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Abstract

Computerised interpretation of the fetal heart rate during labour: a randomised controlled trial (INFANT)

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Background: Continuous electronic fetal monitoring (EFM) in labour is widely used and computerised interpretation has the potential to increase its utility.

Objectives: This trial aimed to find out whether or not the addition of decision support software to assist in the interpretation of the cardiotocograph (CTG) reduced the number of poor neonatal outcomes, and whether or not it was cost-effective.

Design: Two-arm individually randomised controlled trial. The allocations were computer generated using stratified block randomisation employing variable block sizes. The trial was not masked.

Setting: Labour wards in England, Scotland and the Republic of Ireland.

Participants: Women in labour having EFM, with a singleton or twin pregnancy, at ≥ 35 weeks' gestation.

Interventions: Decision support or no decision support.

Main outcome measures: The primary outcomes were (1) a composite of poor neonatal outcome {intrapartum stillbirth or early neonatal death (excluding lethal congenital anomalies), or neonatal morbidity [defined as neonatal encephalopathy (NNE)], or admission to a neonatal unit within 48 hours for ≥ 48 hours (with evidence of feeding difficulties, respiratory illness or NNE when there was evidence of compromise at birth)}; and (2) developmental assessment at the age of 2 years in a subset of surviving children.

Results: Between 6 January 2010 and 31 August 2013, 47,062 women were randomised and 46,042 were included in the primary analysis (22,987 in the decision support group and 23,055 in the no decision support group). The short-term primary outcome event rate was higher than anticipated. There was no evidence of a difference in the incidence of poor neonatal outcome between the groups: 0.7% ($n = 172$) of babies in the decision support group compared with 0.7% ($n = 171$) of babies in the no decision support group [adjusted risk ratio 1.01, 95% confidence interval (CI) 0.82 to 1.25]. There was no evidence of a difference in the long-term primary outcome of the Parent Report of Children's Abilities-Revised with a mean score of 98.0 points [standard deviation (SD) 33.8 points] in the decision support group and 97.2 points (SD 33.4 points) in the no decision support group (mean difference 0.63 points, 95% CI –0.98 to 2.25 points). No evidence of a difference was found for health resource use and total costs. There was evidence that decision support did change practice (with increased fetal blood sampling and a lower rate of repeated alerts).

Limitations: Staff in the control group may learn from exposure to the decision support arm of the trial, resulting in improved outcomes in the control arm. This was identified in the planning stage and felt to be unlikely to have a significant effect on the results. As this was a pragmatic trial, the response to CTG alerts was left to the attending clinicians.

Conclusions: This trial does not support the hypothesis that the use of computerised interpretation of the CTG in women who have EFM in labour improves the clinical outcomes for mothers or babies.

Future work: There continues to be an urgent need to improve knowledge and training about the appropriate response to CTG abnormalities, including timely intervention.

Trial registration: Current Controlled Trials ISRCTN98680152.

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List of abbreviations

aRR	adjusted risk ratio
BMI	body mass index
CESDI	Confidential Enquiry into Stillbirths and Deaths in Infancy
CI	confidence interval
CONSORT	Consolidated Standards of Reporting Trials
CTG	cardiotocograph
DMC	Data Monitoring Committee
ECG	electrocardiography
EFM	continuous electronic fetal monitoring
EQ-5D-3L	EuroQol-5 Dimensions, three-level version
GBP	Great British pounds
GEE	generalised estimating equation
GMR	geometric mean ratio
HRQoL	health-related quality of life
HTA	Health Technology Assessment
IQR	interquartile range
IUGR	intrauterine growth restriction
MRC	Medical Research Council
NHSLA	NHS Litigation Authority
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NNE	neonatal encephalopathy
PARCA-R	Parent Report of Children's Abilities-Revised
PBDC	Post Birth Data Collection
PC	personal computer
RCT	randomised controlled trial
REC	Research Ethics Committee
RR	risk ratio
SD	standard deviation
SE	standard error
TSC	Trial Steering Committee
UCL	University College London
VAS-A	Visual Analogue Scale – Anxiety

Plain English summary

The INFANT study aimed to find out if we can improve how we monitor babies during labour. In the UK, continuous monitoring is used if either the mother or the baby is considered likely to not cope well with contractions during labour. For these labours, a cardiotocograph is used to continuously record the baby's heart rate. The midwives/doctors look at a graph of the heart rate to find out how the baby is coping.

Interpreting the pattern made by the baby's heart rate is complicated. The INFANT study looked at whether or not a computer system that analyses the heart rate can help the midwives/doctors interpret the recording more accurately. The study asked questions about babies' health and well-being, medical procedures experienced by women and whether one approach provided better value for money than the other in terms of delivering high-quality care. Women who agreed to have continuous electronic fetal monitoring were divided at random into two groups. One group had the computer decision support software switched on and the other group had it switched off. This made it possible to assess the effect of the new software fairly, as the groups of women and babies were otherwise almost identical in terms of their health and chance of complications.

Between January 2010 and August 2013, 47,062 women took part in the study. After the different interventions in their care, we found no difference in the chance of babies being unwell between the two groups of women: 0.7% ($n = 172$) of babies were unwell in the decision support group, as were 0.7% ($n = 171$) of babies in the no decision support group. We found no differences in other outcomes, such as the risk of pregnant women requiring an emergency caesarean section.

In this study, decision support software did not improve the care for women in labour.

Scientific summary

Background

Continuous electronic fetal monitoring (EFM) in labour is widely used and has the potential to improve neonatal outcomes. The benefits of EFM have been limited so far. The reasons for this appear to be complex, but include difficulties with interpreting the fetal heart rate trace correctly during labour. Computerised interpretation of the fetal heart rate has the potential to objectively detect abnormalities of the fetal heart rate pattern that are associated with asphyxia but not recognised as abnormal by the birth attendants, bringing to their attention the need to act to prevent stillbirth or exposure to significant asphyxia.

The electronic information capture system used in both arms of the trial, Guardian® (version 2.050.038.001, K2 Medical Systems, Plymouth, UK), is a system for managing information from labour monitoring. It displays the cardiotocograph (CTG) on a computer screen alongside other clinical data (e.g. the partogram and maternal vital signs) that are collected as part of routine clinical care. It can display CTG data obtained from external ultrasound transducers or from fetal scalp electrodes. Guardian acts as an interface to collect and display data at the bedside, centrally on the labour ward, in consultants' offices or remotely. The decision support software (INFANT®; version 2.050.035.001, K2 Medical Systems, Plymouth, UK) analyses the quality of the fetal heart signals and, if adequate, displays baseline fetal heart rate, heart rate variability, accelerations, type and timing of decelerations, the quality of the signal and the contraction pattern. It then makes an assessment of the overall pattern, which can result in a colour-coded alert, depending on the severity of any abnormality detected. The decision support software does not provide recommendations for any action that should be taken in response to these abnormalities. This was left to the discretion of the attending clinicians.

Objectives

Our hypotheses were that:

- A substantial proportion of substandard care results from a failure to correctly identify abnormal fetal heart rate patterns.
- Improved recognition of abnormality would reduce substandard care and poor outcomes.
- Improved recognition of normality would reduce unnecessary intervention.

The aim of the INFANT trial was to determine whether or not the addition of computerised interpretation of the intrapartum CTG to current clinical care could improve the management of labour for women who were judged to require EFM, and also to determine whether or not the use of the decision support software is cost-effective.

Methods

This was a two-arm pragmatic individually randomised controlled trial in labour wards in England, Scotland and the Republic of Ireland.

Eligibility

Eligible women were those:

1. who were judged to require EFM by the local clinical team based on their existing practice, and who had consented to EFM
2. who were pregnant with a single fetus or twin fetuses
3. who were at ≥ 35 weeks' gestation
4. had a fetus with no known major abnormality, including any known heart arrhythmia such as heart block
5. who were aged ≥ 16 years
6. who were able to give consent to participate as judged by the attending clinicians.

Randomisation

Women were allocated, in the ratio of 1 : 1, to (1) CTG monitoring with decision support or (2) CTG monitoring with no decision support. The allocations were computer-generated using stratified block randomisation employing variable block sizes to balance between the two trial arms by singleton or twin pregnancy, and within each participating centre. The trial was not masked.

Primary outcome measures

Primary short-term outcome

A composite of poor neonatal outcome including deaths [intrapartum stillbirths plus neonatal deaths (i.e. deaths up to 28 days after birth) except deaths as a result of congenital anomalies], significant morbidity [moderate or severe neonatal encephalopathy (NNE), defined as the use of whole-body cooling] and admissions to a neonatal unit within 48 hours of birth for ≥ 48 hours (with evidence of feeding difficulties or respiratory illness and when there was evidence of compromise at birth suggesting that the condition was the result of mild asphyxia and/or mild NNE).

Primary long-term outcome

Developmental progress as measured by the Parent Report of Children's Abilities-Revised (PARCA-R) composite score at the age of 2 years for a subset of children.

Secondary outcome measures

Secondary short-term outcomes

Neonatal

- Intrapartum stillbirth (excluding deaths as a result of congenital anomalies).
- Neonatal deaths up to 28 days after birth (excluding deaths as a result of congenital anomalies).
- Moderate or severe NNE.
- Admission to neonatal unit within 48 hours of birth for ≥ 48 hours with evidence of feeding difficulties, respiratory illness or NNE (when there was evidence of compromise at birth).
- Admission to a higher level of care.
- An Apgar score of < 4 at 5 minutes after birth.
- The distribution of cord blood gas data for cord artery pH.
- Metabolic acidosis (defined as a cord artery pH of < 7.05 and a base deficit in extracellular fluid of ≥ 12 mmol/l).
- Resuscitation interventions.
- Seizures.
- Destination immediately after birth.
- Length of hospital stay.

Maternal

- Mode of delivery.
- Operative intervention (caesarean section or instrumental delivery) for:
  - fetal indication or
  - failure to progress or
  - a combination of fetal distress and failure to progress or
  - other reason.
- Grade of caesarean section.
- Episiotomy.
- Any episode of fetal blood sampling.
- Length of:
  - first stage of labour from trial entry
  - second stage of labour from trial entry
  - labour from trial entry (total).
- Destination immediately after birth.
- Admission to a higher level of care.

Secondary long-term outcomes (infant)

Health and development outcomes at 24 months

- Non-verbal cognition scale (PARCA-R).
- Vocabulary subscale (PARCA-R).
- Sentence complexity subscale (PARCA-R).
- Late deaths up to 24 months (after the neonatal period).

Diagnosed with cerebral palsy:

- Non-major disability.
- Major disability.
- Breastfeeding (collected at 12 and 24 months).

Quality-of-care outcomes

In the case of any adverse infant outcomes potentially associated with intrapartum asphyxia (trial primary outcome based on the baby's condition after birth, plus a cord artery pH of < 7.05 with a base deficit of ≥ 12 mmol/l) and all neonatal deaths and intrapartum stillbirths, care during labour was assessed by a panel comprising a senior obstetrician, neonatologist and midwife, to determine if it could be considered to be suboptimal (possible or likely that different management would have prevented the adverse outcome).

Process outcomes

- Total number of CTG abnormalities (blue, yellow and red levels of concern) detected by the decision support software.
- Number of blue levels of concern on the decision support software, indicating a mild abnormality on the CTG.
- Number of yellow levels of concern on the decision support software, indicating a moderate abnormality on the CTG.
- Number of red levels of concern on the decision support software, indicating a severe abnormality on the CTG.

- Number of women with at least one yellow level of concern on the decision support software, indicating an abnormality on the CTG.
- Number of women with at least one red level of concern on the decision support software, indicating a severe abnormality on the CTG.
- Time from first red level of concern to birth.

Data collection schedule

Labour data and immediate outcomes were stored on the Guardian system and sent electronically to the co-ordinating centre. Data were extracted from the notes of babies admitted to the neonatal unit and for all neonatal deaths. All surviving children who were discharged were 'flagged' at the NHS Information Centre (England) and NHS Greater Glasgow & Clyde Safe Haven (Scotland), allowing all deaths to be identified. A sample of surviving children and mothers was followed up at 2 years by means of a parent-completed questionnaire to assess the child's health, development and (health service) resource use and to assess the mother's well-being and resource use.

Sample size and analysis

The required sample size was 46,000 births. We assumed an incidence rate of the primary outcome of 3 per 1000 births. This was calculated using reported rates of intrapartum stillbirth, neonatal death, moderate and severe NNE in broadly similar populations, and mild NNE (reliable data on significant asphyxial morbidity resulting in transfer to neonatal care were not available and so could only be estimated). The effect size that could be detected with 46,000 women (23,000 in each group), assuming a 5% level of significance and 90% power, was a 50% reduction in the poor neonatal outcome rate from 3 to 1.5 per 1000 births.

A statistical analysis plan was developed and approved by the Trial Steering Committee prior to analysis. Participants were analysed in the groups into which they were randomly allocated, regardless of allocation received. All women and babies with available data were included, except women with a missing consent form and women who withdrew consent to use their data. The number of babies with the composite primary outcome was presented for each group, and the risk ratio (RR) plus 95% confidence interval (CI) calculated. The mean [standard deviation (SD)] PARCA-R composite score was calculated and the mean difference plus 95% CI was calculated and compared using linear regression. Hazard ratios were estimated using a Cox proportional hazards model and rate ratios were estimated using Poisson regression. We adjusted for the stratification factors used in the randomisation, and robust variance estimators were used in all models to account for the correlation in outcomes between twins and siblings delivered in a subsequent pregnancy during the trial period. The mean (SD) PARCA-R composite score was calculated and the mean difference plus 95% CI was calculated and compared. For secondary outcomes including the components of the primary outcome, a 1% level of statistical significance was employed.

The following prespecified subgroup analyses were undertaken, using the statistical test of interaction, for all neonatal outcomes, instrumental vaginal deliveries and caesarean section:

1. singletons versus twins
2. suspected growth restriction at labour onset versus no growth restriction
3. centre
4. body mass index (BMI) group [underweight (i.e. a BMI of 12–18.5 kg/m^2), normal (a BMI of 18.5–24.9 kg/m^2), overweight (a BMI of 25–29.9 kg/m^2), obese (a BMI of 30–70 kg/m^2), unrecorded].

For the economic evaluation, health-care resource use was compared using RRs for binomial variables and mean differences for continuous covariates. Parametric methods were used to estimate mean resource use, cost and maternal health-related quality of life EuroQol-5 Dimensions, three-level version (EQ-5D-3L), scores. Differences between treatment arms were adjusted using a random intercept binomial (for RRs) or linear (for mean differences) model adjusting for the stratification factors at randomisation (centre and twin birth) and clustering as a result of twins and multiple-birth episodes. A 95% significance level was

used for all comparisons. A multiple imputation framework with a chained equation was used for estimating resource use and EQ-5D-3L scores at 12 and 24 months.

The INFANT trial was registered with Current Controlled Trials ISRCTN98680152.

Results

Between 6 January 2010 and 31 August 2013, 47,062 women were randomised to the INFANT trial. A total of 1020 women (2.2%) were excluded from the analysis of the primary outcome. Data at the time of birth were available for 100% of women and babies eligible to be analysed. Follow-up data at 2 years were available for 56% of those contacted, although data were sufficiently complete for the analysis for 6707 children (53%).

There was no evidence of a difference in the incidence of the primary outcome of poor neonatal outcome between the groups, with a poor outcome being experienced by 0.7% of babies in both the decision support group ($n = 172$) and the no decision support group ($n = 171$) [adjusted risk ratio (aRR) 1.01, 95% CI 0.82 to 1.25]. Similarly, there was no evidence of a difference in any component of the composite primary outcome between the groups.

There was no evidence of any differences in any of the trial's secondary outcomes for the baby, including Apgar score, admission to a neonatal unit, metabolic acidosis of cord blood samples, the need for neonatal resuscitation and duration of hospital stay.

Just over half of all births were spontaneous vaginal births and there was no statistically significant difference in this outcome between the two groups. Half of the operative births were caesarean sections and half were instrumental. The proportion of women who underwent fetal blood sampling was higher in the decision support group (10.3%) than in the no decision support group (9.5%) (aRR 1.08, 99% CI 1.01 to 1.16). No other statistically significant differences in clinical outcomes were found between the two groups from trial entry to birth.

The overall proportion of cases with poor outcome in which babies were judged to have suboptimal care likely to have affected the outcome was 38% (21/71 cases).

There was evidence of a lower rate of yellow levels of concern in the decision support group (adjusted rate ratio 0.87, 99% CI 0.84 to 0.89).

There was no evidence of a difference between the two groups for any of the 2-year outcomes, including the long-term primary outcome of the PARCA-R, with a mean composite score of 98.0 points (SD 33.8 points) in the decision support group and 97.2 points (SD 33.4 points) in the no decision support group (mean difference 0.63, 95% CI –0.98 to 2.25).

There was no evidence that the decision support software produced different outcomes in any of the prespecified subgroups.

No evidence of a difference was detected in any category of resource use assessed, in categories of costs, or in total costs at 24 months for the infant (£104, 95% CI –£174 to £382) or for the mother (–£149, 95% CI –£314 to £16).

Conclusions

There is no evidence of a difference in the risk of a poor neonatal outcome, or intervention in labour, when using CTG interpretation software to support decision-making versus not using CTG interpretation in 46,000 women.

The strength of this study lies in its contemporaneous data collection and its size. Weaknesses include the potential for staff to learn from exposure to the decision support arm of the trial, resulting in improved outcomes in the control arm. This was identified when the trial was being planned. Part of our prior hypothesis was that, although some poor CTG interpretation is because of a lack of training, some clinicians may have a poor intrinsic pattern recognition ability that is not susceptible to improvement by training. This would not be affected by training and the performance of such clinicians would be particularly improved by assistance from automatic interpretation. There was some evidence that clinician behaviour was changed in the decision support arm of the trial. It may be that different action was taken in response to the alerts in the decision support arm of the trial, for example the clinicians might have reduced the dose of an oxytocin infusion in women having their labour augmented or changed maternal position if the CTG abnormality resulted from vena caval compression. Such actions could have prevented further yellow alerts, leading to a decrease in the incidence of repeat yellow alerts in this group, but we do not have any direct evidence that this was the case.

Detecting abnormalities in the fetal heart rate can improve outcome only if caregivers respond appropriately to the alerts. An expert panel reviewed all severe adverse outcomes in the trial and found no evidence that there were differences in levels of suboptimal care between the two groups. Therefore, we conclude that our hypothesis, that substandard care is largely related to a failure to identify pathological fetal heart rate patterns, is not supported.

There is currently no evidence to support the use of computerised interpretation of the CTG in women who have EFM in labour to improve clinical outcomes for mothers or babies.

Trial registration

This trial is registered as ISRCTN98680152.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research (NIHR). Sara Kenyon was part funded by the NIHR Collaboration for Leadership in Applied Health Research and Care West Midlands.

