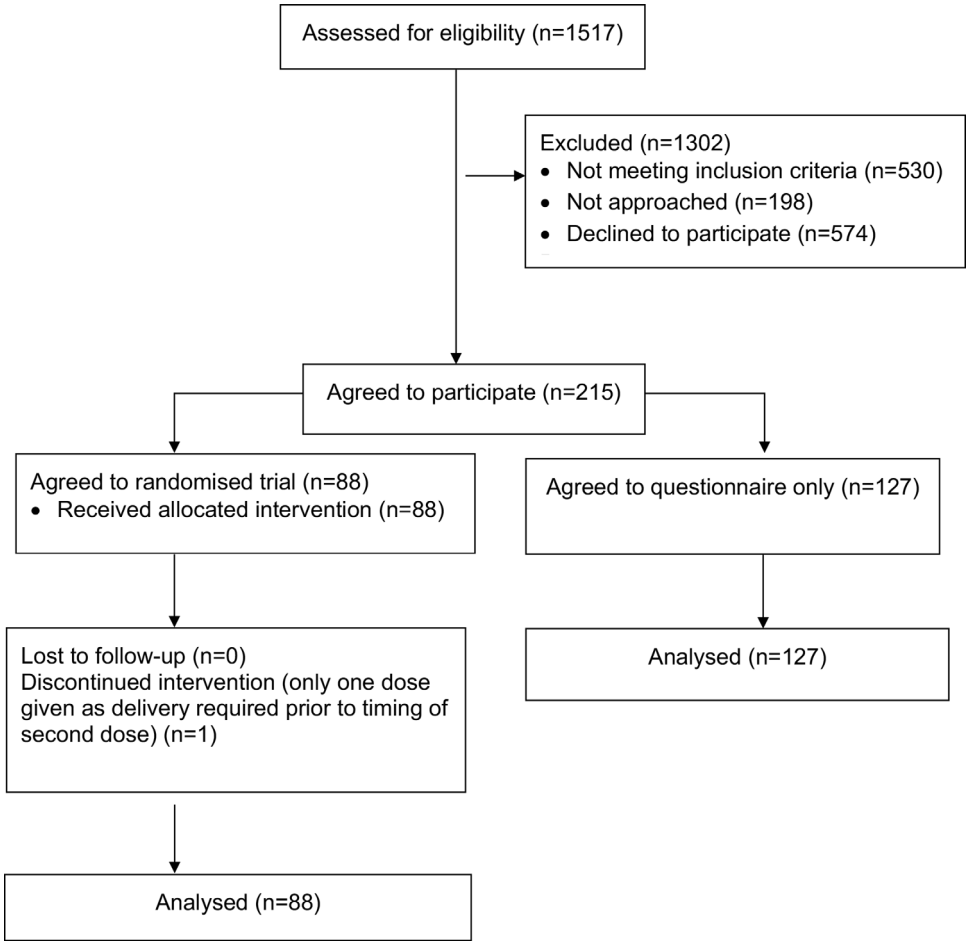

Figure 1 Consolidated Standards of Reporting Trials flow diagram of participation in the C*STEROID Feasibility Study.

Table 1 Rates of recruitment to the C*STEROID Feasibility Study randomised trial

	Recruitment rate n/N (%)
Whole study population	88/987 (8.9)
Study population approached	88/789 (11.2)
Gestational age at time of planned CS birth	
35^{+0} to 36^{+6} weeks	5/30 (16.7)
37^{+0} to 38^{+6} weeks	34/363 (9.4)
39^{+0} to 39^{+6} weeks	49/594 (8.2)
Primary indication for CS birth*	
Placenta praevia and/or accreta	6/26 (23.1)
Breech or transverse lie	5/71 (7.0)
Previous CS	36/407 (8.8)
Twin pregnancy	1/14 (7.1)
SGA/FGR or other fetal concern	2/7 (28.6)
Maternal medical condition	4/36 (11.1)
Maternal request	4/59 (6.8)
Other	3/64 (4.7)
Recruiting site	
Auckland City Hospital	61/684 (8.9)
Tauranga Hospital	21/185 (11.4)
Waikato Hospital†	6/118 (5.1)

