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Antenatal betamethasone and incidence of neonatal respiratory distress after elective caesarean section: pragmatic randomised trial

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Abstract

Objective To test whether steroids reduce respiratory distress in babies born by elective caesarean section at term.

Design Multicentre pragmatic randomised trial.

Setting 10 maternity units.

Participants 998 consenting women randomised at decision to deliver by elective caesarean section; 503 randomised to treatment group.

Interventions The treatment group received two intramuscular doses of 12 mg betamethasone in the 48 hours before delivery. The control group received treatment as usual.

Outcome measures The primary outcome was admission to special care baby unit with respiratory distress. Secondary outcomes were severity of respiratory distress and level of care in response.

Results Sex, birth weight, and gestation were not different between the two groups. Of the 35 babies admitted to special baby units with respiratory distress, 24 were in the control group and 11 in the intervention group ($P=0.02$). The incidence of admission with respiratory distress was 0.051 in the control group and 0.024 in the treatment group (relative risk 0.46, 95% confidence interval 0.23 to 0.93). The incidence of transient tachypnoea of the newborn was 0.040 in the control group and 0.021 in the treatment group (0.54, 0.26 to 1.12). The incidence of respiratory distress syndrome was 0.011 in the control group and 0.002 in the treatment group (0.21, 0.03 to 1.32).

Conclusions Antenatal betamethasone and delaying delivery until 39 weeks both reduce admissions to special care baby units with respiratory distress after elective caesarean section at term.

Introduction

The rate of caesarean section in England rose from 9% in 1980 to 22% in 2003 as a result of changing practice in the management of previous caesarean and breech presentation as well as increased choice for women.^{1 2} This increase has included some women who opted for caesarean section at socially convenient times, without medical reasons.³ One survey reported that 69% of consultant obstetricians in England and Wales agree to women's requests for section in the absence of obstetric indications.⁴ Recent guidelines from the National Institute for Clinical Excellence (NICE, now National Institute for Health and Clinical Excellence) have recommended that a woman's request alone is not an indication for caesarean section.⁵

The consequences of elective caesarean section at term for the baby have received little attention. The incidence of respiratory distress is much higher than in vaginal delivery (0.036 *v* 0.0053).⁶ Other risk factors for respiratory distress include gestational age, mode of delivery, male sex, fetal asphyxia, maternal asthma and diabetes, and type of anaesthesia given during delivery (regional or general).⁶⁻⁹ The development of respiratory distress leads to admission to a special care baby unit or neonatal intensive care unit, often at a distance, separation from the mother, and complications from invasive procedures including artificial ventilation.

Antenatal corticosteroids reduce the incidence of respiratory distress in preterm babies.¹⁰ Guidance has long recommended their routine use when delivery is expected before 34 weeks' gestation.^{11 12} However, no trials have been conducted of antenatal corticosteroids in mothers delivered by elective caesarean section at term.

The antenatal steroids for term caesarean section (ASTECS) randomised trial therefore sought to evaluate whether giving the recommended two doses of betamethasone before delivery¹³ reduces the incidence of respiratory distress in babies delivered by elective caesarean section at term. Five studies lasting between three and 20 years, with more than 1500 patients, have shown no adverse effects of a single course of antenatal corticosteroids, neither through infection of fetus or mother nor in long term neurological or cognitive effects.^{10 12}

Methods

In 1995 the ASTECS team submitted the protocol to the National Perinatal Trial Centre, started recruitment, and invited other obstetric units to participate. By November 1998, altogether 10 units were taking part.

Mothers were eligible for the trial if elective caesarean section was planned at 37 weeks' gestation or beyond. Exclusion criteria included severe maternal hypertension, history of peptic ulceration, severe fetal rhesus sensitisation, and evidence of intrauterine infection. We used an algorithm from the Confidential Enquiry into Sudden Death in Infancy (CESDI) to calculate gestation from last menstrual period, expected date of delivery, and estimates from first ultrasound scan and at birth. Women who were eligible received an explanation of the study and an information sheet. In the 48 hours before elective caesarean section, women received either two intramuscular doses of 12 mg of



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betamethasone, separated by 24 hours, or treatment as usual, without antenatal steroids.