Chapter 1 Introduction

The justification for the trial, the supporting literature and the methods of the trial were published as a trial protocol in BMC Pregnancy and Childbirth. Sections of this chapter are reproduced from Brocklehurst.[1] This is an Open Access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited. The text below includes minor additions and formatting changes to the original text.

Continuous electronic fetal monitoring (EFM) in labour is widely used throughout the developed world. However, its potential for improving fetal and neonatal outcomes has not been realised. The reasons for this are probably complex, but are likely to include difficulty of interpreting the fetal heart rate trace correctly during labour, when the birth attendant has many competing tasks. For intrapartum monitoring to improve fetal and neonatal outcomes, the interpretation of the fetal heart rate has to be substantially and consistently improved. This standard has to be sustained and be independent of any health professional's individual ability. Computerised interpretation of the fetal heart rate and intelligent decision support has the potential to deliver this improvement in care. The aim of EFM is to detect abnormalities of the fetal heart rate pattern during labour that are associated with asphyxia so that action can be taken to expedite delivery and prevent stillbirth and the development of neonatal encephalopathy (NNE). Therefore, the potential benefits of EFM are immense. Prevention of even a modest proportion of perinatal asphyxia will improve the health and well-being of thousands of children and their families throughout the world each year. In addition, the cost to the NHS Litigation Authority (NHSLA) for obstetrics is very large and rising. EFM could contribute to a substantial reduction. Furthermore, if this technology can work in the complex process of labour, it also has the potential to improve patient safety in a wide range of health-care settings.

The problem of perinatal asphyxia

Perinatal asphyxia, if severe, can result in intrapartum stillbirth. If less severe, it results in the development of an encephalopathic state in the newborn. This is characterised by a decreased level of consciousness, altered reflexes, abnormal tone and ultimately permanent damage to the brain. Moderate or severe NNE occurs in approximately 2 out of 1000 births.[2] With more severe asphyxial encephalopathy there is an increased risk of death or neurodevelopmental abnormalities: 25% of infants who have moderate asphyxial encephalopathy will develop cerebral palsy and around 80% of infants who have severe encephalopathy and survive will develop cerebral palsy.[3] Perinatal asphyxia may account for up to 30% of all cases of cerebral palsy[4] and it is a very significant health-care and financial burden on the NHS. A reduction in the number of babies born with perinatal asphyxia would reduce the associated mortality and, among survivors, the burden of ill health and incapacity. It could also result in substantial savings in litigation costs in the UK.

Efficacy of continuous electronic fetal monitoring

Continuous electronic fetal monitoring was invented in the 1960s.[5,6] The recorder displays the fetal heart rate and maternal uterine activity on a continuous line graph, called the cardiotocograph (CTG) tracing. EFM was widely introduced in the 1970s[7] and it became controversial in the 1980s when it was shown to poorly predict Apgar scores and fetal acid–base status at delivery.[8] The largest randomised controlled trial (RCT) (the Dublin trial) showed no reduction in perinatal mortality or in cerebral palsy using EFM.[9] However, systematic reviews and meta-analyses of all trials indicated some benefits of EFM: for example, a 58% reduction in odds of deaths attributable to intrapartum hypoxia [95% confidence interval (CI) 2% to 83%][10] (*Table 1*) and a 50% reduction in risk of neonatal seizures (95% CI 20% to 69%) (*Figure 1*).[20] EFM is widely used on many women during labour in the UK. National Institute for Health and Care Excellence (NICE) guidelines for fetal monitoring in the NHS detail explicit criteria for implementing EFM;

TABLE 1 The effect of EFM vs. intermittent auscultation on the incidence of deaths attributable to intrapartum hypoxia

Study and year of publication	Patients in the (*n*)		Perinatal deaths (*n*)		Perinatal deaths as a result of fetal hypoxia (*n*)	
	EFM group	IA group	EFM	IA	EFM	IA
Haverkamp *et al.*, 1976[11]	242	241	2 (FD 0, ND 2)	1 (FD 0, ND 1)	0	0
Renou *et al.*, 1976[12]	175	175	1 (FD 0, ND 1)	1 (FD 1, ND 0)	0	1 (FD)
Kelso *et al.*, 1978[13]	253	251	0	1 (FD 0, ND 1)	0	1 (ND)
Haverkamp *et al.*, 1979[14]	230	231	3 (FD 0, ND 3)	0	0	0
	229					
Wood *et al.*, 1981[15]	445	482	1 (FD 0, ND 1)	0	0	0
MacDonald *et al.*, 1985[9]	6474	6490	14 (FD 3, ND 11)	14 (FD 2, ND 12)	7 (FD 3, ND 4)	7 (FD 2, ND 5)
Neldam *et al.*, 1986[16]	482	487	0	1 (FD 1, ND 0)	0	1 (FD)
Luthy *et al.*, 1987[17]	122	124	17 (FD 1, ND 16)	18 (FD 1, ND 17)	0	1 (FD)
Vintzileos *et al.*, 1993[18]	746	682	2 (FD 0, ND 2)	9 (FD 2, ND 7)	0	6 (FD 2, ND 4)
Total	9398	9163	40 (4.2/1000)	45 (4.9/1000)	7 (0.7/1000)[a]	17 (1.8/1000)[a]

IA, intermittent auscultation; FD, fetal (intrapartum) death; ND, neonatal death.
a Statistically significant difference; Mantel–Haenszel odds ratio 0.42 (95% CI 0.17 to 0.98).

as a result, EFM is carried out in capproximately 60% of all women in labour.[21] EFM has been shown to be associated with an increase in caesarean sections and instrumental vaginal births. In a review of 11 trials involving a total of 18,961 women, there was a 63% increase in the odds of a caesarean section (95% CI 1.29 to 2.07), and in 10 trials involving a total of 18,615 women there was a 15% increase in the odds of an instrumental vaginal birth (95% CI 1.01 to 1.33).[20]

Human error and systems failure

In the late 1980s it became apparent that a human element might be a factor in the failure of EFM to deliver improved outcomes. In one case–control study, the intrapartum management of 38 babies severely asphyxiated at birth was compared with that of 120 controls.[22] Cardiotography was abnormal in 29% of babies in the control group, but in only 9% was the abnormality severe. In contrast, 87% of the babies asphyxiated at birth had an abnormal CTG and in 61% of cases the abnormality was severe. However, the most striking finding was the length of time required for the staff to recognise the CTG abnormality. With moderate abnormalities, the mean time until recognition was 91 minutes [standard deviation (SD) 61 minutes]; paradoxically, with severe abnormalities it was 128 minutes (SD 100 minutes). The authors could give no plausible reason for the standard of CTG interpretation being so poor. However, it was clear from this study that, if the quality of interpretation of the intrapartum CTG had been higher, the benefits from EFM would almost certainly have been significantly and substantially enhanced.

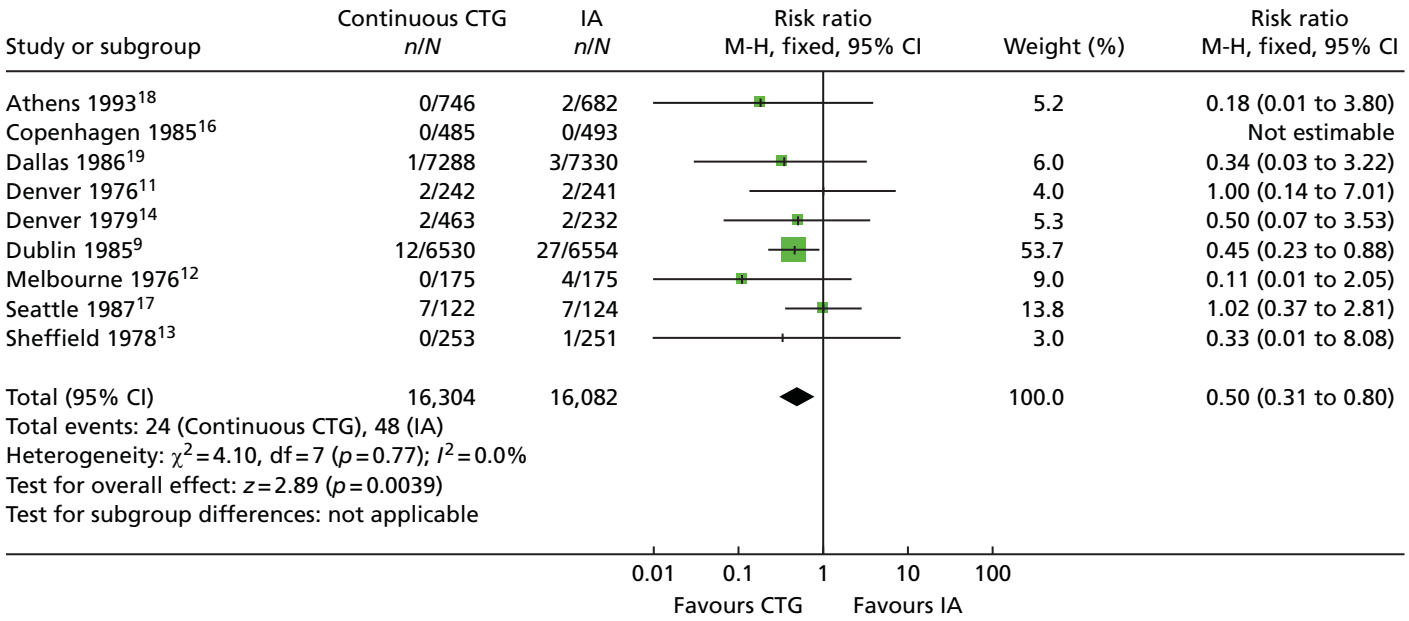

FIGURE 1 The effect of EFM vs. intermittent auscultation on the incidence of neonatal seizures. Review: continuous cardiotocography as a form of EFM for fetal assessment during labour; comparison: continuous cardiotocography vs. intermittent auscultation; outcome: 26 neonatal seizures. CTG, cardiotocography; df, degrees of freedom; FBS, fetal blood sample; IA, intermittent auscultation; M-H, Mantel–Haenszel.

In 1990, Ennis and Vincent published the results of their study of 64 cases of poor perinatal outcome from the archives of the Medical Protection Society.[23] In 11 cases, EFM was not performed, despite being indicated, and in six cases the technical quality of the tracing was inadequate. In 19 cases the CTG trace was missing, and in 14 cases a significant abnormality in the CTG trace either was unnoticed or did not result in any action being taken; in only 14 cases was appropriate monitoring performed and action taken. In only 16 cases was a consultant involved to aid in the interpretation of the CTG. In a further case–control study based in Oxford, published in 1994, intrapartum care was assessed in 141 cases of cerebral palsy and in 62 perinatal deaths with a probable intrapartum cause.[24] The authors found that, compared with control babies, abnormal fetal heart rate patterns were 2.3 times as common in babies who went on to develop cerebral palsy and 6.7 times as common in fetuses that died in the perinatal period. In addition, the authors found that clinicians failed to respond to these clear signs of abnormality in 26% of cerebral palsy cases and 50% of perinatal deaths, compared with 7% of control cases. On the basis of these figures, it can be estimated that approximately one case of cerebral palsy and one perinatal death can possibly be prevented in every 4500 deliveries. If one assumes 700,000 births per annum in the UK, 174 cases of cerebral palsy and 158 perinatal deaths could be prevented each year. Stewart *et al.*[25] reported that perinatal mortality in the UK is twice as high at night as during the day, and twice as high in July and August as in the rest of the year. They suggested that excess deaths may be because of over-reliance on inexperienced staff at night and a shortage of staff during the peak summer holiday months; they also suggested that the excess might be related to physical and mental fatigue of the caregivers. In 1999, the Confidential Enquiry into Stillbirths and Deaths in Infancy (CESDI) studied the proportion of 567 cases for which there was evidence of suboptimal care in labour. CESDI then looked at whether or not improved care could possibly or probably have prevented the adverse outcome.[26] Suboptimal care was identified in 71% of cases; a better outcome could possibly (in 28% of cases) or probably (in 22% of cases) have been anticipated, if care had been adequate. The report authors noted that interpretation of the CTG remained the most frequent problem identified as a cause of suboptimal care.

Does improving training solve the problem?

In a study of the efficacy of intrapartum intervention, Young *et al.*[27] found evidence of substandard care in labour in 74% of babies with low Apgar scores. Following the introduction of regular audit of low Apgar scores, with intensive feedback to clinical staff, this proportion fell to 23%, but then increased to 32% over the following year. However, following the introduction of compulsory training in CTG interpretation for all staff, the proportion of low Apgar score cases associated with substandard care fell back once again to only 9%. It is clear from this study that improved interpretation of CTGs during labour can bring about a striking increase in the quality of care, with measurable impacts on neonatal condition. However, intensive education is not sustainable in most clinical settings. With recent changes in the training of junior medical and midwifery staff, it is clear that there is a need to develop other systems that are less reliant on individual motivation and training. These systems need to work equally well, regardless of the time of day, day of the week, month of the year, and the level of staffing on the labour ward.

Litigation and the costs to families and society

Maternity services are associated with far higher litigation costs than other services. This is reflected in the various arrangements for the development of risk management standards across the UK (Clinical Negligence Scheme for Trusts in England; Welsh Risk Pool; Clinical Negligence and Other Risks Indemnity Schemes and NHS Quality Improvement Scotland in Scotland).

The total cost of claims reported to the NHSLA over the period 1996–2006 was £3.8B [Great British pounds (GBP)]. The annual figures for the value of maternity claims paid out (*Table 2*) demonstrate an increase of almost sixfold over the last 13 years and the rate of increase shows no signs of slowing. In response to a parliamentary question on 29 January 2007, it was stated that the total NHS compensation

TABLE 2 Litigation costs from maternity services

Year maternity claims paid out	Total cost in millions (GBP)
2003/4	96
2004/5	121
2005/6	144
2006/7	171
2007/8	162
2008/9	222
2009/10	197
2010/11	234
2011/12	422
2012/13	508
2013/14	458
2014/15	501
2015/16	578

GBP, Great British pounds.

payout in 2006 was £593M, with £68M resulting from just 10 cases, all of which were related to pregnancy and childbirth. By 2015/16, the total payout had risen to £1.488B, with £578M being attributable to maternity cases alone.[28] In 2007, the BBC reported a settlement of £6M for a child with cerebral palsy after doctors were alleged to have mismanaged the birth.[29] By 2015, the cost of a single case of cerebral palsy had risen to over £10M.[30] Even successful defence can cost up to £0.5M. In 2016, the NHSLA reported that the annual value of submitted claims related to pregnancy-related cerebral palsy had risen from £354M in 2004/5 to £989.7M in 2015/16.[28] In 2000, the *British Medical Journal* highlighted the importance of 'system errors' in medical disasters[31] and analogies were drawn with errors in aviation. It suggested that some techniques used in this industry could be applied effectively to medical care, such as safety drills, revalidation, 'nearmiss' reporting and a 'no blame' culture. The role of expert systems and 'intelligent alarms' was highlighted.

The potential solution: development of the intelligent decision support software

A group in Plymouth has been working on the problem of resolving human error in the management of labour for many years [Medical Research Council (MRC) funded for 10 years] and has developed intelligent computer systems as decision aids to support clinicians. The group was funded by the MRC for development and clinical validation of a decision support tool for the management of labour using the CTG. It comprises feature extraction of all relevant data from the CTG and clinical history which have been found to influence clinicians' decision-making, and then an analysis of these within a rule-based expert system. The specific piece of decision support software to be evaluated in INFANT has been designed by K2 Medical Systems (Plymouth, UK) (a spin-off company from the University of Plymouth) to run on the K2 Medical Systems data collection system (Guardian®). Guardian is a system for managing information from labour monitoring.

The data collection system (Guardian)

The Guardian system consists of a medical-grade personal computer (PC) platform (*Figure 2*) that meets the Medicines and Healthcare products Regulatory Agency standards for a class IIa device. The design has been informed by user preference studies and ethnographic and audio-visual observations of clinical care and decision-making.[32,33] It has a touch-screen user interface (*Figure 3*) and is connected to a conventional CTG recorder at the woman's bedside.

The PC uses the Microsoft Windows® (Microsoft Corporation, Redmond, WA, USA) operating system and runs the decision support software developed by the Plymouth group. The clinician enters clinical information (antenatal risk factors, vaginal examination data, fetal blood sample results, etc.) via the touch-screen. This information is displayed as a partogram (*Figure 4*). It displays the CTG on a computer screen alongside other clinical data [e.g. the partogram, maternal vital signs (including Modified Early Warnings Systems charts) and details of maternal anaesthesia and analgesia] that are collected as part of routine clinical care. Guardian does not interpret any of the data being collected, but acts as an interface to collect and display data at the bedside, centrally on the labour ward, in consultants' offices or remotely. The system requires little or no training to use and has been used for routine clinical care by a number of

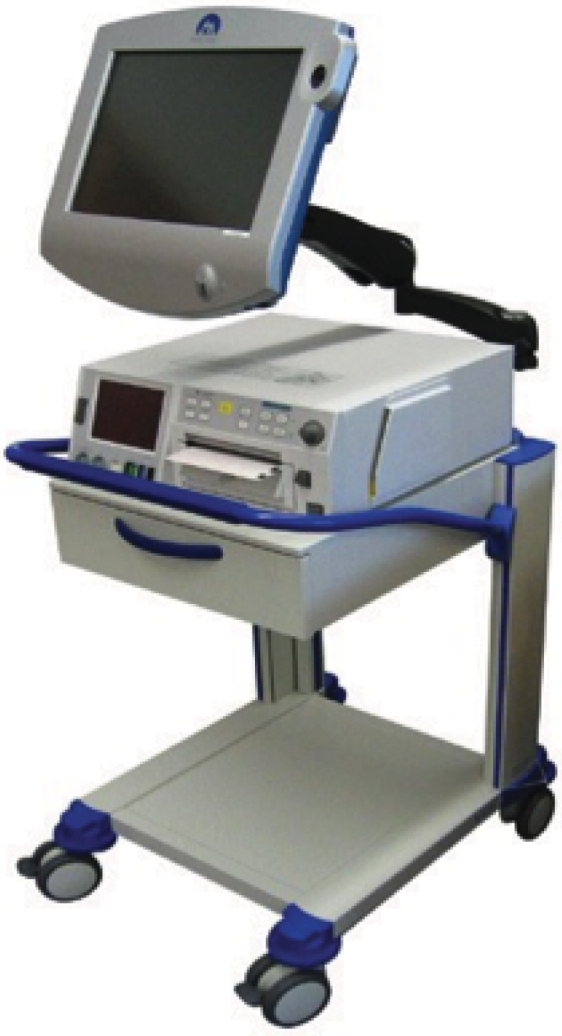

FIGURE 2 Guardian system: example of hardware.