Recruitment rates calculated by the number of participants recruited/number of individuals identified as eligible.
*Data for recruitment rate by primary indication for CS birth includes Auckland participants only due to incomplete denominator data for other sites (n=61/684).
†Waikato Hospital only actively recruiting for 3 months.
CS, caesarean section; FGR, fetal growth restriction; SGA, small-for-gestational age.

Randomised Trial

Demographic and pregnancy characteristics of those in the randomised trial are summarised in table 2. Participants had a mean maternal age 34.7 years (SD 4.8), mean body mass index 25.7 kg/m^2 (SD 5.5), 4 (4.5%) were current smokers, 18 (20.5%) had complications in their pregnancy including gestational hypertension/preeclampsia (5, 5.7%), presumed small-for-gestational-age fetus/fetal growth restriction (10, 11.4%), antepartum haemorrhage >20 weeks (3, 3.4%), preterm prelabour rupture of membranes (1, 1.1%) or an identified fetal anomaly (1, 1.1%). There were 4 (4.5%) women with a twin pregnancy resulting in a total of 92 babies in the randomised trial. The primary indication for CS is shown in table 2; 43 (48.9%) participants also had secondary indications contributing to their plan for CS birth. The majority had CS birth planned for 39^{+0} to 39^{+6} weeks (49/88, 55.7%) or 37^{+0} to 38^{+6} weeks (34/88, 38.6%). Only 5/88 (5.7%) had a planned CS at 35^{+0} to 36^{+6} weeks (table 1).

Table 2 Demographic and obstetric characteristics of participants in the randomised trial and those completing the declined trial questionnaire

	Randomised trial n=88 women	Declined trial questionnaires n=127 women
Recruiting site		
Auckland City	61 (69.3)	104 (81.9)
Tauranga	21 (23.9)	10 (7.9)
Waikato	6 (6.8)	13 (10.2)
Maternal age		
<30 years	12 (13.6)	17 (13.4)
30–39 years	64 (72.7)	92 (72.4)
>40 years	12 (13.6)	18 (14.2)
Primary ethnicity		
Māori	3 (3.4)	9 (7.1)
European	71 (80.7)	85 (66.9)
Pacific peoples	2 (2.3)	0
Asian	10 (11.4)	30 (23.6)
Middle Eastern/ Latin American/ African/other	2 (2.3)	3 (2.4)
CS care public/private*		
Public (including midwifery lead maternity carer and hospital lead maternity carer)	50 (56.7)	59 (47.2)
Private obstetric lead maternity carer	38 (43.2)	66 (52.8)
Number of previous pregnancies >20 weeks†		
0	19 (21.6)	38 (30.1)
1	48 (54.5)	57 (45.2)
≥2	21 (23.9)	31 (24.6)
Number of previous CS†		
0	25 (28.4)	44 (34.9)
1	49 (55.7)	56 (44.4)
≥2	14 (15.9)	26 (20.6)
Primary indication for CS‡		
Placenta praevia and/or accreta	6 (6.8)	3 (2.4)
Breech or transverse lie	7 (8.0)	18 (14.2)
Previous CS	58 (65.9)	73 (57.5)
Twin pregnancy	2 (2.3)	1 (0.8)
SGA/FGR or other fetal concern	3 (3.4)	2 (1.6)

Continued

Table 2 Continued

	Randomised trial n=88 women	Declined trial questionnaires n=127 women
Maternal medical condition	4 (4.5)	12 (9.4)
Maternal request	4 (4.5)	8 (6.3)
Other	4 (4.5)	11 (8.7)

*Two declined trial questionnaire participants did not respond to this question (n=125).
†One declined trial questionnaire participants did not respond to this question (n=126).
‡Primary indication for CS was identified by ranking each criteria for CS in the following order: placenta praevia, placenta accreta, breech or transverse lie, previous caesarean section, twin pregnancy, SGA/FGR fetus, maternal medical condition, maternal request, other fetal concern, other (including large baby, advanced maternal age, obstetric history, surgical history). Many participants had more than one indication for CS, most of which could be considered relative indications.
CS, caesarean section; FGR, fetal growth restriction; SGA, small-for-gestational-age.