The trial centre in Rhyl held a list of treatment allocations derived from the random number generator in MS Excel but concealed from all participants. Midwives with signed consent from a mother phoned Rhyl and received the next allocation on the list. They informed the mother and recorded the allocation in her notes. As ASTECS was a pragmatic trial to estimate the effectiveness of betamethasone for caesarean section at term in routine clinical practice, blinding participants and professionals was neither desirable nor possible.

Outcome measures

The primary outcome was admission to a special care baby unit with respiratory distress. Secondary outcomes were severity of respiratory distress and level of care needed.¹⁴ To diagnose respiratory distress within 24 hours of birth needed tachypnoea (more than 60 breaths per minute) with grunting, recession, or nasal flaring. From reported arterial gases and oximetry measurements, we graded respiratory distress as mild if the baby received less than 30% oxygen, severe if it received more than 70% oxygen or ventilatory support, otherwise moderate. We asked for chest radiographs of babies admitted with respiratory distress. Two neonatal radiologists (David Pilling, consultant radiologist at Alder Hey Children's Hospital, and Alan Sprigg, consultant radiologist at Sheffield Children's Hospital) independently assessed these for the radiological features of transient tachypnoea of the newborn or the reticular granular pattern of respiratory distress syndrome.¹⁵

Sample size and analysis

Recruiting 1100 mothers would have yielded 80% power of detecting a reduction in the percentage of babies admitted to special baby units with respiratory distress from 8% to 4% when a 5% significance level was used. Because antenatal steroids do not reduce respiratory distress syndrome in twin pregnancy,¹⁶ we analyse only singleton deliveries. Analysis was by intention to treat, *t* test for normally distributed data, and χ^2 test for categorical data, using logistic regression to adjust for confounding variables.

Results

Recruitment began in Rhyl in February 1995 and another nine centres by November 1998. The last pregnant woman entered the trial in April 2002. Follow-up continued until December 2002, when all babies had left hospital. In all 998 women entered the study—313 from Bradford Royal Infirmary, 233 from Ipswich Hospital, 210 from Glan Clwyd Hospital, 135 from Southmead Hospital, and 107 from the remaining six centres.

Figure 1 shows the flow of participants through the trial. The trial centre received no data after randomisation on 29 women. There were 20 sets of twins, and seven mothers gave birth before 37 weeks' gestation. Hence 942 babies were available for intention to treat analysis, 467 in the treatment group and 475 in the control group. These two groups were similar in mothers' age, asthma, and smoking, and in babies' sex and birth weight (table 1). Eighty six (9.1%) were born at 37 weeks' working gestation, 434 (46.1%) at 38 weeks, 357 (37.9%) at 39 weeks, 46 (4.9%) at 40 weeks, 13 (1.4%) at 41 weeks, and 6 (0.6%) at 42 or more weeks. Ten women (four in the treatment group) had diabetes: six had gestational diabetes that was controlled by diet, three had type 1 diabetes and one type 2 diabetes. None of their babies developed respiratory distress. In all, 51 women delivered by emergency section before random allocation came into effect.

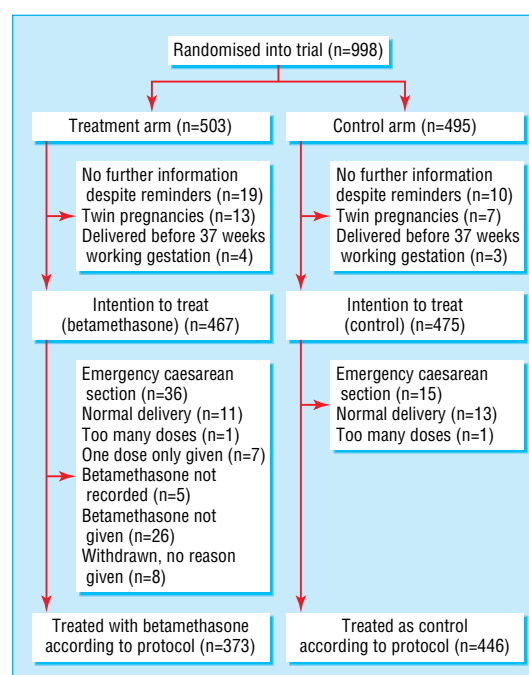


Fig 1 Flow of participants through the trial

Primary outcome: admission to special care baby unit

Table 2 shows that 35 babies entered these units with respiratory distress, 24 in the control group and 11 in the treatment group ($P=0.021$). The incidence of admission with respiratory distress was therefore 0.051 in the control group and 0.024 in the treatment group—a relative risk of 0.46 in favour of treatment (95% confidence interval 0.23 to 0.93).