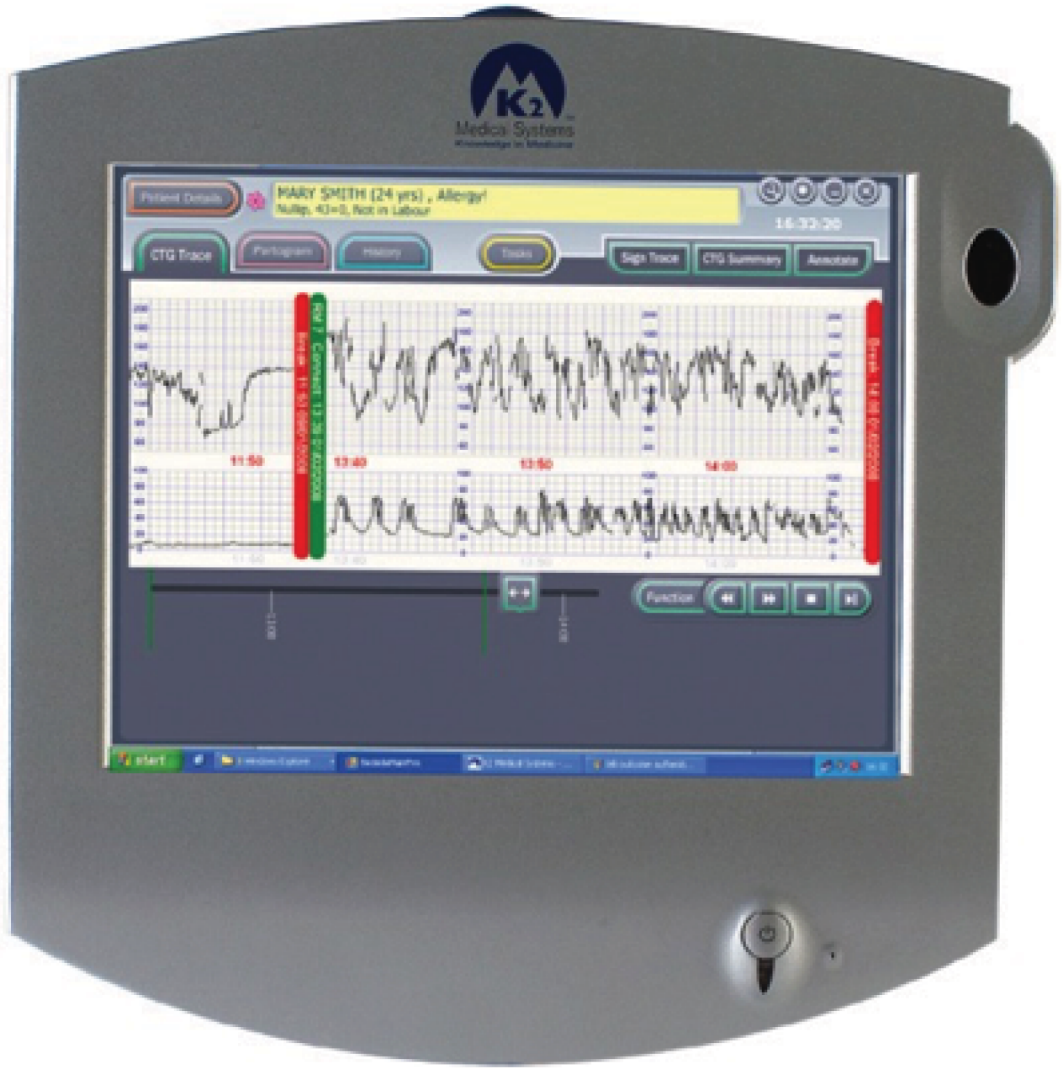

FIGURE 3 Guardian system: example of screen.

hospitals throughout the UK.[34] If CTG is performed by ultrasound or electrocardiography (ECG) clip, the PC system automatically collects these data from the RS 232 digital data port of any CTG recorder. The system displays the CTG data on the screen (*Figure 5*).

The decision support software

The decision support software is a specific piece of software that has been developed to run on the Guardian system. It extracts the important features of baseline heart rate, heart rate variability, accelerations, type and timing of decelerations, the quality of the signal and the contraction pattern from the CTG. The decision support software then analyses these data along with the quality of the signals. The system's assessment of the CTG is presented as a series of colour-coded alerts depending on the severity of the abnormality detected (*Figures 6–8*). The system can therefore be viewed as an intelligent prompt, but by recording the chronology of events it also offers the opportunity to later audit the actual clinical decision-making process in a similar way to an aircraft's black box.

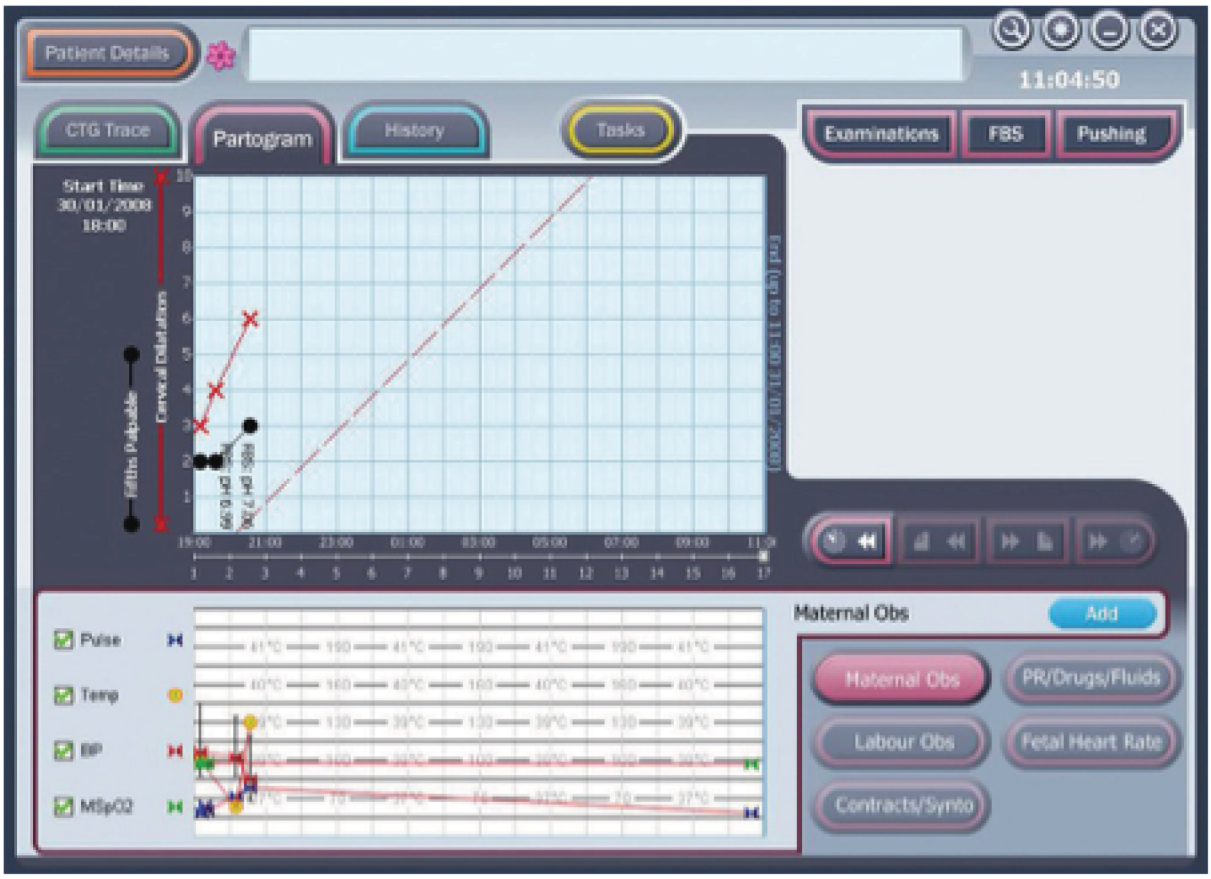

FIGURE 4 Guardian system: example of partogram on screen.

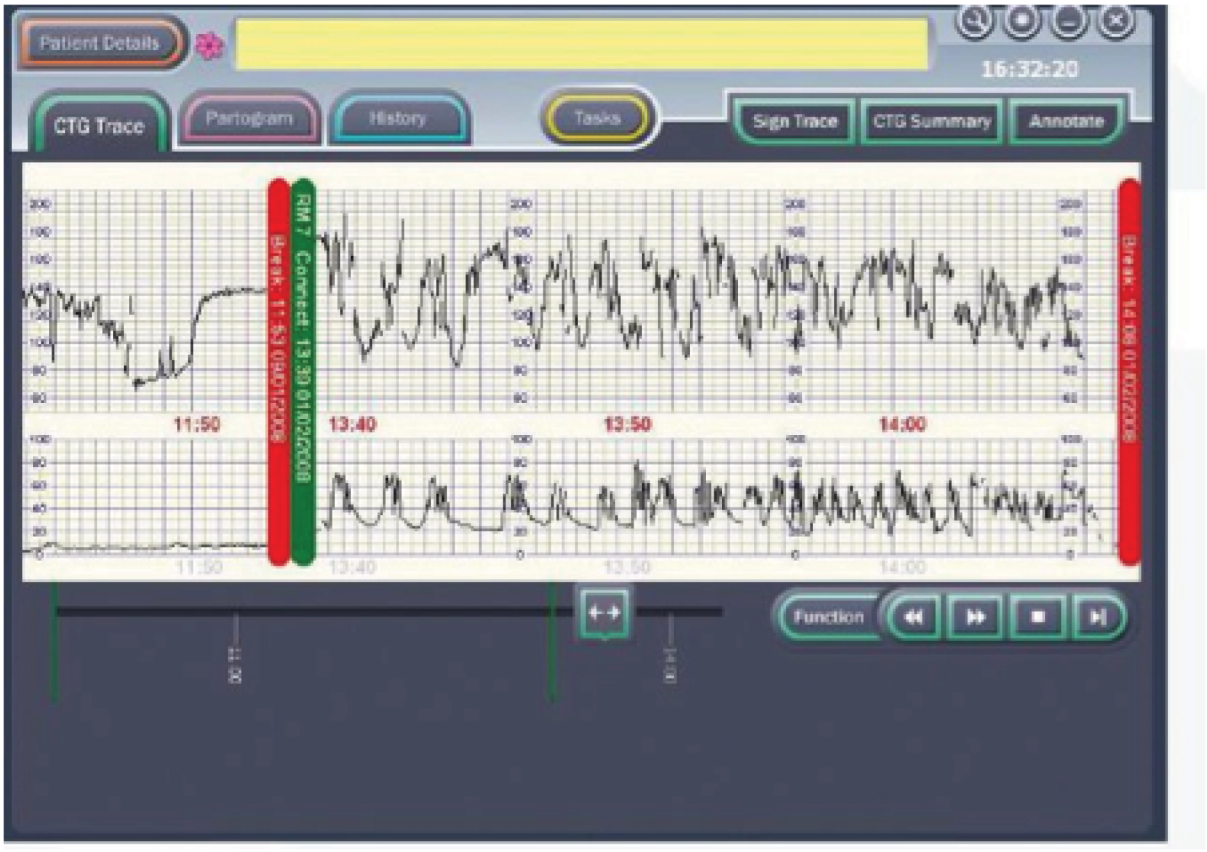

FIGURE 5 Guardian system: example of decision support on screen.

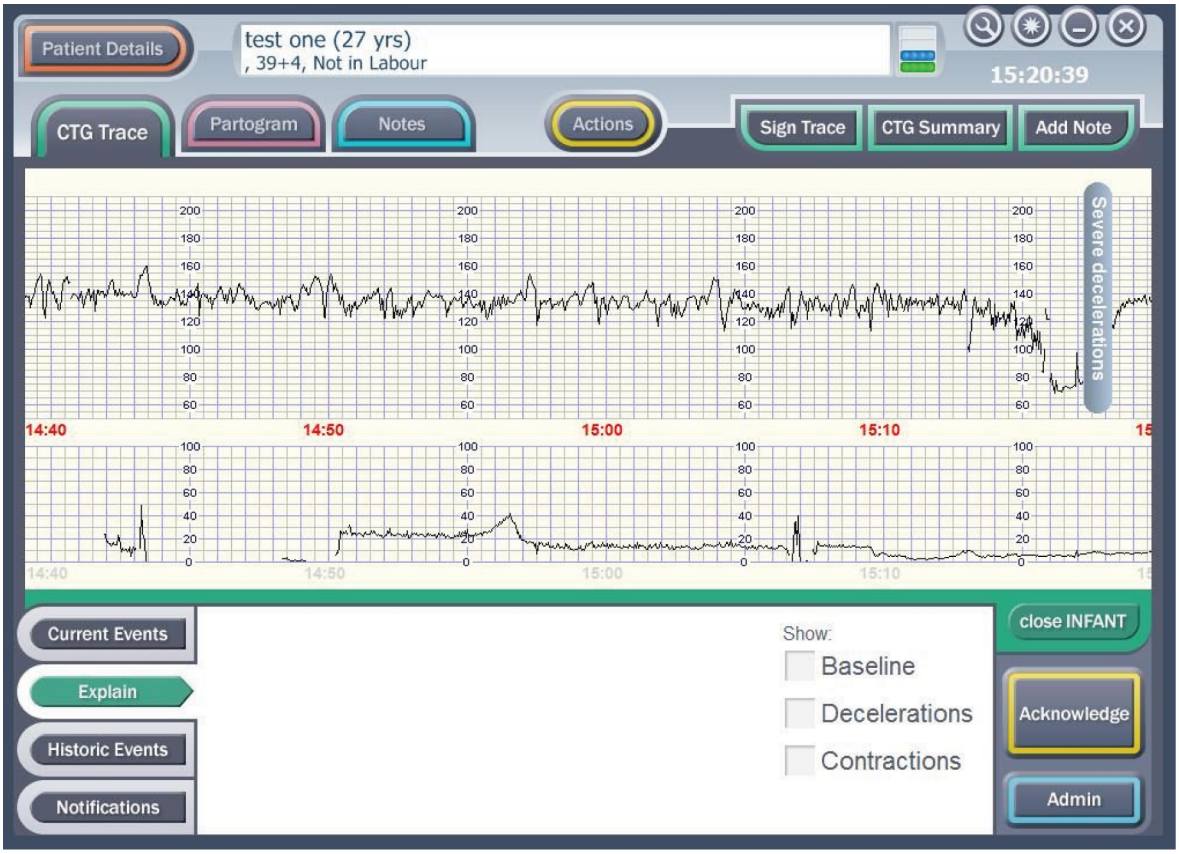

FIGURE 6 Example of a 'blue level of concern'.

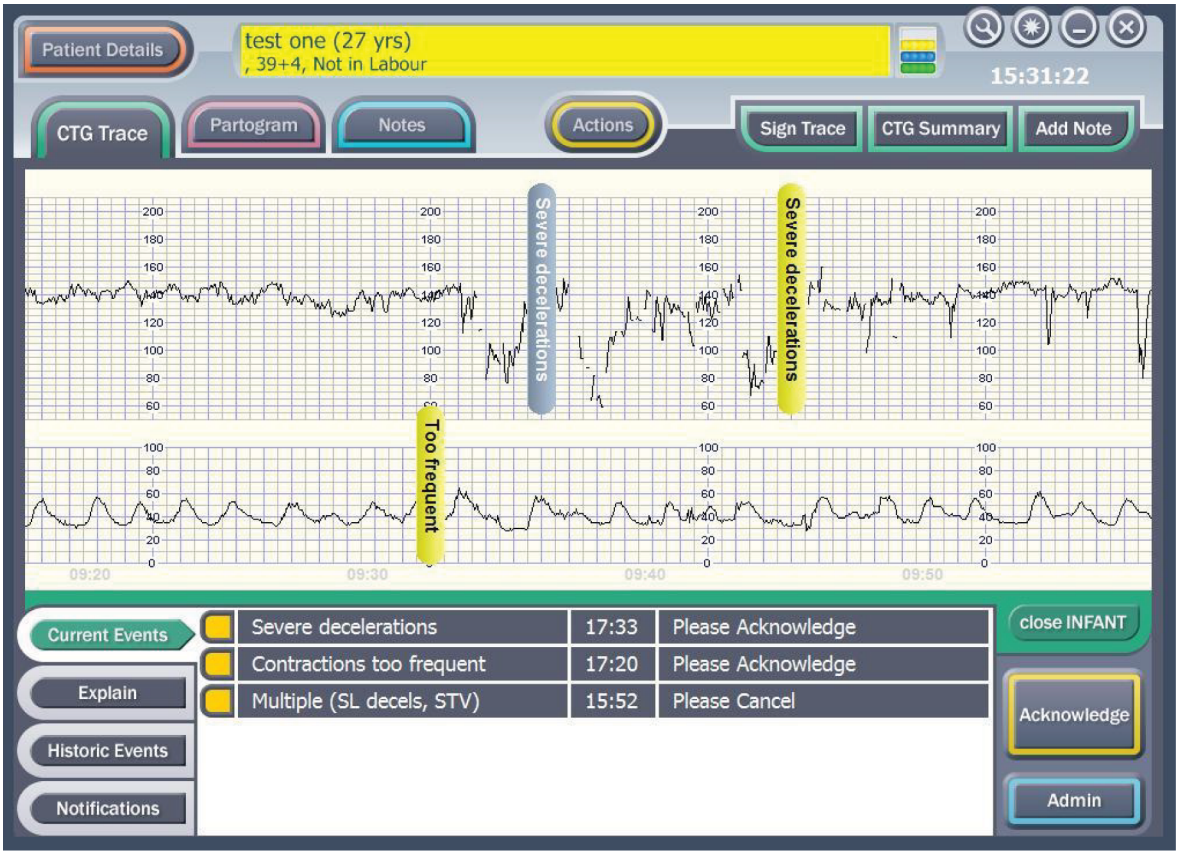

FIGURE 7 Example of a 'yellow level of concern'.