A coding error (gestational age at recruitment rather than at planned CS birth) resulted in 47 women being allocated to an incorrect gestational age stratification group; this had no impact on the primary or any secondary outcomes of the study. The vast majority of participants (87/88, 98.8%) received both doses of study drug, one woman received only one dose as delivery was required prior to the scheduled second dose due to deteriorating maternal health. The mean time interval from first dose of study drug to birth was 3.6 days (SD 1.8). The mean gestational age at birth was 38^{+5} weeks (SD 5.9 days). Twenty participants gave birth prior to, or later than, their planned CS date, resulting in a discrepancy between actual gestational age at birth and stratified gestational age group for five participants.

Measurement of neonatal blood glucose concentrations as per protocol was achieved in 87/92 (94.6%) babies. Only one baby did not receive any blood glucose concentration measurements following an out-of-hours emergency CS birth after the onset of labour. Ten (10.9%) babies had respiratory distress requiring >60 min of respiratory support, all of whom required continuous positive airways pressure support. This was most common in those babies born at 35^{+0} to 36^{+6} weeks (5/7, 71.4%) but also occurred at term gestations (37^{+0} to 38^{+6} weeks 2/35, 5.7% and 39^{+0} to 39^{+6} weeks 3/50, 6.0%, respectively). Neonatal hypoglycaemia occurred in 44 (47.8%) babies and at similar rates in all gestational age groups: 35^{+0} to 36^{+6} weeks—3/7 (42.9%); 37^{+0} to 38^{+6} weeks—19/35 (54.3%) and; 39^{+0} to 39^{+6} weeks 22/50 (44.0%).

Participant questionnaires

All but one of the randomised trial participants (87/88, 98.9%) and 127 women who declined to participate in the randomised trial completed a questionnaire at recruitment (table 3). Women who agreed to participate in the randomised trial were more likely to have had the risks and benefits of planned CS (86/87, 98.9%) and antenatal corticosteroids (40/87, 46.0%) discussed with them by their care providers than those who declined participation (113/127, 89.0% and 31/127, 24.4%, respectively). The proportion of women willing to consider participation in a randomised trial varied by gestational age for planned CS.

The most common enablers to participation for those in the randomised trial included: wish to contribute to research and improving care for the future (75, 86.2%); good understanding of the trial (based on written and/or verbal information) (40, 46.5%); the trial was relevant to them and their baby (40, 46.5%); trial processes seemed simple and easy to follow (33, 38.4%); concern about safety for their baby's health (27, 31.4%); opportunity to receive corticosteroids (or placebo) (26, 29.9%); interested in having the longer-term outcomes for their baby being formally assessed (24, 27.9%); participation recommended by a healthcare provider (24, 27.9%); blood sugar testing for their baby (20, 23.3%); previous obstetric experience (own or family/friend) (8, 9.3%); ease of access/minimal extra commitment (8, 9.3%); participation recommended by family member or friend (7, 8.1%), and potential benefits to baby (7, 8.1%). The most common factor of concern regarding participation related to concern over safety for baby's health (21, 24.1%) and this was addressed by discussion with trial (12, 57.1%) and clinical staff (10, 45.5%) and rereading study information (7, 31.8%). Supporting quotes for each theme are included in online supplemental appendix 1.