Secondary outcomes

No mother of a control baby admitted to a special care baby unit received general anaesthetic, compared with five (45%) in the treatment group ($P<0.001$). Three (12%) of the control babies so admitted received neonatal resuscitation, compared with eight (73%) in the treatment group ($P<0.001$). Four (36%) of these intervention babies also received ventilation through a mask, and two (18%) also received intubation, compared with none in the control group ($P=0.006$ and $P=0.09$, respectively). The two groups did, however, not differ significantly with regard to the sex, birth weight, or gestation of infants admitted to a special baby unit.

Table 3 shows that the severity of respiratory distress in babies admitted to special care baby unit was similar in both groups. We received radiographs relating to 22 of the 35 babies admitted with respiratory distress. The remaining 13 babies had diagnoses of transient tachypnoea of the newborn on discharge. Nineteen control babies had transient tachypnoea of the newborn and five had respiratory distress syndrome, compared with 10 treated babies with transient tachypnoea and one with respiratory distress syndrome. The incidence of respiratory distress syndrome was therefore 0.011 in the control group and 0.002 in the treatment group (relative risk 0.21, 0.03 to 1.32), and the incidence of transient tachypnoea of the newborn was 0.040 in the control group and 0.021 in the treatment group (0.54, 0.26 to 1.12).

Only two intervention babies received intensive care—one at level 1 for one day and level 2 (high dependency) for three days, the other at level 2 for one day (fig 2). In contrast, 14 control babies received intensive care; three with respiratory distress

Table 1 Mothers' and babies' characteristics by intention to treat

Characteristics	Treated according to protocol			Not treated according to protocol			Total (intention to treat)		
	Betamethasone group	Control group	Total	Betamethasone group	Control group	Total	Betamethasone group	Control group	Total
Binary*									
Male baby	190/373 (51.3)	229/446 (50.9)	419/819 (51.2)	44/94 (43)	14/29 (48)	58/123 (47)	234/467 (50.1)	243/475 (51.2)	477/942 (50.6)
Maternal asthma	33/373 (8.8)	53/446 (11.9)	86/819 (10.5)	11/94 (12)	5/29 (17)	16/123 (13)	44/467 (9.4)	58/475 (12.2)	102/942 (10.8)
Maternal smoking	63/373 (16.9)	101/446 (22.6)	164/819 (20.0)	26/94 (28)	9/29 (31)	35/123 (28)	89/467 (19.1)	110/475 (23.2)	199/942 (21.1)
General anaesthetic	28/372 (7.5)	24/443 (5.4)	52/815 (6.4)	14/83 (17)	2/15 (13)	16/98 (16)	42/455 (9.2)	26/458 (5.7)	68/913 (7.4)
Quantitative†									
Mother's age (years)	31.1(5.2)	30.6(5.2)	30.8(5.2)	30.8(5.0)	29.8(4.8)	30.6(4.9)	31.1 (5.2)	30.5 (5.1)	30.9 (5.2)
Birth weight (g)	3280 (450)	3320(470)	300 (460)	3170 (490)	3310 (550)	3200 (500)	3260 (470)	3320 (470)	3290 (470)
Working gestation (days)	269 (5.3)	269 (5.3)	269 (5.3)	269 (7.9)	272 (11.2)	270 (8.8)	269 (5.9)	269 (5.9)	269 (5.9)
Corrected gestation (days)	261 (6.6)	269 (6.3)	269 (6.4)	269 (6.8)	272 (10.3)	270 (7.8)	269 (6.7)	270 (6.6)	269 (6.6)

*Values are numbers (percentages). Denominator varies according to number of valid responses.

†Values are means (standard deviations).

syndrome required ventilation for between two and five days and stays of between 12 and 18 days. Antenatal betamethasone thus substantially reduced resource use in special baby units.