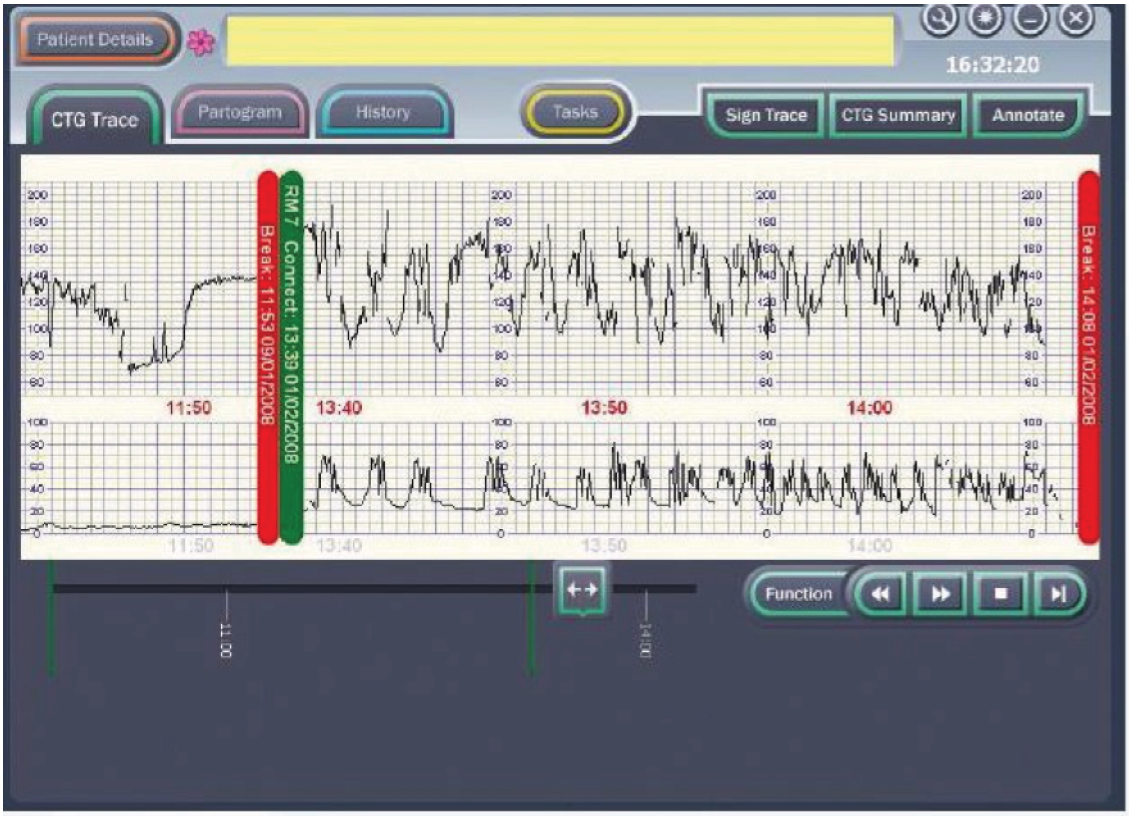

FIGURE 8 Example of a 'red level of concern'.

Studies using the intelligent support software

Three studies conducted by the Plymouth group[35–37] demonstrated that the software, when used 'offline', performed as well as expert obstetricians in interpreting the CTG and managing labour subsequently, and that the system performed better than routine clinical practice. The system identified more cases that went on to have a poor outcome and anticipated clinical decision-making. In one of these studies involving labours that had resulted in a stillbirth, the system 'intervened' (i.e. recognised the abnormality which would have prompted delivery) more than 6 hours earlier than happened in actual clinical practice and more than 2 hours before the experts. If this translated into clinical practice, it would be reasonable to expect that a number of such deaths might have been prevented if the software had been in use at the time. In all other poor-outcome groups the system 'intervened' much earlier than had happened in routine clinical practice and at a similar time as the experts. The system failed to predict one perinatal death, whereas the experts in the 'offline' study, and those functioning in routine clinical practice, failed to predict several deaths. These extensive 'offline' validation studies have shown that the system matches the performance of an expert obstetrician in interpreting the CTG and performed considerably better than routine clinical practice. Furthermore, the system is not overinterventional. From these data it seems reasonable to hypothesise that the clinical use of this computer-based decision support software would decrease the incidence of perinatal mortality and morbidity.

Current practice

Continuous electronic fetal monitoring is widely used for the majority of women during labour and birth in the UK. NICE guidelines for fetal monitoring detail explicit criteria indicating which women should be offered EFM during labour; approximately 60% of all women in labour meet these criteria.[21] This study did not aim to influence the number of women who received EFM.

Research objectives

Our hypotheses were that:

1. a substantial proportion of substandard care results from a failure to correctly identify abnormal fetal heart rate patterns
2. improved recognition of abnormality would reduce substandard care and poor outcomes
3. improved recognition of normality would reduce unnecessary intervention.

These led to the objectives of the study, to:

1. determine whether or not intelligent decision support can improve interpretation of the intrapartum CTG and, therefore, improve the management of labour for women who are judged to require EFM. Specifically, will the system, compared with current clinical practice:

    i. identify more clinically significant heart rate abnormalities?
    ii. result in more prompts and timely action on clinically significant heart rate abnormalities?
    iii. result in fewer poor neonatal outcomes?
    iv. change the incidence of operative interventions?

2. assess whether or not the use of intelligent decision support improved the quality of routine care received by women undergoing EFM during labour. This information was important for evaluating whether or not the decision support software decreases the risk of suboptimal care in labour; it was also useful to explore the effect that such an intervention may have on litigation costs for obstetrics
3. determine whether or not the use of the decision support software was cost-effective in terms of the incremental cost per poor perinatal outcome prevented
4. determine whether or not use of the decision support software had any effect on the longer-term neurodevelopment of children born to women participating in the INFANT study.

Chapter 2 Methods

The INFANT study was an individually randomised controlled trial of 46,000 women who were judged to require EFM in labour. Follow-up was completed at 2 years for a sample of 7000 surviving children born to women participating in the INFANT study.

Trial eligibility and randomisation

Inclusion criteria

Women admitted to a participating labour ward who fulfilled all of the following criteria were eligible to be recruited and randomised.

- Women were judged to require EFM by the local clinical team based on existing guidelines, and the woman consented to have EFM, and EFM was possible.
    - Note that EFM is defined as the active decision of the health-care professional and the woman to initiate EFM for the purpose of fetal monitoring, usually because of perceived risk factor(s) that increase the likelihood of fetal compromise occurring in labour.
    - The decision to initiate EFM can occur at any time during labour. Some women with known factors that place them at higher risk of fetal compromise during labour would already know that EFM throughout labour was planned. Others started labour with intermittent monitoring and then were judged to require EFM at some point during the labour. Women were eligible to participate at any stage of labour.
- Women were pregnant with a single fetus or twins.
- Gestational stage was ≥ 35 weeks (≥ 245 days).
- There was no known gross fetal abnormality, including any known fetal heart arrhythmia such as heart block.
- Women were aged ≥ 16 years.
- Women were able to give consent to participate in the trial as judged by the attending clinicians.

Exclusion criteria

- Triplet or higher-order pregnancy.
- Criteria for EFM not met, including elective caesarean section prior to the onset of labour.

Information for women and obtaining informed consent

Information about the trial was provided to women during the antenatal period (see *Appendix 1*), after their booking appointment. This process was individualised for each participating centre depending on their routine practices. For example, in some centres, women were provided with information about the trial at their routine ultrasound scan appointment (18–22 weeks). All women had the opportunity to ask questions.

When a woman presented in early labour to the labour ward in a participating centre, she was given a copy of the participant information leaflet (see *Appendix 2*) and a verbal explanation of the INFANT trial. She was then asked whether or not she would like to participate in the study and, if she agreed, she was asked to sign an INFANT trial consent form. Then, if at any point EFM was commenced during labour, the midwife responsible for the woman's care checked her eligibility to participate in the trial and that she was still happy to take part. This was documented, and then the woman was randomised by the Guardian system to either the decision support (intervention) arm or the no decision support (control) arm.

All women in labour admitted to the participating centres were expected to have their labour information recorded in the Guardian system, in accordance with the current practice in each centre. This did not change the way health professionals managed labour; it merely changed the way they managed the information generated by the process of monitoring labour and how they recorded this information. It was clearly stated that women were free to withdraw from the study at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal.

Written informed consent was obtained by means of a dated signature from the woman and the signature of the person who obtained informed consent (see *Appendix 3*); this would be the principal investigator (or a qualified health-care professional with delegated authority). A copy of the signed informed consent document was given to the woman. A further copy was retained in the woman's medical notes, a copy was retained by the principal investigator and a final copy was sent to the trial co-ordinating centre.

A senior investigator was available at all times to discuss concerns raised by women or clinicians during the course of the trial.

Randomisation

The Guardian system prompted the health professional providing care to consider whether or not the woman was eligible for the INFANT trial when EFM had been used for > 5 minutes. Intermittent use of EFM for durations of up to 5 minutes could be employed for intermittent monitoring, but when used for longer periods of time this would indicate that a decision had been made to initiate EFM, in which case the woman may have been eligible to participate in the trial. If the health-care professional indicated that the woman was not yet eligible because an active decision had not been made to initiate EFM, then the Guardian system prompted the health-care professional again, if the CTG continued to be recorded for longer than 5 minutes in that or any subsequent episode of monitoring.

When the health-care professional indicated that a woman was eligible to participate, the Guardian system clarified that the necessary eligibility criteria for trial entry had been met (i.e. that the health professional gave the required answers to a number of questions posed by the Guardian system, and then the Guardian system randomly allocated the women in the ratio 1 : 1 to either 'CTG with no decision support' or 'CTG with decision support') (*Figure 9*). The allocations were computer generated in Stata® version 10 (StataCorp LP, College Station, TX, USA) using stratified block randomisation employing variable block sizes to balance between the two trial arms by singleton or twin pregnancy, and within each participating centre. The procedures for randomisation were fully documented, reviewed and signed off prior to the start of the trial and monitored by the co-ordinating centre during the trial.

Planned interventions

The intervention was the use of decision support software. In order to accurately reflect any potential impact of the decision support software in contemporary NHS practice, such as changes in midwifery presence during labour consequent upon knowledge of the allocation, it was desirable that clinicians were not masked to allocation.

Clinical management

The Guardian system was developed to be used with all women in labour in the participating centres. It was only the decision support software that runs on this system that was being tested in this trial.

Clinicians in all participating centres were initially trained in the use of the decision support software by staff from the trial co-ordinating centre (see *Appendix 4*). This process included developing a 'training team' at each site which was responsible for cascading training among the local clinicians. The clinical management of women in the trial was not altered by their participation; however, staff caring for women in the decision support arm received a series of graded alerts or alarms when abnormalities of the CTG

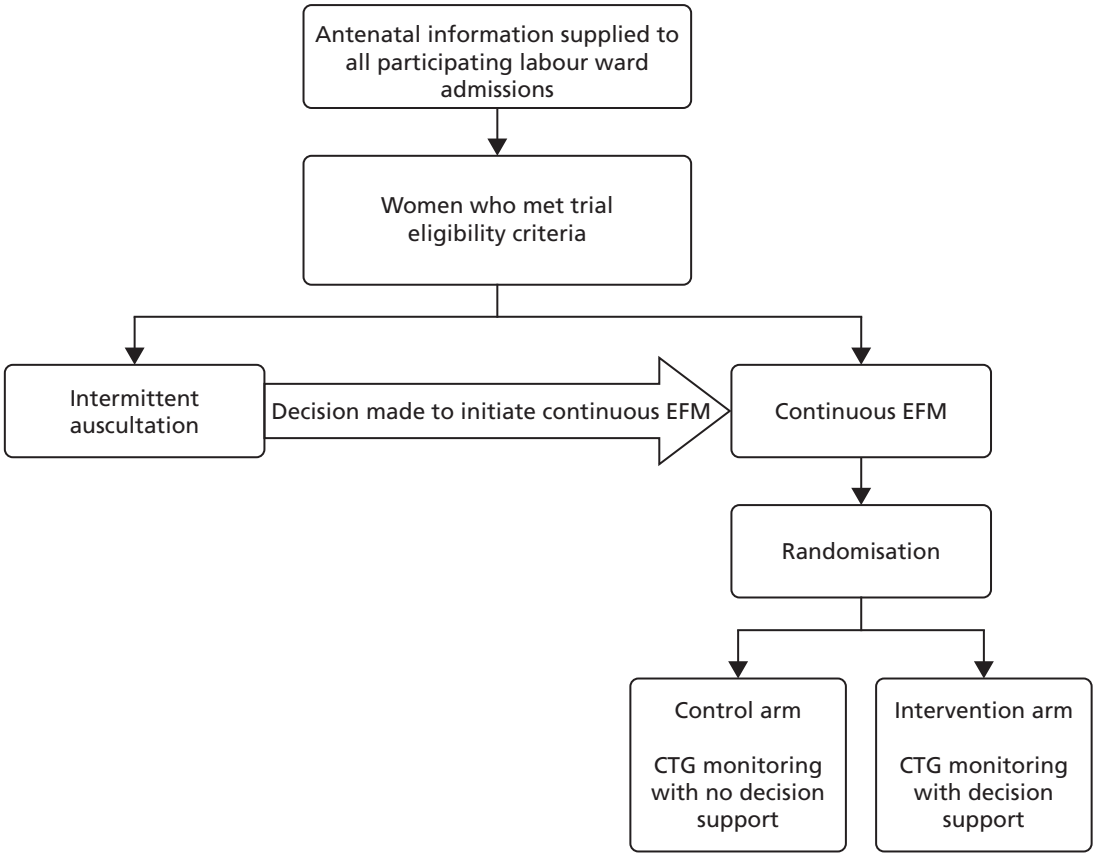

FIGURE 9 Flow diagram.

were detected by the system, which increased in urgency with the severity of the abnormality as judged by the system. No additional training was provided to clinical staff in how to respond to fetal heart rate abnormalities as part of their participation in the trial because, in the UK and Republic of Ireland, staff supervising labour and delivery are expected to have had such training, for example by completing computer-based training packages every 6–12 months, attending annual lectures and attending regular CTG review meetings.

Primary outcome measures

Primary short-term outcome

The primary short-term outcome was a composite of poor neonatal outcome including deaths [intrapartum stillbirths plus neonatal deaths (i.e. deaths up to 28 days after birth) except deaths as a result of congenital anomalies], significant morbidity (moderate or severe NNE, defined as the use of whole-body cooling) and admissions to a neonatal unit within 48 hours of birth for ≥ 48 hours (with evidence of feeding difficulties or respiratory illness and when there was evidence of compromise at birth suggesting that the condition was the result of mild asphyxia and/or mild encephalopathy).

Note: we recognised that the signs of mild encephalopathy can be subtle and hence a number of babies identified as having this condition were likely to have a range of non-specific signs such as respiratory difficulty and poor feeding rather than features more specifically associated with encephalopathy.[38] Therefore, we included 'admission to the neonatal unit within 48 hours of birth for ≥ 48 hours where there is evidence of compromise at birth'. Since this was a mature group of babies (born ≥ 35 weeks), any difference in the incidence of these admissions was felt likely to result from differences in perinatal asphyxia.

Primary long-term outcome

The primary long-term outcome was the Parent Report of Children's Abilities-Revised (PARCA-R) composite score[39,40] at the age of 2 years for a subset of 7000 infants.

Note: neurodevelopmental delay and cerebral palsy are the most important long-term adverse outcomes associated with perinatal asphyxia. However, the incidence of moderate or severe cerebral palsy is around 1.5–2.5 per 1000 live births, depending on the definition and the method of ascertainment. There is also uncertainty about the proportion of these cases that results from intrapartum asphyxia in mature infants; however, 30% appears to be a reasonable estimate.[4] Therefore, given the rarity of this outcome, it was unlikely that a clear difference could be demonstrated between the two groups in a trial of 46,000 births. In order to have reassurance that any benefits of the intervention, with respect to short-term outcomes, had not occurred at the expense of later neurodevelopmental delay, we measured neurodevelopment in a proportion of the surviving children at the age of 2 years.

Secondary outcome measures

Secondary short-term outcomes

Neonatal

- Intrapartum stillbirth (excluding deaths as a result of congenital anomalies).
- Neonatal deaths up to 28 days after birth (excluding deaths as a result of congenital anomalies).
- Moderate or severe encephalopathy.
- Admission to neonatal unit within 48 hours of birth for ≥ 48 hours with evidence of feeding difficulties, respiratory illness or encephalopathy (when there was evidence of compromise at birth).
- Admission to a higher level of care.
- An Apgar score of < 4 at 5 minutes after birth.
- The distribution of cord blood gas data for cord artery pH.
- Metabolic acidosis (defined as a cord artery pH of < 7.05 and a base deficit in extracellular fluid of ≥ 12 mmol/l).
- Resuscitation interventions.
- Seizures.
- Destination immediately after birth.
- Length of hospital stay.

Maternal

- Mode of delivery.
- Operative intervention (caesarean section or instrumental delivery) for:
  - fetal indication or
  - failure to progress or
  - a combination of fetal distress and failure to progress or
  - other reason.
- Grade of caesarean section.
- Episiotomy.
- Any episode of fetal blood sampling.
- Length of:
  - first stage of labour from trial entry
  - second stage of labour from trial entry
  - labour from trial entry (total).

- Destination immediately after birth.
- Admission to a higher level of care.

Secondary long-term outcomes (infant)

Health and development outcomes at 24 months

- Non-verbal cognition scale (PARCA-R).
- Vocabulary subscale (PARCA-R).
- Sentence complexity subscale (PARCA-R).
- Late deaths up to 24 months (after the neonatal period).
- Diagnosed with cerebral palsy.
- Non-major disability.
- Major disability.
- Breastfeeding (collected at 12 and 24 months).

Quality-of-care outcomes

- Adverse outcome (trial composite primary outcome plus metabolic acidosis) when it is judged that suboptimal care has occurred in labour: levels 1 to 3 separately and combined.
- Level 1: suboptimal care, but different management would have made no difference to outcome.
- Level 2: suboptimal care, and different management might have made a difference to outcome.
- Level 3: suboptimal care, and different management would reasonably be expected to have made a difference to the outcome.

Note: in all cases of adverse outcome (trial primary outcome plus a cord artery pH of < 7.05 with a base deficit of ≥ 12 mmol/l) and all neonatal deaths and intrapartum stillbirths care in labour was assessed, to determine if it was suboptimal, by panel review similar to that undertaken by the Confidential Enquiry into Maternal and Child Health (CEMACH).[26] Intrapartum notes were copied and anonymised, and all references to trial allocation removed. The notes were then examined by a panel of an experienced obstetrician, midwife and neonatologist to identify if there was suboptimal care, particularly in relation to interpretation of the CTG and actions that flowed from any identification of CTG abnormalities.

Process outcomes (after trial entry)

- Total number of CTG abnormalities (blue, yellow and red levels of concern) detected by the decision support software.
- Number of blue levels of concern on the decision support software, indicating a mild abnormality on the CTG.
- Number of yellow levels of concern on the decision support software, indicating a moderate abnormality on the CTG.
- Number of red levels of concern on the decision support software, indicating a severe abnormality on the CTG.
- Number of women with at least one yellow level of concern on the decision support software, indicating an abnormality on the CTG.
- Number of women with at least one red level of concern on the decision support software, indicating a severe abnormality on the CTG.
- Time from first red level of concern to birth.

Note that it was important to collect and analyse process outcomes in the trial, as a failure to detect differences in clinical or quality-of-care outcomes between the two randomised groups may be because of poor adherence with the alerts of the system, rather than the system not correctly identifying abnormalities

with the CTG. In addition, as the trial allocation was not masked, it was important to measure any change that resulted from clinicians being aware of whether or not the decision support system was in operation.