The most common barriers to participation for those who declined the randomised trial included: concern about safety for baby's health (68, 53.5%); concern about safety for own health (39, 30.7%); lack of understanding of potential effects of corticosteroids (37, 29.1%); not relevant to them and baby (35, 27.6%); unable/unwilling to attend hospital appointments for study injections (34, 26.8%); wish to avoid blood sugar testing for their baby (31, 24.4%); avoid longer term involvement in research (21, 16.5%); avoid injections for themselves (19, 15.0%); not enough time to consider involvement (16 12.6%); prefer to minimise unnecessary intervention (15, 11.8%); lack of understanding of the trial (based on written and/or verbal information) (14, 11.0%); avoid questionnaires 6 weeks after baby was born (10, 7.9%); experiences in previous or current pregnancy, or difficulty conceiving (10, 7.9%); lack of discussion and/or endorsement or advised not to participate by a healthcare provider (10, 7.9%). Factors that could be modified to increase recruitment included: earlier information and approach; more information about safety to mother and baby, and discussion and recommendation by own care provider. Factors

Table 3 Questionnaire responses regarding caesarean section (CS) risk, corticosteroid use and willingness to participate in a randomised trial by gestational age

	Randomised trial n=87 women (1 non-responder)	Declined trial questionnaires n=127 women	P value*
Have you received corticosteroids in a previous pregnancy for any reason?			
Not applicable (first pregnancy)	18 (20.7)	38 (29.9)	0.06
Yes	1 (1.1)	7 (5.5)	
No	68 (78.2)	82 (64.6)	
Has your main pregnancy care provider or any other medical staff discussed the risk and benefits of planned CS with you?			
Yes	86 (98.9)	113 (89.0)	0.005
No	1 (1.1)	14 (11.0)	
Prior to consideration of this trial has your main pregnancy care provider or any other medical staff discussed the risks and benefits of antenatal corticosteroids before your planned CS with you?			
Yes	40 (46.0)	31 (24.4)	<0.0001
No	47 (54.0)	96 (75.6)	
If antenatal corticosteroids were offered to you (outside of this clinical trial) before your planned CS, would you accept them?			
Yes	70 (80.4)	39 (30.7)	<0.0001
No	16 (18.3)	83 (65.3)	
No response	1 (1.1)	5 (3.9)	
Would you have been willing to participate in a clinical trial of antenatal corticosteroids vs placebo before your planned CS if it was offered by the team caring for you if your CS was planned at 35^{+0} to 36^{+6} weeks?			
Yes	72 (82.8)	45 (35.4)	<0.0001
No	8 (9.2)	66 (52.0)	
Not applicable (CS at this gestation)	3 (3.4)	8 (6.3)	
No response	4 (4.6)	8 (6.3)	
Would you have been willing to participate in a clinical trial of antenatal corticosteroids vs placebo before your planned CS if it was offered by the team caring for you if your CS was planned at 37^{+0} to 38^{+6} weeks?			
Yes	65 (74.7)	19 (15.0)	<0.0001
No	3 (9.2)	85 (66.9)	
Not applicable (CS at this gestation)	15 (17.2)	14 (11.0)	
No response	4 (4.6)	9 (7.8)	
Would you have been willing to participate in a clinical trial of antenatal corticosteroids vs placebo before your planned CS if it was offered by the team caring for you if your CS was planned at 37^{+0} to 38^{+6} weeks?			
Yes	55 (63.2)	8 (6.3)	<0.0001
No	5 (5.7)	72 (56.6)	
Not applicable (CS at this gestation)	21 (24.1)	37 (29.1)	
No response	6 (6.9)	10 (7.8)	

*χ^2 test.

that may be modifiable included: better information about relevance of the trial and potential benefits of corticosteroids, and avoiding the need to travel for participation. Supporting quotes for each theme are included in online supplemental appendix 1.