The logistic regression model in figure 3 predicts the probability of admission to special care baby unit with respiratory distress from the gestational age of the baby. The predicted probability of admission at 37 weeks was 11.4% in the control group and 5.2% in the treatment group, at 38 weeks it was 6.2% and 2.8%, respectively, and at 39 weeks it was 1.5% and 0.6%.

Adverse effects

Reports of side effects came from seven mothers in the treatment group who had received two doses of betamethasone and one who had received only one. Five reported generalised flushing, one nausea, one tenderness at the injection site, and one increased energy with difficulty in sleeping. No such reports came from the control group. No reports were made of wound infection or neonatal sepsis.

Table 2 Outcomes by group

Outcomes*	Treated according to protocol			Not treated according to protocol			Total (intention to treat)		
	Betamethasone group	Control group	Net benefit from steroid (95% confidence interval)	Betamethasone group	Control group	Net benefit from steroid (95% confidence interval)	Betamethasone group	Control group	Net benefit from steroid (95% confidence interval)
Binary*									
Resuscitated	31/373 (8.3)	46/446 (10.3)	2.0 (−2.1 to 6.0)	13/94 (14)	8/29 (28)	14 (−2 to 33)	44/467 (9.4)	54/475 (11.4)	2.0 (−2.0 to 6.0)
Resuscitation:									
Mask ventilation	15/373 (4.0)	17/446 (3.8)	0.2 (−2.5 to 3.1)	7/94 (7)	3/29 (10)	3 (−7 to 20)	22/467 (4.7)	20/475 (4.2)	−0.5 (−3.3 to 2.2)
Intubation	2/373 (0.5)	1/446 (0.2)	0.3 (−0.7 to 1.7)	2/94 (2)	0/29 (0)	−2 (−10 to 8)	4/467 (0.9)	1/475 (0.2)	−0.6 (−2.0 to 0.4)
Admitted to special care baby unit with respiratory distress	7/373 (1.9)	22/446 (4.9)	3.1 (0.6 to 5.7)	4/94 (4)	2/29 (7)	3 (−5 to 18)	11/467 (2.4)	24/475 (5.1)	2.7 (0.3 to 5.3)
Quantitative†									
Apgar score at 1 minute	8.53 (0.07)	8.59 (0.05)	−0.06 (−0.23 to 0.10)	8.27 (0.20)	8.14 (0.32)	0.13 (−0.67 to 0.93)	8.48 (0.07)	8.57 (0.05)	−0.09 (−0.26 to 0.08)
Apgar score at 5 minutes	9.36 (0.05)	9.30 (0.05)	0.05 (−0.09 to 0.20)	8.94 (0.24)	9.10 (0.21)	−0.18 (−1.05 to 0.72)	9.27 (0.06)	9.29 (0.05)	−0.02 (−0.18 to 0.14)
Time in special care baby unit in days	0.14 (0.05)	0.32 (0.09)	0.18 (−0.02 to 0.37)	0.33 (0.14)	0.93 (0.42)	0.60 (−0.53 to 1.73)	0.18 (0.05)	0.35 (0.09)	0.18 (−0.02 to 0.37)
Time on oxygen in hours	0.74 (0.43)	2.80 (1.12)	2.06 (−0.31 to 4.43)	0.27 (0.17)	13.24 (9.14)	12.98 (−6.02 to 31.97)	0.64 (0.35)	3.44 (1.20)	2.80 (0.34 to 5.25)
Maximum inspired oxygen concentration in %	21.27 (0.16)	21.93 (0.33)	0.65 (0.19 to 1.42)	21.35 (0.19)	22.76 (1.22)	1.37 (−0.47 to 4.39)	21.29 (0.13)	21.99 (0.31)	0.68 (0.12 to 1.42)

*Values are numbers (percentages). Denominator varies according to number of valid responses. Net benefit is percentage in control minus percentage in treatment group.

†Values are means (standard errors). Net benefit is difference between control mean and treatment mean with negative sign when controls performed better.