- Number of thumb entries per hour from time of trial entry to first yellow level of concern or until fully dilated (10 cm) if no abnormality detected or first yellow level of concern occurred prior to trial entry.
- Number of vaginal examinations.
- Epidural analgesia.
- Labour augmentation.
- Presence of meconium.

Note: some of these later process outcomes (e.g. the number of thumb entries per hour) were proxy measures to determine the presence of a health professional in the delivery room during the labour, which allowed us to quantify any differences between the groups with respect to support offered to women during labour. Although unlikely, knowledge of the trial allocation could have resulted in less frequent contact with the woman allocated decision support in labour. Less frequent contact would have resulted in a lower number of these process measures.

Data collection

For all participating women and babies, labour variables and outcomes were stored automatically and contemporaneously on the Guardian system. Data collected via the system were sent electronically to the trial co-ordinating centre. Data were extracted from the notes of babies admitted to the neonatal unit and for all neonatal deaths (see *Appendices 5–7*), as well as for mothers admitted for a higher level of care (see *Appendix 8*). Not all data fields were collected at every centre. However, when an item was collected, these data were sent to the clinical trials unit. The trial did not collect the reason why EFM was being used, as this was not recorded. All children surviving to be discharged home from hospital following their birth were 'flagged' at the NHS Information Centre for those born in England, and for those born in Scotland comparable systems were used. All deaths occurring after discharge home from hospital were notified to the trial co-ordinating centre. At 2 years after trial entry a sample of 7000 surviving children (3500 in each group) were followed up. The family was sent a two-part parent-completed questionnaire to assess the child's health, development and well-being (see *Appendix 9*). The first part of the questionnaire comprised the PARCA-R, which had been previously validated as a means of assessing neurodevelopment in a trial setting.[39,40] The second part focused on general health issues, and had also been used previously.

Calculation of proposed sample size

The proposed total sample size was 46,000 births.

The following data sources and assumptions were used in the calculation of the trial sample size.

Incidence of intrapartum stillbirth

This was estimated as 0.35 per 1000 births. This estimate was derived from the following incidence data: 0.51 per 1000 births for women of all gestation periods (England, Wales and Northern Ireland, 2004)[41] and 0.27 per 1000 births for women at ≥ 37 weeks' gestation (Trent Region, 2005).[42] This trial restricted eligibility to women at ≥ 35 weeks' gestation; therefore, the incidence was expected to be lower than in women at all gestational ages, which includes those who deliver preterm. However, it was also expected to be higher than for all women at term. As the women being recruited were all judged to require EFM and it was assumed that women in this 'risk group' would be at increased risk of adverse outcomes, the incidence was likely to be higher. In addition, these estimates used a denominator of all modes of births and so they included women having elective caesarean sections, who are not at risk of intrapartum stillbirth as there is no intrapartum period. Approximately 7% of women have elective caesarean sections, and removal of these women would increase the incidence further. Therefore, an estimate of an incidence of 0.35 per 1000 births appeared reasonable.

Incidence of neonatal death

This was estimated as 0.7 per 1000 births. This estimate was derived from the following data: 3.4 per 1000 births for women of all gestation periods (England, Wales and Northern Ireland, 2004)[41] and 0.89 per 1000 births in those women at ≥ 37 weeks' gestation (Trent Region, 2005).[42] This trial restricted eligibility to women at ≥ 35 weeks' gestation; therefore, the incidence would be expected to be lower than among women of all gestational ages, which includes those who deliver preterm. However, it would be higher than for all women at term. A reasonable estimate of neonatal death for babies at 35 weeks' gestation or more was therefore considered to be 1.0 per 1000 births. Using data from the Trent Survey 2005[42], 30% of neonatal deaths were as a result of congenital anomalies. Therefore, this rate was reduced to 0.7 per 1000 births. As the women being recruited were all judged to require EFM and it was assumed that women in this 'risk group' would be at increased risk of adverse outcomes, the incidence may have been higher. Therefore, an estimate of an incidence of 0.7 per 1000 births appeared reasonable.

Incidence of severe and moderate neonatal encephalopathy

The most appropriate estimate of the incidence of NNE in babies born at ≥ 35 weeks' gestation was 1.3 per 1000 births (Trent & Northern Region, 2002).[43] However, as above, women being recruited to this trial were all judged to require EFM, which means that they may have been at increased risk of adverse outcomes; therefore, the incidence may have been higher.

Combined outcomes

Data were available on some combined outcomes. For example, the incidence of intrapartum stillbirths plus deaths on the labour ward assumed to be as a result of intrapartum asphyxia (the incidence of which is much lower than neonatal mortality) plus severe and moderate NNE was 1.7 per 1000 births (95% CI 1.5 to 1.9; range 0.8–2.3) (18 hospitals, Trent, 2003–4) and 1.9 per 1000 births (95% CI 1.6 to 2.3; range 0.6–2.3) (12 hospitals, Yorkshire Neonatal Network, 2004–5).[43] These data are for babies born at ≥ 35 weeks' gestation, with the incidence of these outcomes being higher in the larger hospitals, which attract women with more complicated pregnancies.

Incidence of primary outcome for INFANT

We assumed an incidence of the primary outcome of 3 per 1000 births. This was calculated by summing the rate of intrapartum stillbirth, neonatal death, and moderate and severe encephalopathy, which gave an incidence of 2.35 per 1000 births. However, added to this figure was mild encephalopathy, which was reported to occur in 1.25 per 1000 births, and other significant morbidity [other admissions to the neonatal unit within 48 hours of birth for ≥ 48 hours (e.g. with feeding difficulties, respiratory symptoms or seizures)], for which there were no good estimates of incidence. The estimate of 3 per 1000 births erred on the side of caution and an increased incidence of this outcome in the trial would either (a) increase the power of the trial to demonstrate the same effect size or (b) allow detection of a smaller effect size with the same trial size or (c) necessitate a smaller trial if the postulated effect size (or larger) was detected.

Effect size

The effect size that can be detected with 46,000 women (23,000 in each group), assuming a 5% level of significance and 90% power, was a 50% reduction in poor neonatal outcome rate from 3 to 1.5 per 1000 births. We approximated the number of women recruited with the number of infants born, even though women with a twin pregnancy were eligible to join the trial. Approximately 1 in 80 pregnancies are twin pregnancies; however, a proportion of these births will occur at < 35 weeks' gestation and a large proportion of the term births would be by elective caesarean section. Therefore, we estimated that < 1% of all births in the study would be twins. In a study of 164 preterm infants,[40] the mean PARCA-R composite score at 2 years was 80 points (SD 33 points) and the mean Mental Development Index (Bayley Scales of Infant Development II) score was approximately half a SD below the standardised mean of 100. We assumed that a normal group of term-born infants would have a PARCA-R composite score half a SD above this sample of preterm infants, so we estimated a mean 2-year score of 96 points (SD 33 points). Based on this estimate, a follow-up sample of 7000 children (3500 per arm) in the INFANT study would have over 90% power to detect a difference of 3 points in the PARCA-R composite score with a two-sided

5% significance level. The incidence of severe metabolic acidosis (a cord artery pH of < 7.05) has been reported as 10 per 1000 births.[44–47] The proposed sample size was therefore able to detect a 28% relative risk reduction in this incidence with > 80% power in those babies who had their cord artery pH measured.

Assumptions

Variations in some of the assumptions of incidence produced marked variations in the required sample size as the anticipated overall incidence was so low. For example, *Table 3* illustrates the impact on the required sample size of varying the incidence of the primary outcome, assuming a 5% level of significance and 90% power for the same effect size (a 50% relative risk reduction).

Table 4 illustrates the variation on the effect size that could be detected with a sample size of approximately 46,000 women with variations in incidence.

Loss to follow-up

It was assumed that loss to follow-up for the short-term primary outcome would be negligible, as most of this information would be collected before the woman left the delivery room in which she had been recruited. For neonatal outcomes, a small number of babies were admitted to a neonatal unit separate from where they were born or planned to be born, in which case data were collected from these sites through the research midwives employed by the study in the participating centres. At the time of entry to the study all women were asked for permission for their contact details to be downloaded to the trial co-ordinating centre along with their clinical details from the Guardian system. The families selected for follow-up at 2 years were contacted by post 8 weeks after birth and informed that they had been selected for the follow-up study. Contact with families who agreed to take part was maintained during the period between birth and the follow-up assessment by sending a birthday card each year along with a FREEPOST change-of-address card to facilitate communication with University College London (UCL) Comprehensive Clinical Trials Unit about updated contact details.

TABLE 3 Sample size assuming 5% level of significance, 90% power and 50% relative risk reduction

Incidence of primary outcome in (per 1000 births)			
No decision support group	Decision support group	Relative risk	Total sample size required
3.0	1.5	0.5	46,000
4.0	2.0	0.5	34,000
5.0	2.5	0.5	27,000
6.0	3.0	0.5	22,000

TABLE 4 Effect size detectable assuming 5% level of significance and 90% power, with variation in incidence of primary outcome in the no decision support group

		Incidence of primary outcome in (per 1000 births)	
Total sample size	Relative risk	No decision support group	Decision support group
46,000	0.50	3.00	1.50
46,000	0.56	4.00	2.25
46,000	0.61	5.00	3.05
46,000	0.64	6.00	3.85

Trial management

Research governance

The sponsor of the trial was initially the University of Oxford (January 2009 to May 2012), but changed to UCL when the trial moved (May 2012 to June 2016). The trial was run on a day-to-day basis by the project management group. This group reported to the Trial Steering Committee (TSC), which was responsible to the research sponsor. At each participating centre, local principal investigators reported to the project management group via the project-funded staff based at the UCL Comprehensive Clinical Trials Unit.

Insurance

NHS indemnity operated in respect of the clinical treatment being provided. In addition, the sponsor had appropriate insurance-related arrangements in place.

Trial Steering Committee

The trial was supervised by an independent TSC. The precise terms of reference for the TSC were agreed at its first meeting. A TSC charter similar to that used by the Data Monitoring Committee (DMC) (see *Data Monitoring Committee*) was completed.

Data Monitoring Committee

An independent DMC was established for the trial. This was independent of the trial organisers. The terms of reference for the DMC were agreed at the first meeting. A DMC charter was completed following the recommendations of the DAMOCLES (DAta MOnitoring Committees: Lessons, Ethics, Statistics) study.[48]

During the period of recruitment to the trial, interim analyses were supplied, in strict confidence, to the DMC, together with any other analyses the DMC requested. In the light of interim data, and other evidence from relevant studies, the DMC would inform the TSC if, in its view, there was proof beyond reasonable doubt that the data indicated that any part of the protocol under investigation was either clearly indicated or contraindicated, either for all women or for a particular subgroup of trial participants. A decision to inform the TSC would in part be based on statistical considerations. Appropriate criteria for proof beyond reasonable doubt could not be specified precisely. A difference of at least three standard errors (SEs) in the interim analysis of a major endpoint may have been needed to justify halting, or modifying, the study prematurely. This criterion had the practical advantage that the exact number of interim analyses would be of little importance, and so no fixed schedule was proposed.[49] Unless modification or cessation of the protocol was recommended by the DMC, the TSC, collaborators and administrative staff (except those who supply the confidential information) would remain masked to the results of the interim analysis. Collaborators and all others associated with the study were able to write, through the trial office, to the DMC, to draw attention to any concerns they may have about the possibility of harm arising from the treatment under study, or about any other matters that may have been relevant.

Publication policy

The chief investigator was responsible for co-ordinating the dissemination of data from this study. All publications using data from the study to undertake original analyses were submitted to the TSC for review before release. To safeguard the scientific integrity of the trial, it was agreed that data from the study would not be presented in public before the main results were published, without the prior consent of the TSC. The success of the trial depended on a large number of midwives and obstetricians. For this reason, chief credit for the results would be given not to the committees or central organisers, but to all who collaborated and participated in the study. It was agreed that authorship at the head of the primary results paper would take the form 'The INFANT Collaborative Group', to avoid giving undue prominence to any individual.

Chapter 3 Substudy of maternal anxiety in labour during recruitment to the pilot phase of the INFANT trial

During the process of application to the Research Ethics Committee (REC) for approval to undertake the INFANT trial, the committee was concerned that the use of the decision support technology during labour may increase anxiety among the women taking part. The committee asked the trial team to provide some reassurance that participating in the trial would not result in unacceptable anxiety for the women taking part.

We developed the study described below to address this. Sections of this chapter have been reproduced with permission from Barber *et al.*[50] Copyright © 2013, MA Healthcare Limited. Quotations from participants in this qualitative study have been reproduced verbatim from this publication with permission from the journal.

Introduction

Anxiety is common in pregnancy[51] and EFM can lead to increased anxiety.[52] A study in Australia reported interviews with 100 women shortly after a straightforward birth and found that only 15% reported no anxiety during labour and birth.[53]

Confidential enquiries into perinatal deaths have repeatedly demonstrated that most poor infant outcomes arise during labour. EFM was introduced into clinical practice to try to prevent these poor outcomes; however, we know that poor interpretation of fetal heart rate patterns occurs. Improvements in CTG interpretation have to be sustainable and ideally be independent of clinicians' abilities. Computerised interpretation and decision support have the potential to improve care.

If women are aware of an effective method of interpreting their baby's heart rate during labour, and understand that this is safer than an individual clinician's interpretation, this may result in reduced anxiety.

The INFANT decision support software assesses the CTG and provides a colour-coded 'ladder of concern', which appears on the CTG screen (see *Chapter 1* for more detail).

The aim of this study was to explore whether or not the use of EFM during labour increases or reduces anxiety levels among women and whether or not the addition of the INFANT decision support software has a positive or negative effect on these anxiety levels. We initially used a survey to measure anxiety in women randomised to each arm of the INFANT trial. We then used qualitative interviews in a smaller number of women to explore their feelings of anxiety associated with the use of monitoring in labour and the decision support system.

Methods

Survey

From 5 January 2010 to 18 July 2010, 469 women were recruited to the pilot phase of the INFANT trial from the Royal Blackburn Hospital. A total of 234 women were recruited to the CTG monitoring only (control) group and 235 were recruited to the CTG monitoring plus decision support (intervention) group. The eligibility criteria and process of recruitment are described in *Chapter 2*. In a subset of women approached to participate in the INFANT trial, we measured anxiety in the latent phase of labour when cervical dilatation was ≤ 3 cm with an effaced cervix. If the woman was recruited into the trial, we measured anxiety at a

further two time points: during the active phase of labour when the cervical dilatation was 4–7 cm, and within 48 hours post partum. At each time point, the midwife asked women to rate their anxiety using a visual analogue scale – anxiety (VAS-A) from 1 (not at all) to 10 (very much so). Their responses were recorded on the VAS-A study form (*Figure 10*).

Statistical analysis

The change in VAS-A scores in the two groups (control and intervention) (1) from the latent to the active phase of labour and (2) from the latent phase to the postpartum period was analysed using repeated measures analysis of covariance (ANCOVA). This enabled us to include all women in the analysis, even those with data at only one time point. The correlation between scores between phases was calculated using the Pearson correlation coefficient. Two-sided significance tests were used, taking a *p*-value of 0.05 as significant. The analysis was conducted using statistical software Stata version 11.1.

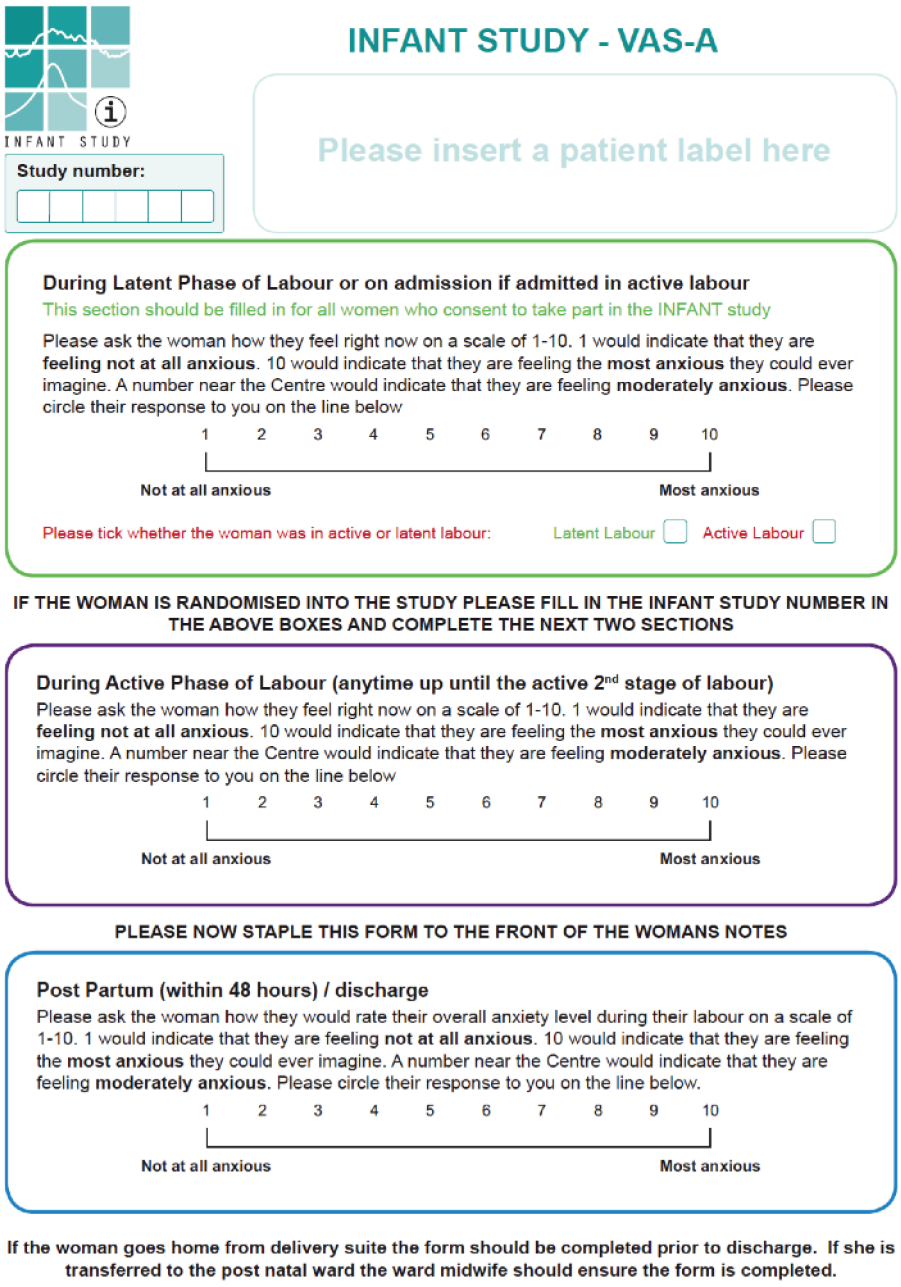

FIGURE 10 The INFANT study visual analogue scale form.