Six weeks after birth, 77/88 (87.5%) randomised trial participants completed a questionnaire. Satisfaction rates with care provided for the C*STEROID Feasibility Study (64/77, 83.1%) were similar to those for care at the time of birth (62/77, 80.5%) and for overall postnatal care (62/77, 80.5%). The vast majority would recommend the trial to friend in a similar position (66, 85.7%) and be willing to participate again in the future (66, 85.7%). The most common factors identified by participants that they liked the best about participation were: contributing to research and knowledge (28, 46.7%); a supportive research team (16, 26.7%), and newborn blood sugar tests (13, 21.7%). The most common factors identified by participants that they liked the least about participation were: newborn blood sugar tests (22, 37.3%); nothing/not applicable (14, 23.7%), and needing to receive injections (9, 15.3%).

Clinician and local researcher focus groups

Two clinician focus groups included six hospital-employed midwives, two self-employed midwives and five obstetric doctors. Two local researcher groups included four research-specific staff (research midwives and nurses and a trial co-ordinator), two hospital-employed midwives and two obstetric doctors. Five main themes were identified as both barriers and enablers to trial participation and processes:

- Relevance of research: the importance of research as a whole and this specific research question, the concept and value of embedding research within day-to-day clinical practice, and if the research question is relevant to clinical practice and the individual participant.
- Resource challenges: for the maternity workforce in general with staff shortages at many levels leading to resentment and reluctance to undertake work perceived as extra or unnecessary. A lack of funded research positions in the secondary unit limited opportunity for trial activities.
- Awareness, knowledge and communication: for participants, maternity carers and research teams including trial promotion and general awareness. Approaches to individuals, and systems for communication with and within the research team including across site communication.
- Influences on women's decision-making: these ranged from practicalities, such as being able to attend appointments, to influences by trusted people and preconceived mindsets and ideas.
- Practical aspects of the trial process: these included: systems for identifying eligible women; arranging attendance; completing recruitment; drug administration; neonatal blood glucose concentration measurements, and the site researcher own appraisals of trial progress.

Supporting quotes for each theme are included in online supplemental appendix 1 (Supplementary file). For each theme barriers identified as modifiable or non-modifiable and enablers identified as those that were principles and values or as factors to be continued, emphasised or developed and reinforced or supported are shown in table 4.

DISCUSSION

The C*STEROID Feasibility Study has identified that some women are willing to participate in a randomised placebo-controlled trial of corticosteroids prior to a planned CS birth 35^{+0} to 39^{+6} weeks but that the recruitment rate was lower than anticipated. Wanting to contribute to research and improving outcomes for the future, along with a good understanding of the trial and feeling of relevance were leading enablers to participation. Lack of relevance and understanding and safety concerns were key factors contributing to decisions not to participate. Trial processes were effective, including the ability to monitor neonatal blood glucose concentrations for the vast majority. Workforce resources and clinician appreciation of the trial posed challenges to trial processes including recruitment, monitoring and data collection that can be improved to achieve higher recruitment rates.

A major strength of this study is the inclusion of three types of recruiting sites that face different challenges in contributing to multisite randomised trials making results generalisable and applicable to sites across New Zealand and Australia that are expected to contribute to the C*STEROID Trial. Learnings from this feasibility study will optimise recruitment rates and trial processes at all sites thereby improving the quality and efficiency of the definitive trial. The feasibility study was also able to identify process issues, such as the stratification coding error, to allow them to be rectified in advance of a larger trial. A further strength is the inclusion of opinions from those who did and did not participate in the randomised trial and from site clinicians and researchers on the barriers and enablers to trial participation and completion. These learnings have more broad implications for other multisite clinical trials and can be used by investigator groups in maternal and perinatal health and beyond. However, opinion from a third group of women, those who declined participation in the trial or to complete a questionnaire, may differ significantly and has not been able to be accounted for within this study.