Table 3 Reason for admission to special care baby unit by group

Reason for admission	Betamethasone group	Control group
Respiratory distress by severity:		
Mild	4	9
Moderate	6	10
Severe	1	5
Respiratory distress by type:		
Transient tachypnoea of the newborn	10	19
Respiratory distress syndrome	1	5
Total No of babies admitted	26	32
With respiratory distress (subtotal)	11	24
Other (without respiratory distress)	15	8

Discussion

Betamethasone given immediately before elective caesarean section at term reduces respiratory distress and admission to a special care baby unit. The rate of such admission was 0.050 in the control group and 0.024 in the treatment group. This rate falls with increasing gestation, supporting the recommendation to delay elective caesarean section until the 39th week.⁶ Nevertheless, the benefits of antenatal steroids persist until 39 weeks.

Strengths and weaknesses of the trial

We designed ASTECS as a pragmatic trial to estimate the effectiveness of betamethasone for caesarean section at term in routine practice in 10 diverse maternity units. Blinding participants and professionals was therefore neither desirable nor possible. Similarly the use of placebos was not practical. Furthermore the primary outcome, respiratory distress requiring admission to special care baby unit, is hardly susceptible to maternal influence.

To simplify, and thus increase, recruitment we did not stratify treatment allocation by gestation or centre; no imbalance in allocation resulted. The need to alter clinical practice to permit two injections in the 48 hours before delivery slowed recruitment to the trial, which finished before reaching its target; nevertheless, the trial detected significant differences between groups. Although race reportedly modifies the effect of antenatal steroids, the evidence is conflicting.^{7 16} The trial lacked power to tackle this secondary issue.

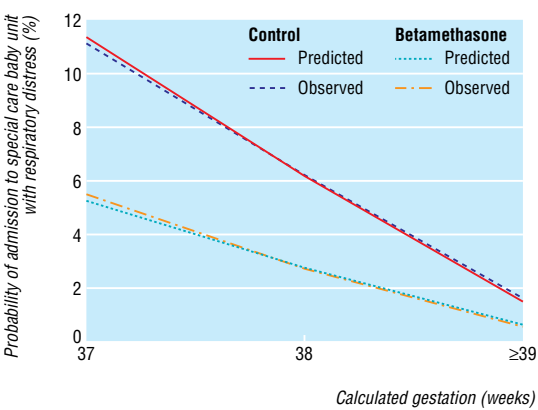


Fig 3 Probability of admission to special care baby unit with respiratory distress by gestation (observed and predicted by logistic model): intention to treat analysis. Logistic regression model: $z = -5.034 + 2.139$ (if baby is 37 weeks) $+ 1.472$ (if baby is 38 weeks) $+ 0.840$ (if mother was not randomised to receive betamethasone) where the default is randomised to receive betamethasone at 39 weeks. Predicted probability = $\exp(z) / [1 + \exp(z)]$

Unanswered questions

Reducing the number of babies born by elective caesarean section before 39 weeks' gestation will reduce admissions with respiratory distress to special care baby units. However, many clinical factors influence the timing of elective caesareans. There may be uncertainty regarding gestation, medical indications for earlier delivery, and concerns about spontaneous onset of labour resulting in emergency caesareans with risks for mother and baby.¹⁷ Social factors also influence timing.⁴ Plans for changing clinical management should take all these factors into account.

Meaning of the study

Independent radiological review confirmed that antenatal betamethasone reduced the incidence of transient tachypnoea of the newborn from 4% of elective caesarean sections to 2.1% and that of respiratory distress syndrome from 1.1% to 0.2%. To our knowledge this is the first report that antenatal steroids prevent transient tachypnoea. During labour and at birth, the mature lung switches from active chloride and fluid secretion to active