Qualitative study

Women from two of the study sites in the INFANT trial (Warrington Hospital and University Hospital of North Staffordshire) were approached to be interviewed about their experiences of birth and fetal monitoring by a single trained qualitative researcher. Women were approached after giving birth and before hospital discharge. A purposive sampling approach was used to ensure that equal numbers of women from the two arms of the trial were recruited, and that the number and severity of alerts was wide-ranging and well balanced between the two groups. The trial's statistician identified potential women to be included and informed the qualitative researcher of their study number. The interviewer was masked to the women's trial allocation and pattern of alerts until after the interviews were complete.

The interviews collected views of the whole birth experience but included semistructured prompting to explore women's feelings about monitoring and their understanding of the INFANT trial. The interviewer and another senior qualitative researcher undertook the analysis jointly. An initial thematic analysis was undertaken using NVivo (QSR International, Warrington, UK) software to support the coding process. This was followed by a framework analysis, summarising the experiences and attitudes of each woman and mapping these against the woman's characteristics (hospital of birth, study allocation, maternal age, gestation at trial entry and number of yellow and red alerts).

Results

Quantitative study

The VAS-A score sheets were completed by 275 out of 469 (59%) women [CTG monitoring only: 142 out of 234 (61%); CTG monitoring plus decision support: 133 out of 235 (57%)]. In the control group, data were available for 128 (55%) women from the latent phase, 104 (44%) for the active phase and 81 (35%) for the postpartum period. In the intervention group, data were available for 124 (53%) women for the latent phase, 106 (45%) for the active phase and 81 (34%) for the postpartum period.

The VAS-A scores are shown in *Table 5*. The scores were approximately normally distributed. In each group, anxiety levels increased from a score of around 5 points in the latent phase to around 6 points in the active phase, then dropped below 5 points in the postpartum period. There was no difference between groups in the change in anxiety from the latent to the active phase ($p = 0.84$) or from the latent phase to the postpartum period ($p = 0.88$). The scores were positively correlated: 0.48 between latent and active phase, 0.41 between the latent phase and the postpartum period, and 0.44 between the active phase and the postpartum period.

Qualitative study

A total of 18 women were interviewed, including six with their birthing partner, who was either their partner or mother. *Table 6* provides a list of the women interviewed with details of their hospital of birth,

TABLE 5 Change in anxiety (VAS-A) scores between phases of labour by allocation group

	VAS-A scores					
	CTG monitoring only		CTG monitoring plus decision support		Between-group difference in mean change (95% CI)	*p*-value
Phase	*n*	Mean (SD)	*n*	Mean (SD)		
Latent	128	5.0 (2.7)	124	4.8 (2.6)		
Active	104	5.7 (2.7)	106	5.5 (2.9)	–0.08 (–0.93 to 0.76)	0.84
Postpartum	81	4.5 (2.4)	81	4.4 (2.4)	–0.06 (–0.84 to 0.71)	0.88

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TABLE 6 Details of participants in the qualitative study

Interview ID[a]	Hospital	Trial arm	Maternal age (years)	Gestation at randomisation (weeks)	Number of yellow alerts	Number of red alerts
01	Warrington	Control	30	41	2	2
02	Warrington	Control	23	39	3	0
08	Warrington	Control	30	40	1	0
14	Warrington	Control	23	26	4	1
21	Warrington	Control	29	40	5	1
22	Warrington	Control	36	38 twins	13	2
07	Warrington	Decision support	49	41	5	0
15	Warrington	Decision support	28	39	0	0
18	Warrington	Decision support	26	41	1	0
19	Warrington	Decision support	38	37	4	2
20	Warrington	Decision support	36	38	3	0
04	North Staffs	Control	37	39	0	0
05	North Staffs	Control	31	37	0	0
11	North Staffs	Control	39	42	3	0
03	North Staffs	Decision support	27	40	0	0
09	North Staffs	Decision support	28	41	8	2
10	North Staffs	Decision support	21	41	6	1
16	North Staffs	Decision support	31	38	4	0

Warrington, Warrington Hospital; North Staffs, University Hospital of North Staffordshire.
a Numbers 06, 12, 13 and 17 were originally contacted and then declined to take part.

trial group, age, gestation at trial entry and number of alerts. Four women had no alerts, seven had at least one yellow but no red alerts and seven had at least one red alert. The number of red and yellow alerts were evenly distributed across the trial groups.

Levels of understanding

Among participants, there was a patchy understanding of what the trial was about, beyond a general view that it was seeking to understand people's experiences in labour and improve care for other women in the future. This is a finding that is widely reflected in the literature.[54–56] Women were frequently unclear about what is 'normal' monitoring of the baby in labour and what is part of the trial, and whether or not they would have been monitored anyway:

> *It was nothing, you know, that was intervening with anything, so I hadn't minded at all. I just hadn't been totally aware that I'd be hooked up to a machine the whole time. I just thought it was if you needed to be on the machine, they'd then monitor it through the computer . . . I wasn't sure whether I had to be on the machine for the sake, you know, for the baby's sake and whatnot or whether it was because I was, because of the study. I wasn't too sure what it was that I had to actually be on it for.*
>
> *Participant 02, control arm*

> *My understanding at the time of it was really just that it would be somebody maybe 1 or 2 years after the birth would be following up with a questionnaire and maybe a phone call or something just to see what my experience was . . . I don't recall the monitoring being part of the study but a huge deal wasn't made of it anyway, but as I say it wouldn't have been a problem if it was, but I was going to be monitored anyway with being induced.*
>
> *Participant 05, control arm*

Participant 05 (control arm) also said, 'I didn't remember them saying which group I was in. Is there different groups?'. Similarly, participant 14 (control group) said, 'I don't remember anything to do with groups'. Furthermore, she did not clearly recall any monitoring at all. This participant had a vague recollection of 'bands' being used for monitoring her baby's heart, and that the baby's heartbeat had dropped at one stage, but said, 'I definitely don't remember anything being put round me' other than her transcutaneous electrical nerve stimulation machine. Similarly, a woman in the intervention arm (participant 18) said, 'Groups? They might have mentioned it but I don't remember it'.

One couple (04, control arm) knew they had been allocated to a group but were unaware of how and why they had been selected for participation. The male partner had spent quite a lot of time trying to work out for himself what the monitor readings meant:

> Female: *It would be nice to know.*
>
> Male: *You know, why your specific case was chosen. Was it just it was randomly chosen or was it because they wanted to, to look at it for a certain reason?*
>
> Female: *Or is it just that we were placed in this particular bracket, you know?*
>
> Male: *Well, was it just random that our, you know, results were picked out? Or was it because, like we think, [female] had a rapid delivery? Or, you know, or something come up on the results why they decide?*

However, other participants in both groups were aware that there were different arms and demonstrated an awareness of which arm they were in as well as how they were allocated to a group:

> *Basically what they told us, well it says in the leaflet as well, that you might not be selected for the trial on a computer. Basically she tapped in some information on the screen and then it come up whether you'd be selected for it. And she typed it in and she said we weren't selected for it.*
>
> *Participant 01, control arm*

It was frequently suggested by participants that being given information about the trial towards the end of pregnancy rather than during the labour episode may improve understanding, as it was difficult for people to absorb the information or give it any priority during labour. This approach of providing information during pregnancy should have been happening in the centres, and a few women did recall discussing it at antenatal appointments or seeing posters about it in previous visits, but others did not. Women also mentioned feeling 'vague' or 'confused' about the information provided during labour because of the pain relief medication they had taken.

There was little evidence that feeling underinformed had led women to regret taking part. This was because EFM was commonly seen as routine care and not particularly invasive. Even women who disliked not being able to mobilise because of the monitoring failed to express major concerns about the information and consent process.

One exception to this was a woman in the decision support arm who said that she felt 'mithered' by having to answer all the questions needed to take part in the trial:

> *I didn't want to be asked; I just wanted to be left alone to get on with going through the labour . . . I just wanted to be left alone and that took like 15, 20 minutes to do all that so like she was asking me questions and I was contracting as well . . . I signed it because I thought – and I said this to my mum this morning – the only reason that I signed it was because I thought if the midwife thinks that we're co-operating with this then she'll give us some drugs [laughter]. She'll give me some more drugs, that's what I thought . . . It was something that was so shoved in my face and I didn't really have a choice basically . . . because I wanted to keep my midwife nice and sweet.*
>
> *Participant 15, decision support arm*

She complained that she 'hated' being monitored because it restricted her movements. It did not make her feel more anxious, but she regretted taking part because she felt that it spoilt her otherwise good experience of a spontaneous vaginal birth. She was so bothered by the restrictions on movement that she requested that the monitoring be stopped. It is clear from her interview that she did not understand that she would have had monitoring anyway and that it was not a consequence of taking part in the trial. She said that monitoring should be used 'only if it's an emergency for the baby' and did not understand that the purpose of monitoring was to detect concerns before they become emergencies. When this was discussed during the interview she commented:

> *So in that case it does change my views differently then, then yes, if I would have known it was something to do with protecting the baby then yes I would have had it on in labour.*
>
> *Participant 15, decision support arm*

Monitoring and reassurance

Women in both groups of the trial reported finding monitoring reassuring. There was no difference in the pattern of responses between the two groups, or between women with few alerts and those with many.

For example, one woman said:

> *That showed what the heartbeat was doing, you know, ranging from sort of whatever it was, 100 to 150. And there was a guide next to it to say what's acceptable and what's, you know, risky. [um] So that was quite reassuring, wasn't it?*
>
> *Participant 04, control arm, no alerts*

> *Oh, I thought it was brill, to be honest, because as I say a lot of the time I felt a little bit out of the loop. From where I was sitting I could see all the screens and what was going on so I found that, you know, sort of quite comforting.*
>
> *Participant 03, decision support arm, no alerts*

> *Being able to monitor what was happening with [baby 1] and sort of midway through what was happening with [baby 2] with their heart rates and things made me very reassured.*
>
> *Participant 22, control arm, 13 yellow and two red alerts*

> *I did quite enjoy having the monitors on actually. . . . you can just see, see sort of their heartbeat and how strong your contractions were, whereas normally you couldn't, you haven't got that.*
>
> *Participant 09, decision support arm, eight yellow and two red alerts*

Several women (or their partners) said that the monitor also helped reassure the partner. This generated a sense of involvement because they could observe a contraction and support their partner appropriately. Participant 19 (decision support arm) said that her partner 'kept checking the paper. I think he was fascinated by it'.

Monitoring and restriction of movement

On those occasions when objections were raised about monitoring, this was most usually because of the restrictions it placed on movement. Some women said that they did not find the monitor restrictive or uncomfortable, including participant 19 (decision support arm). When asked if she could move around she said:

> Participant 19: *Yes, I was on my side for most of it, they said that's the most comfortable position for me so I just stayed on my side.*
>
> Interviewer: *Did you mind being monitored at all?*
>
> Participant 19: *No, no anything that helps really.*
>
> Interviewer: *When you say helps, in what way?*
>
> Participant 19: *I mean, well like just in case there's any complications, I'd rather be monitored and have them spot them, so.*
>
> Interviewer: *You found it sort of reassuring?*
>
> Participant 19: *Yes, yes extra reassurance.*

However, other women talked about wanting to alleviate pain by moving around or to be able to go to the toilet. The monitor restricted this movement and some women felt that the monitor straps were uncomfortable. Some women expressed a preference for a wireless monitor. One woman had heard that this was available in other hospitals. Women who disliked being monitored expressed varying degrees of resignation, assuming that they would have their movement restricted anyway (e.g. because of an epidural) or that the disadvantages of limited movement had to be balanced against the benefits for the baby and their own peace of mind:

> *The fact that it restricted me, that was a bit of a pain, but I don't know whether I would have moved round that much or, you know. Because I mean I could have sat on the ball, you know, the blow up ball . . . rather than the chair, which is one of the things they recommend. But I didn't want it. I just wanted to sit on the chair . . . No, it's reassuring, I think because you know you don't want your baby's heart rate to go down. And it was quite good as well in that my husband could see when the contractions were coming on . . . I think we, it made no difference to us taking part, you know, it wasn't detrimental, it wasn't, I was going to be monitored anyway whether I took part in the trial or not.*
>
> *Participant 20, decision support arm, three yellow alerts*

> *And the reason I agreed, why I thought it was brilliant, was because it's extra checks, it's extra checks for him. And I think well he's going to be monitored closely from now on which is amazing but, you know, because I'd do anything for him, you know, healthy baby, and if it picks up on something, fantastic, and it's doing research for everything else, so yes . . . So it turned out that I was on this monitor for this and my heart and everything so I couldn't move off the bed for all them hours, they wouldn't let me move. So I couldn't walk round, so my plan had gone way out the window. I wasn't walking round, I'd not had my bath at all, I'm stuck on this bed, I've been induced. . . . The birth plan was just sit on the ball, stay upright and move as much as you can. That was basically it. And nothing happened like that and I'm saying 'Can I get off this bed?' 'No, you're being monitored for this and you're being monitored for your heart, you're being monitored, baby's being monitored because of the poo because that's dangerous, no you can't move off this bed'. I was like 'Ohhhh', so I just lay down the whole day. Which was really nice and very boring.*
>
> *Participant 11, control arm, three yellow alerts*

Monitoring and anxiety

Women did describe anxious moments during their labour; however, these did not seem to be associated with monitoring, but were more related to the urgent comments and behaviour of staff as they responded to the monitoring results or to other clinical concerns.

There was only one clear exception to this:

> *So it was quite good because obviously people could see what was going on . . . because the doctor come in and said I've been watching you on the screen . . . Sometimes, I kept hearing her say when the heartbeat, because they kept saying she's being naughty, they just kept saying that, and it was flashing messages up to them and I heard her say a couple of times 'I think that heartbeat's okay for the minute' but that was telling her it was, so . . . They did talk about it quite a bit, they used it as a guide but said they would use their own judgement to make any decisions . . . In a way I don't know if it's a good thing or a bad thing, though, because right towards the end because her heartbeat had been playing up all day, we were all focused on it . . . Everyone was just focused on this monitor and the heartbeat, so I think that got a little bit stressful, because I did end up telling him [partner] 'Stop telling me what's happening or talking about it' because it was making me panic . . . He says to me afterwards that he was, it was the most scared he'd ever been in his life but at the time he seemed really quite cool and took it all in his stride but obviously he was just putting a show on for me.*
>
> *Participant 16, decision support arm, four yellow alerts*

Nonetheless, participant 16 concluded: 'The study didn't really affect the birthing experience at all so that, you know, I'd do it again, that's fine'.

This woman's interpretation was that the staff used the decision support to justify postponing any intervention. She was glad not to have a caesarean section, but she felt that she could have had an instrumental delivery earlier: 'I do think that because her heartbeat had been playing up so long throughout the day and things weren't moving on for me that they should have looked at me a bit earlier and made a decision a bit earlier'. The woman's mother, who was present during the labour and birth, and was interviewed with her, was even more convinced of the need for an early delivery:

> *It was about half nine and I can remember the midwife saying, 'We're going to leave you till eleven and if nothing's happened by eleven we'll get the doctor and we'll see about taking you to theatre. But then when 11 o'clock came they had a look at you and you'd dilated quite a bit by then so they said we'll leave you another hour, that took you to 12.00 and then again we'll leave you another 2 hours, and that annoyed me because that's what they kept saying. Although, you know, she was well into labour I think they should have took her for a C-section at about 11 o'clock, I do.*
>
> *Mother of participant 16, decision support arm*

This example suggests that CTG with decision support could lead to some cases of raised anxiety levels. There were two examples in the control group in which monitoring without decision support also caused some anxiety. Participant 08 reported that her mother had been worried at one point, although she herself was relaxed and asleep:

> *My mum was watching where they was monitoring me and I think I fell asleep so as I had diamorphine. And at one point, because they had one on me and one obviously for the baby's heartbeat, and the baby must have moved so it went to zero and my mum thought it was me. She said she couldn't see my chest rising or anything and thought I wasn't breathing and she looked at this monitor and seen zero and she was like, 'She's not breathing, she's not breathing' and I woke up and I was like 'What?' [laughter].*
>
> *Participant 08, control arm*

The partner of participant 21 (five yellow alerts and one red alert) recalled his own fears:

> Partner: *Yes it was helpful, but it was also, I think, in some respects that she couldn't see it was as well because there was quite a few scary moments.*
>
> Woman: *You see, I couldn't see that because it was . . .*
>
> Partner: *Yes, I mean his heart, I could see his heartbeat going down and she couldn't see it, so I was a bit worried there.*
>
> Woman: *But as soon as his heartbeat started going down they all, them sitting on their desk came in to have a look.*

They were both surprised at the amount of paperwork the monitoring generated for the midwife, and felt that this detracted staff from providing reassurance and support:

> *You need somebody that's talking to you, explaining things and actually maintaining the relationship with you as opposed to just doing, writing down and checking the monitors and things like that because otherwise you end up panicked and it's not good.*
>
> *Participant 21, control arm, 5 yellow alerts and 1 red alert*

Discussion

We found no evidence from the quantitative analysis of anxiety, using VAS-A scores, that CTG monitoring plus decision support is associated with a change in women's anxiety levels compared with CTG monitoring alone. Labour appears to be an anxious time for most women, and uncertainty about whether or not their baby will be all right contributes to this anxiety. Alerts indicating abnormalities of the fetal heart rate are very likely to lead to anxiety for parents and clinicians, but this anxiety is appropriate if the alert also prompts a response that ensures that the baby is kept safe. If the decision support software results in the number of false 'abnormal' heart rate patterns being reduced, and the true-positive rate is optimised (i.e. abnormal CTGs are not overlooked), then any anxiety engendered by monitoring would be minimised and would probably be acceptable to women.

Findings from the qualitative interview illustrate that EFM per se did lead to significant anxiety for the women interviewed. Concerns about monitoring were commonly to do with discomfort and restriction of movement. Some women reported finding the activity of monitoring reassuring. There is a possibility that the use of monitoring itself leads to a belief that birth is a risky process, which therefore needs careful monitoring. This in turn may lead people to report that they find monitoring reassuring. It has been argued that women in labour 'became very susceptible to the reassurance of the cultural props around them. The symbolic messages of the hospital setting gave them something to cling onto'.[57] Women's feelings of control during labour are an important predictor of a positive birth experience, and may help in decreasing anxiety.[58] This paper also argued that information giving during labour and participation in decision-making were crucial in helping women to achieve feelings of control. It is possible that the trial information, given out in the booking appointment in early pregnancy, at the time of the 22-week anomaly scan and at the routine 34-week appointment, contributed to women achieving these feelings of control. In a trial examining different approaches to the presentation of information about prenatal screening,[59] the information provided did not increase anxiety. Very detailed information has been shown to have the potential to reduce anxiety.[59]

This small qualitative sample cannot be generalised to all of the women who participated in the trial. However, when considered alongside the results of the survey, we feel confident that raised anxiety levels resulting directly from EFM with decision support is uncommon. When women are anxious in labour, it appears to be more to do with general feelings of anxiety about the baby's health, which may be exacerbated by staff behaviours. However, there was one woman in our sample whose anxiety seemed to be directly linked to the use of decision support. This means that we need to be aware of the possibility of this happening with other women and consider ways to provide reassurance and explanation. We also found that CTG monitoring without decision support caused some anxiety and we need to consider how further explanation and reassurance can help these women.