For our primary outcome, the recruitment rate of 8.9% of all those eligible and 11.2% of all those approached is lower than expected and a potential concern for the much larger C*STEROID Trial. Variation in recruitment by site and over the course of the trial, as well as the information gained from other aspects of the feasibility study, suggests significant opportunities to increase recruitment towards more typical perinatal trial recruitment rates of 20%–25%.[25] Key themes identified from those who participated in the randomised trial, those who declined the randomised trial, local site researchers and local site clinicians related to awareness about the trial, information on relevance, safety and trial processes and endorsement by own healthcare providers. In response, a number of resources were developed including a participants' stories Facebook page, a participant introductory video available on the Facebook page and our trial website, participant information flyers in seven languages, pop-up clinic banners, a clinician video aide on trial introduction, clinician-focused educational webinar, site-specific PowerPoint presentations and clinician lanyards, trial pens and 'post-it notes'. The duration of the feasibility study meant that we were unable to assess the impact of these resources on recruitment rates.

Trial processes have been further developed to support both participant and trial site staff involvement. Electronic consent and questionnaires reduce trial-specific visits. To enable participation for those less able to travel for financial or distance reasons there will be provision of funds to support petrol and parking costs, trial-specific visits at peripheral clinics closer to their home and home or general practice visits for second study drug

Table 4 Themes of barriers and enablers to participation and trial processes identified from local site researchers and clinicians

Theme	Barrier	Enabler
Relevance of research	**Modifiable**	**Principle/value**
	Study question does not feel relevant	Clinicians feel research is important and should be embedded within clinical practice
	Clinicians have preconceived ideas	**Continue/emphasise/develop/reinforce/support**
	Not modifiable	Clinicians feel this is an important question that could change practice, women respond well to framing this way
	Another trial is competing and appeals more to potential participants	As familiarity with the trial improves, 'buy-in' improves
		Additional unexpected benefits from involvement in research include support with antenatal expressing, breast feeding and newborn period from trial staff
Resource challenges	**Modifiable**	**Principle/value**
	Lack of funded research positions	Site collegiality
	Not modifiable	**Continue/emphasise/develop/reinforce/support**
	Staffing crisis, resistance to additional workload	Awareness of trial processes minimises additional workload for ward staff
		Arranging study processes separate from acute clinical areas
		Research staff available and provide additional support to participants on postnatal ward
		Overtime rates can be paid to clinical staff to support research activity
		Clinicians are not responsible for completing all study processes
Awareness, knowledge and communication	**Modifiable**	**Continue/emphasise/develop/reinforce/support**
	Lack of awareness of the trial among potential participants and maternity carers	Creating awareness for clinicians by research presentations at clinical meetings, private practices, teaching sessions. Individual phone calls by research team to maternity carers
	Lack of awareness about role of antenatal corticosteroids in general public and clinicians	Creating awareness for potential participants (will be more receptive to contact by research team if already aware): posters, banners and information pamphlets in clinical areas including private obstetric practices, and by post with CS booking information
	Research staff often have difficulty in making contact with potential participants	Women are more receptive when research staff introduce themselves as 'research midwife' from 'university' or 'hospital'
	Maternity carers and potential participants often have difficulty in contacting research team as there is no clearly established communication system to register interest in the trial	Contact with potential participants can be via phone-call, email or text
	Not modifiable	A single C*STEROID email address and cellphone number creates ease of contact
	Isolation from central research team	Research staff available 5 days per week for timely replies to potential participants and maternity carers
	Lack of time for clinicians to discuss the trial with women	Staff incentives encourage interest and involvement: regular cake deliveries, monthly prize draw
		Central research team is in regular contact with sites
Influences on women's decision-making	**Modifiable**	**Continue/emphasise/develop/reinforce/ support**
	Difficulty in attending appointments	Appointment times can be coordinated to suit the participant
	Partner may decline (partners are not often directly involved in discussion)	Free parking to attend study visits
	Not modifiable	Second study drug can be given at home or alternate location
	Previous obstetric experiences	Support from carers
	Concern over study drug injections and/or of heel pricks for babies deters some	Support from family/partner
	Some potential participants do not want placebo; or wish to know what they are receiving	Prior awareness of the trial including recommendation by word of mouth
	Belief that 'nothing is best' when it comes to medications in pregnancy	
	Lack of certainty on possible harms to baby	
	Reluctance to be involved in any sort of research	