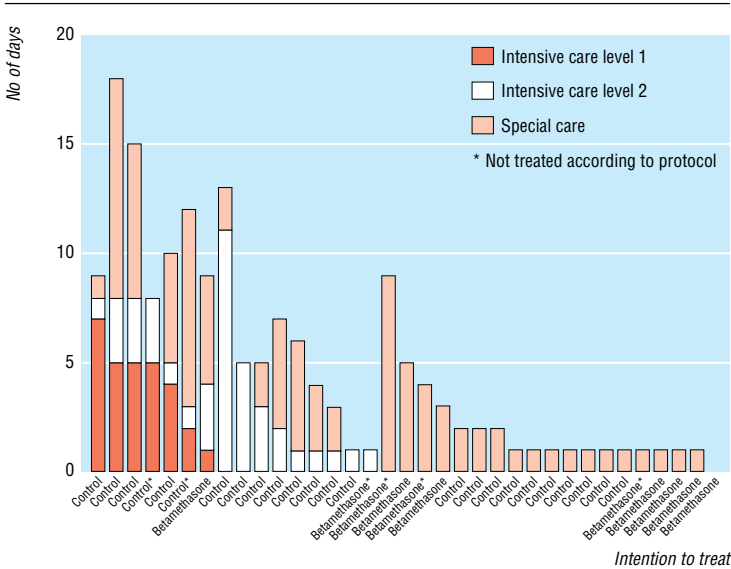


Fig 2 Babies admitted to a special care baby unit in descending order of intensity of care and of length of stay: intention to treat analysis

What is already known on this topic

Two antenatal doses of betamethasone reduce the incidence of respiratory distress syndrome by more than 50% in babies born before 34 weeks' gestation, thus reducing morbidity and mortality

Although this is now recommended practice, the treatment is considered of no benefit beyond this gestational age

The treatment's effect is thought to be mediated through increased surfactant production, a shortage of which leads to respiratory distress syndrome, which is common in preterm babies

Long term studies have shown no harmful effect of a single course of betamethasone

What this study adds

Babies born after 37 weeks by elective caesarean section also benefit from antenatal betamethasone

This reduces the incidence of respiratory distress by more than 50%, mainly by reducing transient tachypnoea of the newborn

These findings imply that antenatal steroids can aid the clearing of lung fluid after delivery

When counselling a mother before elective caesarean section at term, the increased risk of admission with respiratory distress should be considered

The likely benefits of antenatal betamethasone should be compared with those of delaying caesarean section until 39 weeks when possible

sodium and fluid absorption.^{18–20} The reduced incidence of transient tachypnoea in the steroid group is consistent with the hypothesis that corticosteroids, increased in mother and fetus through the stress of labour, encourage the expression of the epithelial channel gene and allow the lung to switch from fluid secretion to fluid absorption. Without another source of corticosteroid, elective caesarean section will disrupt this process. Thereafter admission with respiratory distress to a special unit separates mother and baby, potentially disrupting bonding, and increasing the cost of care and the risk of complications.^{21–22} Furthermore, neonatal respiratory morbidity increases the risk of asthma in childhood.²³

Conclusion

Antenatal betamethasone is effective in reducing admission to special care baby unit with respiratory distress after elective caesarean section at term. In planning elective caesareans, the risk of respiratory distress should be considered and the likely benefits of antenatal corticosteroids should be compared with those of delaying delivery until 39 weeks when possible.

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Contributors: Authors and other members of the ASTECS trial team contributed as follows. PS is consultant paediatrician and neonatologist at Glan Clwyd Hospital, which provides a neonatal intensive care service for North Wales. He developed the protocol, initiated and coordinated the trial,

recruited other centres, supervised collection, validation and analysis of data, and drafted this paper. He guarantees its clinical content. Philip Banfield, consultant obstetrician at Glan Clwyd Hospital, recruited patients to the trial. Jeff Berry and James Satelle, information analysts at Glan Clwyd Hospital, developed and managed the trial database. Nigel Bickerton, consultant obstetrician at Glan Clwyd Hospital, contributed to the protocol and recruited patients to the trial. Duncan Cameron, consultant paediatrician and neonatologist at Glan Clwyd Hospital, contributed to the protocol, the newsletter for participating centres and data collection. Lesley Furneaux, personal secretary to PS, acted as research coordinator, randomising patients, collating and entering data, and checking their completeness. David Pilling, consultant radiologist at Alder Hey Children's Hospital, and Alan Sprigg, consultant radiologist at Sheffield Children's Hospital, independently assessed the chest radiographs submitted. IR contributed to analysing, interpreting, and writing this paper. He guarantees its statistical content. RW validated and analysed data, and contributed to interpreting and writing this paper. Matouk Zbaeda, previously senior paediatric registrar at Glan Clwyd Hospital, reviewed elective caesarean sections at term, thus stimulating the trial, and contributed to the protocol.

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Competing interests: None declared.

Ethical approval: North West Multi-centre Research Ethics Committee and the 10 relevant local research ethics committees approved the trial protocol.

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