Details of ethics approval

The Northern and Yorkshire REC gave approval to the study. The reference number of the ethics approval is 09/H0903/31.

Chapter 4 Analysis plan for the trial

Primary analysis

An outline analysis plan was developed and agreed by the TSC and the DMC before any data were collected, and a detailed plan was agreed before data were unmasked and analysed. Demographic factors and clinical characteristics were summarised with counts (percentages) for categorical variables, means (SDs) for normally distributed continuous variables or medians [interquartile ranges (IQRs) or entire ranges] for other continuous variables. The primary analysis was a comparison of the management approaches assigned at randomisation. Participants were analysed in the groups to which they were randomly assigned regardless of deviation from the protocol or treatment received. Comparative statistical analysis entailed calculating the risk ratio (RR) plus 95% CI for the primary outcome (99% CIs for all other dichotomous outcomes), the mean difference (plus 99% CI) for normally distributed continuous outcomes or the median difference (plus 99% CI) for skewed continuous variables. Analyses were adjusted for the stratification factors used in the randomisation procedure: centre and singleton/twin pregnancy. Analysis of secondary outcomes was clearly delineated from the primary analysis in the statistical reports produced. For secondary outcomes, a 1% level of statistical significance was employed to take account of the number of comparisons. The trial is reported according to the principles of the Consolidated Standards of Reporting Trials (CONSORT) statement.

Prespecified subgroup analysis

The consistency of the effect of decision support on the babies of groups of women recruited to the trial was explored to see whether or not decision support is of particular help to the babies of specific subgroups of women using the statistical test of interaction. Therefore, the categories of prespecified subgroup analysis were:

1. singletons versus twins
2. suspected growth restriction at labour onset versus no growth restriction
3. centre
4. body mass index (BMI) group [underweight (12–18.4 kg/m^2), normal (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2) and/or unrecorded obese (30–70 kg/m^2)].

Data collection schedule

Information was to be collected at the following times:

- electronically during labour via the Guardian system
  - all women
- Post Birth Data Collection (PBDC) Form M (Mother) (see *Appendix 8*)
  - all women receiving a higher level of care, surgery or a procedure in theatre following delivery
- PBDC Form B (Baby) (see *Appendix 5*)
  - all babies receiving a higher level of care or surgery following birth
- PBDC Chart B (Baby) Neonatal Encephalopathy Data (see *Appendix 6*)
  - all babies receiving a higher level of care and classified as having NNE

- Death of a baby in the INFANT study form (see *Appendix 7*)
  - all intrapartum stillbirths and neonatal deaths up to 28 days after birth
- Parent's Questionnaire at 24 months (health and development outcomes)
  - a subset of 7000 participants consenting to follow-up
- Parent's Questionnaire at 12 and 24 months (health economic items)
  - a subset of 700 participants within the follow-up sample of 7000.

Derivation of variables

Primary outcomes

- Composite of poor neonatal outcomes, defined as any of:
  - intrapartum stillbirths, except deaths as a result of congenital anomalies (*Table 7*)
  - neonatal deaths up to 28 days after birth, except deaths as a result of congenital anomalies (*Table 8*)
  - moderate or severe NNE (*Table 9*)
  - admission to neonatal unit within 48 hours of birth for ≥ 48 hours with evidence of feeding difficulties, respiratory illness or NNE (*Table 10*).
- PARCA-R composite score at 24 months:
  - Total sum of scores on the PARCA-R in section A, B and C of the Parent Questionnaire at 24 months (*Appendix 9*).

TABLE 7 Intrapartum stillbirths except deaths as a result of congenital anomalies

	Baby outcome = 'Stillbirth' in Guardian
MINUS	Any deaths as a result of congenital anomalies recorded on the death of a baby in the INFANT study form

TABLE 8 Neonatal deaths up to 28 days after birth except deaths as a result of congenital anomalies

	Baby outcome = 'Early neonatal death' in Guardian and died within 28 days after birth
OR	A 'Yes' response to Q14 on the PBDC Form B (Baby) and died within 28 days after birth
OR	A completed death of a baby in the INFANT study form and died within 28 days after birth
OR	Deaths notified by the NHS Information Centre (England) and the NHS Greater Glasgow & Clyde Safe Haven (Scotland) up to 28 days after birth
MINUS	Any deaths as a result of congenital anomalies recorded on the death of a baby in the INFANT study form

TABLE 9 Moderate or severe encephalopathy

	A 'Yes' response to therapeutic hypothermia on the PBDC Chart B (Baby) Neonatal Encephalopathy Data
AND	Confirmed by a masked review committee

TABLE 10 Admission to neonatal unit within 48 hours of birth for ≥ 48 hours with evidence of feeding difficulties, respiratory illness or encephalopathy

	A 'Yes' response to Q2 on the PBDC Form B (Baby)
AND	A 'Yes' response to Q5 or Q6 on the PBDC Form B (Baby)
AND	A 'Yes' response to Q8 on the PBDC Form B (Baby)
AND	A 'Yes' response to Q9 on the PBDC Form B (Baby)
AND	Confirmed as compromised at birth by a masked review committee (score of ≥ 3 on Primary Outcome Review Scoring Sheet)

Neonatal secondary outcomes

- Intrapartum stillbirth except deaths as a result of congenital anomalies.
- Neonatal deaths up to 28 days after birth except deaths as a result of congenital anomalies.
- Moderate or severe NNE.
- Admission to neonatal unit within 48 hours of birth for ≥ 48 hours with evidence of feeding difficulties, respiratory illness or NNE.
    - (For the above, see definition in *Primary outcomes*.)
- Admission to a higher level of care within 48 hours of birth for ≥ 48 hours [A 'Yes' response to Q2 on the PBDC Form B (Baby)].
- An Apgar score of < 4 (from the Guardian variable 'Apgars 5 mins').
- Distribution of cord blood gas data for cord artery pH (summarise the variable cord artery results in Guardian).
- Metabolic acidosis.
    - A cord artery pH of < 7.05 and a base excess of ≥ 12 mmol/l for the variable cord artery results in Guardian.
- Resuscitation interventions.
    - Count of the number of interventions (listed under 'Resuscitation Type' in Guardian).
- Seizures.
    - A 'Yes' response to Q7 on the PBDC Form B (Baby).
- Destination immediately after birth.
    - Summarise the Guardian variable 'infant transfer dest'.
- Length of stay (*Table 11*).

TABLE 11 Length of hospital stay (baby)

	'Infant Discharge Date' in Guardian
OR	Date of discharge recorded in Q12 of the PBDC Form B (Baby)
MINUS	'Delivery Date Time' in Guardian

Maternal secondary outcomes

- Mode of delivery.
  - Recorded in Guardian in field 'Mode of Delivery'.
- Operative intervention (caesarean section and instrumental delivery) for:
  - fetal distress or
  - failure to progress or
  - combination of fetal distress and failure to progress or
  - other reason.
    - Indications in Guardian recorded in the fields: 'Forceps Indicators', 'Ventouse Indicators' and 'CS Indicators' were coded into these four categories according the rules listed in *Table 12*. When a woman had more than one indication recorded and at least one was fetal distress and at least one was failure to progress, she was classified as category iii.

TABLE 12 Classification of indications for instrumental vaginal delivery and caesarean section

Indications for instrumental vaginal delivery and caesarean section	Fetal distress	Failure to progress	Other
Abnormal CTG	Yes		
Abnormal FBS pH	Yes		
Abnormal presentation or lie		Yes	
APH	Yes		
Intrapartum haemorrhage	Yes		
Breech presentation		Yes	
Cephalopelvic disproportion		Yes	
Chorioamnionitis	Yes		
Cord prolapse or presentation	Yes		
Delay in first stage		Yes	
Delay in second stage		Yes	
Eclampsia			Yes
Failed induction		Yes	
Failed forceps/ventouse		Yes	
Failed trial of forceps		Yes	
Failed trial of ventouse		Yes	
Failure to progress		Yes	
Fetal compromise – abnormal CTG	Yes		
Fetal compromise – meconium stained liquor	Yes		
Fetal compromise suspected or indicated	Yes		
Fetal reason	Yes		
HELLP			Yes
Intrapartum haemorrhage	Yes		

TABLE 12 Classification of indications for instrumental vaginal delivery and caesarean section (*continued*)

Indications for instrumental vaginal delivery and caesarean section	Fetal distress	Failure to progress	Other
IUGR	Yes		
Low scalp pH	Yes		
Malpresentation		Yes	
Malpresentation/unstable lie		Yes	
Maternal condition			Yes
Maternal distress/exhaustion		Yes	
Maternal effort contraindicated			Yes
Maternal hypertension			Yes
Maternal medical condition			Yes
Maternal medical disease			Yes
Maternal request			Yes
Multiple pregnancy			Yes
Non-reassuring CTG	Yes		
Non-reassuring FBS	Yes		
Obstructed twin/triplet		Yes	
Other			Yes
Other (fetal)	Yes		
Other (maternal)		Yes	
Other maternal medical history			Yes
Placenta abruption	Yes		
Placenta praevia			Yes
Planned as elective			Yes
Pre-eclampsia			Yes
Presumed fetal compromise	Yes		
Previous caesarean section			Yes
Previous infertility			Yes
Previous lower-segment caesarean section			Yes
Previous poor obstetric outcome			Yes
Previous obstetric history			Yes
Previous traumatic vaginal delivery			Yes
Previous uterine surgery			Yes
Prolonged second stage			
Pyrexia in labour	Yes		
Ruptured uterus	Yes		
Slow progress in first stage		Yes	
Slow progress in second stage		Yes	
Suspected fetal distress	Yes		
Unstable lie		Yes	

FBS, fetal blood sample; APH, antepartum haemorrhage; HELLP, haemolysis, elevated liver enzymes, low platelet count.

- Grade of caesarean section.
  - Recorded in Guardian in field 'CS Priority'.
- Episiotomy.
  - Recorded in Guardian in field 'Episiotomy'.
- Any episode of fetal blood sampling.
  - Recorded in Guardian in field 'No of FBS'.
- Length of first stage, second stage and total length of labour from trial entry.
  - Recorded in Guardian, was calculated from fields 'Labour start time', 'Second stage/fully dilated' and 'Delivery Date Time'.
- Destination immediately after birth.
  - Recorded in Guardian in field 'Mother transfer dest'.

Quality-of-care outcome

Adverse outcome and suboptimal care (*Table 13*).

Process outcomes

Process outcomes were derived for the control group in the same way as the intervention group; the decision support software was running in the background even though it was not displayed, so it was possible to review the pattern of alerts retrospectively across the trace.

- Number of CTG abnormalities (blue, yellow and red levels of concern) detected by the decision support software, after trial entry.
  - Recorded in Guardian in fields 'Number of Blue after randomisation', 'Number of Yellow after randomisation' and 'Number of Red after randomisation'.
- Number of blue levels of concern on the decision support software, indicating a mild abnormality on the CTG, after trial entry.
  - Recorded in Guardian in field 'Number of Blue after randomisation'.
- Number of yellow levels of concern on the decision support software, indicating a moderate abnormality on the CTG, after trial entry.
  - Recorded in Guardian in field 'Number of Yellow after randomisation'.

TABLE 13 Adverse outcome and suboptimal care

	Composite primary outcome (see definition in *Primary outcomes*)
AND	Metabolic acidosis (see definition in *Neonatal secondary outcomes*)
AND	Judged to have experienced suboptimal care in labour by a panel of experienced clinicians masked to allocation
OR	Stillbirth or neonatal death not as a result of a congenital anomaly

- Number of red levels of concern on the decision support software, indicating a severe abnormality on the CTG, after trial entry.
  - Recorded in Guardian in field 'Number of Red after randomisation'.
- Number of women with at least one yellow level of concern on the decision support software, indicating an abnormality on the CTG, after trial entry.
  - Recorded in Guardian in field 'Number of Yellow after randomisation'.
- Number of women with at least one red level of concern on the decision support software, indicating a severe abnormality on the CTG, after trial entry.
  - Recorded in Guardian in field 'Number of Red after randomisation'.
- Time from first red level of concern after trial entry to birth.
  - Recorded in Guardian, calculated from fields 'Date Time 1st Red after randomisation' and 'Delivery Date Time'.
- Number of thumb entries per hour from time of trial entry to first yellow level of concern or until fully dilated (10 cm) if no abnormality detected or first yellow level of concern occurred prior to trial entry.
  - Recorded in Guardian in fields 'Count of thumbprints between randomisation and first yellow' and 'Count of thumbprints between randomisation and fully dilated'. The rate will be calculated using the fields 'Date time 1st yellow after randomisation', 'Second stage/fully dilated' and 'Delivery Date Time'.
- Number of vaginal examinations after trial entry.
  - Recorded in Guardian in field 'No of VEs after randomisation'.
- Epidural analgesia after trial entry.
  - Recorded in Guardian in fields 'PD did woman have an epidural' and 'PD did woman have an epidural time'. Only count if first recorded after the time of trial entry.
- Labour augmentation after trial entry.
  - Recorded in Guardian in fields, 'Syntocinon in 1st or 2nd stage' and 'Syntocinon in 1st or 2nd stage time'. Only counted if the first recording was after the time of trial entry.
- Presence of meconium after trial entry.
  - Recorded in Guardian in field 'PD any meconium recorded during labour' and 'PD any meconium recorded during labour time'. Only counted if the first recording was after the time of trial entry.

Health and development outcomes at 24 months

- Components of the PARCA-R:
  - Non-verbal cognition scale. (Sum of scores in Section A of the Parent Questionnaire at 24 months: 'Your child at play' Q1–33.)

  - Vocabulary subscale. (Sum of scores of the 100 items in Section B of the Parent Questionnaire at 24 months: 'What your child can say'.)
  - Sentence complexity subscale. (Sum of scores in Section C of the Parent Questionnaire at 24 months: 'Your child's understanding' Q1–18.)

- Infant deaths at 24 months (*Table 14*).
- Disability status at age 2 years (*Table 15*).
- Cerebral palsy diagnosis.
  - A 'Yes' response to Q9 in Section G of the Parent Questionnaire at 24 months.
- Health economic outcomes.
  - Ever been given breast milk or put to the breast.
    - A 'Yes' response in Section 1 of the Health Economic Parent Questionnaire at 24 months.
  - Age when last breastfed or put to the breast (days).
    - Convert response categories to days in Section 1 of the Health Economic Parent Questionnaire at 24 months.

Missing data for any components of the disability classification questions meant that the overall classification may result in several categories:

- Major.
  - At least one component in sections A–G is classified as major.
- At least non-major.
  - One component in sections A–G is classified as non-major, but one item is missing and therefore it is not possible to conclude that the overall classification is not major.
- Non-major.
  - The most severe item in sections A–G is classified as non-major and there are no other missing data.
- At most non-major.
  - Any missing items in sections A–G could only be classified as non-major or no disability and all other items are classified as no disability.

TABLE 14 Infant deaths at 24 months

	Baby outcome = 'Early neonatal death' in Guardian
OR	A 'Yes' response to Q14 on the PBDC Form B (Baby)
OR	A completed Death of a baby in the INFANT study form
MINUS	Any deaths as a result of congenital anomalies recorded on the death of a baby in the INFANT study form
AND	Deaths notified by the NHS Information Centre (England) and NHS Greater Glasgow & Clyde Safe Haven (Scotland) up to 2 years after birth

TABLE 15 Disability status at 2 years. Classified as non-major disability or major disability at 2 years if the infant meets any one of the following criteria from the Parent Questionnaire at 24 months (criteria for major disability is italicised)[60,61]

Sections A–C: cognitive function	• PARCA-R composite score 2–3 SDs below mean for age • *PARCA-R composite score > 3 SDs below mean for age*
Sections B–C: communication	• < 10 out of 100 words from word list • ≥ 10 out of 100 words from word list and question C6 = 'Not yet' to the question 'Has your child begun to put words together yet' • *Does not use any recognisable words (including signed words)* • *Does not use any sounds that can be understood* • *Does not show understanding of any words or signs*
Section D: physical ability	Walking: • Has an unsteady walk but does not need help • *Unable to walk without help* • *Unable to walk even with help* Sitting: • Sits unsupported but unstable • Sits only with support • *Unable to sit* Hand use: • Picks up by other means (right or left) • *Unable to pick up object (right or left)* • Has difficulty using one hand • *Unable to use both hands* Head control: • Poor control but does not need support • *Can control head only with support*
Section E: vision	• Some difficulty but sees well enough for everyday activities • Has considerable difficulty but can see objects if near • *Is able to see light only or has no vision*
Section F: hearing	• Has some hearing problems but does not need a hearing aid • Hears well or with only a little difficulty with a hearing aid • (Do not count if because of recurrent ear infections or glue ear and no aid) • *Has severe hearing difficulty even with a hearing aid or hearing is not helped with an aid*
Section G: growth	• Height or weight 2–3 SDs below mean for age • *Height or weight > 3 SDs below mean for age*
Section G: seizures	• Fits, seizures or convulsions (not because of fever) but no treatment required • On treatment now and has no seizures • Has up to one seizure every month on treatment • *Has more than one seizure every month on treatment*
Section G: feeding	• *Is fed with tube passed directly into the stomach (gastrostomy)* • *Is fed with tube passed from nose to stomach*
Section G: respiratory	• Wheezing more than once a week and taking any medication for chest symptoms when needed • Currently on any medications for chest symptoms and taking relievers, preventers or steroids every day • *Requires continuous oxygen therapy or mechanical ventilation*
Section G: other disability	• Other long-term problem that has some limitation on everyday activities but able to function independently (review case by case) • Needs assistance or aids for some activities • *Is completely dependent on carer*

- None.
    - No data re missing and all items in sections A–G are classified as no disability.
- Not known.
    - No disability reported but when some data items in sections A–G are missing.

In order to derive the classification 'Major' or 'Non-major' in the final report, all infants with 'At least non-major' disability were classified as 'Non-major' and all infants with 'At most non-major' disability were classified as 'None'.

Protocol violation

A protocol violation is the intended failure to comply with the final study protocol as approved by the REC and research and development departments, an example being serious non-compliance with the protocol resulting from fraud or misconduct that affects participant rights, safety and/or the integrity of the resultant data. Any violations were reported to the sponsor and REC as soon as possible.