Continued

Table 4 Continued

Theme	Barrier	Enabler
Practical aspects of the trial process	**Modifiable**	**Principle/value**
	Initial confusion with study processes and individual site team member responsibilities	Small team provides good continuity
	Lack of timely contact to participants by research team	Researchers have some prior familiarity with REDCap (data entry system)
	REDCap (data entry system) is time consuming; programme not intuitive when switching between pages	Clinical staff are familiar with i-STAT for neonatal blood glucose measurements
	Lack of easy computer access for research staff	**Continue/emphasise/develop/reinforce/support**
	Participants have been surprised by numbers of blood glucose measurements required for baby	Good processes for identification of eligible women
	Confusion around need for neonatal blood glucose measurements if participant has birth earlier than planned	Clear recruitment systems within research team
	Lack of familiarity with equipment (i-STAT) for neonatal blood glucose measurements	Step-by-step written instructions are available; randomisation can be done quickly once familiar
	Neonatal blood glucose concentration recording sheet can be confusing	Drug administration can often be accommodated to suit the participant
	Pressure to move participants from theatre recovery area to ward at time of neonatal blood glucose measurements	Ensuring participants are aware of minimum number blood glucose measurements required for baby, possibility of low level and how that will be treated
	Delays in receiving information from primary unit (when postnatal transfer has occurred) or through electronic records	Yellow stickers for clinical note alerts have been helpful
	Not meeting expectations with low recruitment rate despite significant effort required for each recruit can be demoralising	Research staff perform majority of blood glucose measurements
	Not modifiable	Data entry is straightforward
	CS booked late can be missed	Regular communication and support from central research team
	Timing of elective CS lists and coordination with study drug injections can be problematic	Morale improved knowing site recruitment rate was better than lead research site
	Study drug has short expiry	
	i-STAT for neonatal blood glucose measures is time consuming	

Barriers were identified as modifiable or non-modifiable. For the non-modifiable barriers, the underlying issue cannot be changed but the barrier may still be able to be ameliorated. Enablers were identified as those that were positive and helpful underlying principles and values or as factors that need to be continued, emphasised or developed and reinforced or supported.
CS, caesarean section.

doses. The availability of a video tutorial for measuring newborn blood glucose concentrations supports clinical staff contributions to postnatal monitoring. The primary investigator team has supported local funding applications to enhance per participant payments supplied from the central research budget to fund site research staff or enable additional payments to clinical staff to reward their contributions.

The safety and effectiveness of corticosteroids prior to planned CS from 35^{+0} weeks gestation remain unknown. Data from this feasibility study has significantly strengthened the C*STEROID Trial to be a high-quality trial with sufficient power to answer this question. The C*STEROID Trial (ACTRN12620000914965) has been awarded competitive peer-reviewed funding from government funding bodies in New Zealand (Health Research Council) and Australia (Medical Research Futures Fund) and commenced recruitment using the tools and resources developed in response to this study.

CONCLUSION

Some women are willing to participate in a randomised placebo-controlled trial of corticosteroids prior to a planned CS birth at late preterm and term gestational ages. Participation in such a trial can be enhanced.

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Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

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Data availability statement Data are available upon reasonable request. The deidentified data that support the findings of this study may be made available upon request to researchers who provide a methodologically sound proposal, whose proposed use of the data has been approved by an independent review committee for a purpose directly related to the objectives of the C*STEROID Trial and the proposed use is consistent with Māori Data Sovereignty principles. Data by treatment group will not be available until the conclusion of the C*STEROID Trial and following publication of the primary C*STEROID Trial results.

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