Protocol deviation

A protocol deviation is an unintended failure to adhere to the final study protocol.

In this trial, the following were defined as protocol deviations.

Participants randomised in error

These include women:

- who did not receive EFM
- who had triplets or a higher-order pregnancy
- who were at < 35 weeks' gestation
- whose infant had a known gross fetal abnormality
- who were aged < 16 years
- who were not able to give consent to participate as judged by the attending clinicians
- who received an elective caesarean section prior to the onset of labour.

Participants who do not receive the allocated intervention

These included women in the following arms:

- 'CTG with no decision support' arm who received partial or full decision support
- 'CTG with decision support' arm who did not receive decision support.

Follow-up completed outside set time window

This included infants who were aged 2 years ± 3 months when the 2-year follow-up questionnaire was completed.

Primary analysis strategy

For the primary analysis, participants were analysed in the groups into which they were randomly allocated (i.e. comparing the outcomes of all women and babies allocated 'CTG with no decision support' with 'CTG with decision support'), regardless of the allocation received.

The two groups were compared by calculating the treatment difference adjusted for the stratification factors used in the randomisation (centre and singleton/twin pregnancy). The adjusted analysis took account of the correlation between treatment groups introduced by stratifying the randomisation (which forces outcomes between treatment arms to be similar apart from any treatment effect).[62] Both adjusted

and unadjusted estimates were presented for all outcomes, but the primary inference was based on the adjusted analysis.

The unit of randomisation was birth episode, which raises the issue of non-independence of observations. Some women had more than one delivery over the study period and may have been randomised into the trial more than once if they were eligible, but this was estimated to be very unlikely. Based on national statistics and average interpregnancy intervals in the UK, we anticipated that around 10% of women in this cohort would have a subsequent delivery within the study period, but a smaller proportion would have two consecutive births monitored by CTG.[63,64] In addition, around 1.5% of women would be expected to have twin deliveries,[65] but this proportion was likely to be lower in this cohort as some twin births will occur before 35 weeks' gestation and a large proportion of twin term births are by elective caesarean section.

We anticipated the proportion of non-independent observations within and between pregnancies to be much lower than 10%; however, some outcomes can have a large intracluster correlation coefficient – in particular the 2-year outcomes collected via the parent questionnaire – so clustering was taken into account in the analysis.[66,67]

Descriptive analysis population

Baseline demographic and clinical characteristics were reported for each delivery for all women randomised for whom we had data available, excluding protocol violations and women randomised in error who did not give consent or who were aged < 16 years.

Comparative analysis population

- Maternal outcomes.
    - All women randomised for whom data were available, excluding protocol violations and women randomised in error who did not give consent or who were aged < 16 years. For women with more than one birth episode during the study period, baseline characteristics and maternal outcomes were reported on each occasion. For twin births the mode of delivery of the first twin delivered was reported.
- Short-term neonatal outcomes.
    - All babies including both twins, excluding protocol violations and women randomised in error who did not give consent or who were aged < 16 years.
- The 24-month health and development outcomes.
    - A sample of 7000 infants recruited during the first 2 years of the trial, excluding protocol violations, women randomised in error who did not give consent or who were aged < 16 years and adopted children.

Interim analysis population

Different denominators were used in the annual interim analysis.

- The total number of trial participants, excluding protocol violations and women randomised in error who did not give consent or who were aged < 16 years.
- The number of women with post-birth data.
- The number of babies with post-birth and/or 24-month follow-up data.

Representativeness of trial population and participant throughput

The flow of participants through each stage of the trial was summarised using a CONSORT diagram.[68] We reported the numbers of women who:

- were randomly assigned
- received the intended intervention
- withdrew before or during CTG monitoring
- were included in the primary analysis at discharge
- were lost to follow-up
- were included in the analysis at 24 months.

Baseline comparability of randomised groups

Participants in the original two randomised groups were described separately with respect to:

- maternal age
- ethnic group
- singleton or twin pregnancy
- gestational age at trial entry
- BMI at booking visit (if recorded)
- smoking history at booking visit (if recorded)
- parity
- obstetric history
- cervical dilatation at trial entry (if recorded)
- intrauterine growth restriction (IUGR) suspected at labour onset
- labour induction.

Numbers (with percentages) for binary and categorical variables, and means (and SDs) or medians (with lower and upper quartiles) for continuous variables were presented; no tests of statistical significance were performed nor were CIs calculated for differences between randomised groups on any baseline variable.

Losses to follow-up

The numbers (with percentages) of losses to follow-up among women selected for the 24-month assessment were reported and compared between the two trial arms, and the reasons recorded. Any deaths (and their causes) were reported separately.

Description of available data

The pattern of missing data for primary and secondary outcomes, from baseline to the end of follow-up, was summarised for the two treatment groups, with differentiation between fully and partially completed forms/Guardian fields and those that were missing completely.

Not all data are routinely collected by all hospitals, for example BMI, smoking history, cervical dilatation, cord artery pH and base deficit. These data were reported separately for the subset of hospitals that do collect them routinely.

Description of compliance with intervention

A summary of the intervention received was provided, which included intermittent use of the decision support software and/or withdrawal of consent during labour.

Unmasking of randomised treatments

In order to accurately reflect any potential impact of the decision support software in contemporary NHS practice, such as changes in midwifery presence during labour consequent on knowledge of the allocation, the clinicians were not masked to allocation. The local community midwives and participants may also have been aware of the allocation. All other persons involved in the trial (except for the trial statistician and trial

programmer), including the UCL trial co-ordinating centre, did not have access to the aggregate list of randomisation codes. K2 Medical Systems remained masked until the data were frozen at the end of the trial.

Statistical methods used for analysis of primary outcomes

The numbers (percentages) of babies with poor neonatal outcomes were presented for each group and the RR plus 95% CI calculated. RRs were estimated using generalised estimating equations (GEEs), or a similar method, adjusting for the stratification factors used in the randomisation (centre and singleton/twin pregnancy). This method of analysis accounted for the correlation in outcomes between twins and siblings delivered in a subsequent pregnancy during the trial period. A log binomial model was planned to be used in the first instance but, if convergence was not achieved, then a log-Poisson model would be used with a robust variance estimator.[69] The mean (SD) PARCA-R composite score was presented for each group and the mean difference between groups plus 95% CI was calculated and compared using GEE (Gaussian model with identity link), adjusting for stratification factors.

Significance levels

For the analysis of the primary outcomes, a *p*-value of 0.05 (5% significance level) was used to indicate statistical significance. Comparisons of all other outcomes including the components of the primary outcome were reported in full for completeness and transparency. For all other analyses, a *p*-value of 0.01 (1% significance level) was used to indicate statistical significance, to take into account the number of comparisons. Two-sided statistical tests and corresponding *p*-values were presented throughout.

Missing data

Missing data for the short-term primary outcome were likely to be negligible, as most of the data were collected electronically on the Guardian system before the woman left the delivery room. If any data items were missing on the PBDC forms, completed for babies and women admitted to a higher level of care, every effort was made to extract these data from the hospital involved.

For any partially completed PARCA-R scales in the 24-month parent questionnaires, the following strategies for estimation of the total and subscale scores were employed when items were missing:

- Non-verbal cognition scale (PARCA-R: 'Your child at play' Q1–33)
  - pro rata estimation if < 10% of (up to three) items are missing
  - if Q6 is 'No', and Q6a is missing, code 'No' for Q6a
  - if Q6 is 'Don't know', and Q6a is missing, code 'Don't know' for Q6a.
- Vocabulary subscale (PARCA-R: 'What your child can say')
  - non-ticked items were coded to zero.
- Sentence complexity subscale (PARCA-R: 'Your child's understanding Q1–18)
  - if Q1–6 were missing, coded to zero and analysed as 'Not Yet'
  - if Q6 is 'Often' or 'Sometimes' and any of Q7–18 were not completed, coded to zero.

Prespecified subgroup analysis

To examine whether or not the effect of decision support was consistent across specific subgroups of women and babies, the following subgroup analyses were planned and carried out:

- singletons versus twins
- suspected IUGR at labour onset compared with no growth restriction
- BMI group [underweight (< 18.5 kg/m^2), normal (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), obese (≥ 30 kg/m^2) or unrecorded]
- centre.

For the trial composite primary outcome, results were presented in forest plots showing the RR plus 95% CI for each subgroup, by treatment group, with the *p*-value for the statistical test of interaction.[70] For the PARCA-R composite score, the difference between the mean treatment effects was reported, within each subgroup, with a 95% CI and the corresponding *p*-value.[71]

Using these statistical methods, we performed subgroup analyses for all prespecified neonatal outcomes and instrumental vaginal deliveries. In addition, we analysed process outcomes by centre.

Prespecified sensitivity analysis

Following early DMC meetings, it was reported that the number of babies admitted to a neonatal unit within 48 hours for ≥ 48 hours exceeded the number anticipated in the sample size calculation by an order of magnitude. Following a review of cases by the masked review panel at the end of the trial, the number still exceeded that anticipated in the sample size calculation, although to a lesser degree. Hence this component far outweighed the other rarer components, such as stillbirth, neonatal death and moderate or severe NNE, and strongly influenced the composite primary outcome. To explore the impact of this on the main findings, a sensitivity analysis of the primary composite outcome was performed, including only the most severely affected babies admitted to a neonatal unit and allocated a score of ≥ 7 points on the Primary Outcome Review Scoring Sheet by the masked review panel.

Statistical software employed

Stata/SE version 13 for Microsoft Windows was used for this analysis.

Statistical methods used for analysis of secondary outcomes

Generalised estimating equations, or a similar method, was used for the analysis of secondary outcomes, adjusting for the stratification factors used in the randomisation procedure (centre and singleton/twin pregnancy). For normally distributed continuous outcomes, we presented the mean and SD for each group, calculating the mean difference plus 99% CI using a Gaussian model with the identity link. For the length of labour, we presented the geometric mean ratio (GMR). For binary and categorical outcomes, we presented counts and percentages for each group and calculated the RR with corresponding 99% CI using a binomial or Poisson model with the log-link. For the number of thumb entries per hour from trial entry to the first yellow level of concern or full dilatation, the rate ratio plus 99% CI was calculated using a Poisson model with the log-link. For skewed continuous outcomes, we presented the median and IQR (or entire range, whichever was appropriate) for each group and compared the difference in medians between groups using quantile regression. We were unable to adjust for the correlation among twins and siblings using this method.

Deviation from analysis described in protocol

For the count variables, median differences were all zero with zero CIs, although some were statistically significant and adjusted quantile regression models were not performing well (lack of convergence), so rate ratios were presented as the effect measure instead of median differences. Medians (IQR) were still presented for each variable as planned. In addition, the hazard ratio was presented for the time from the first red alert to birth instead of the median difference, in keeping with the comparison of rates for the rest of the process outcomes. This was agreed at the INFANT project management group meeting on 23 October 2014.

The outcome time from the first red level of concern to delivery was changed to time from the last red level of concern to delivery. This was agreed at the INFANT coinvestigator group meeting on 15 July 2015 following a review by Professor Philip Steer. It was found that the first red level of concern was frequently an artefact and, therefore, did not accurately capture information relating to prompt action at or around delivery following a red alert.

Chapter 5 Trial conduct

Training

An extensive programme of training in the trial processes was delivered by the trial team at each participating site. This included training about the use of the decision support software, how to complete the electronic data input in preparation for download to the trial co-ordinating centre and how to complete the necessary paper data collection forms for babies of women admitted to higher-level care (see *Appendix 4*).

Recruitment

The aim was to randomise 46,000 women in the trial over 36 months. Therefore, approximately 320 women per week needed to be recruited. A conservative estimate of the proportion of women who receive EFM in labour, and were therefore eligible for trial entry, was 60%. The eligibility rate was expected to be higher in some centres; for example, in one study, 80% of primigravid women who gave birth in Liverpool Women's Hospital were monitored continuously. In total, there were around 42,500 deliveries per annum in the centres originally planned to participate in INFANT (the average for each centre was 4250 deliveries per annum). This was approximately 817 deliveries per week, among which an estimated 490 women per week (60%) would receive EFM.

Pilot work carried out in Plymouth to investigate recruitment rates found that only 2 out of 105 eligible women declined to take part. Although this indicated that uptake was likely to be high, strategies to promote and support recruitment were implemented in all participating centres.

During the course of the trial, recruitment graphs (e.g. *Figure 11*) were sent to all recruiting sites each month. This showed the percentage of target recruitment over the years of the trial. In the example below, this centre exceeded its recruitment target throughout the duration of the trial, achieving a very high recruitment rate of approximately 230% of its target in 2011.

Overall, despite most centres exceeding their recruitment target, there was a delay in reaching the final recruitment target (*Figure 12*). This was caused by longer than expected delays in initiating new centres into the trial.

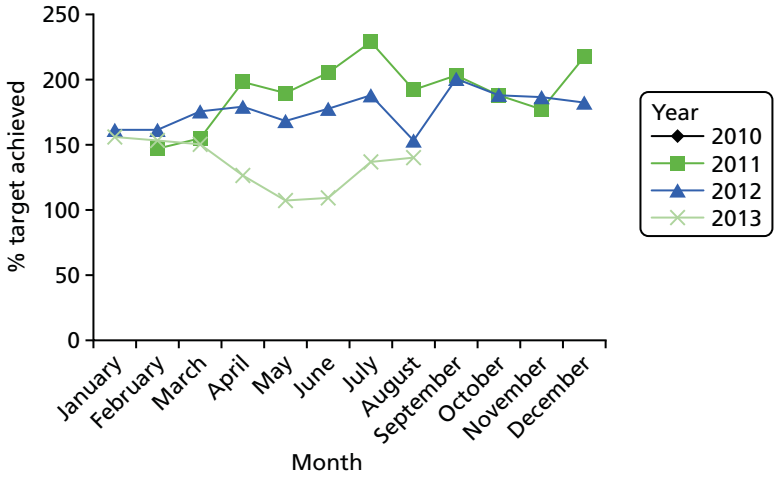


FIGURE 11 Example of monthly recruitment data sent to the centres.

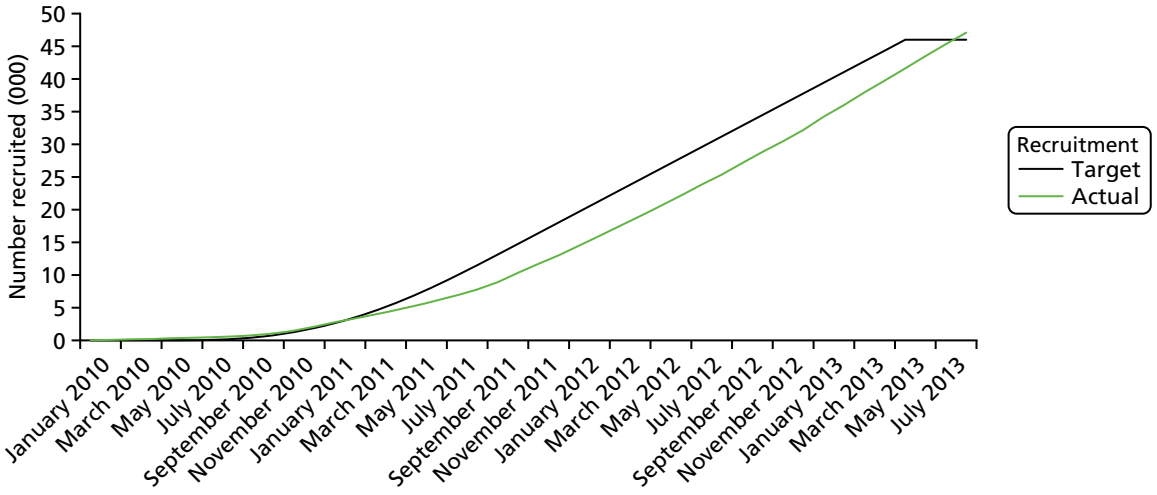


FIGURE 12 Actual vs. target recruitment.

Review of primary outcome

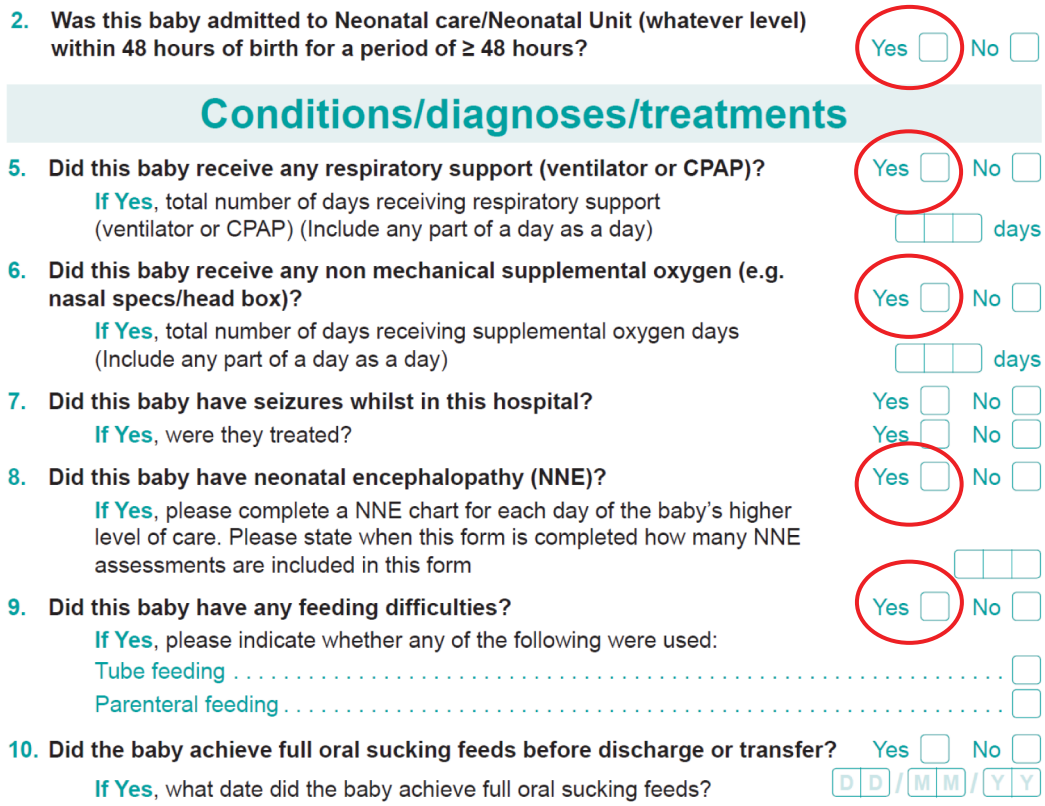
Following the TSC meeting on 2 October 2013, the INFANT project management group agreed to undertake further work to clarify the classification of the primary outcome for the trial. This issue had arisen because the incidence of one of the components of the composite primary outcome (admission to the neonatal unit within 48 hours of birth for ≥ 48 hours with evidence of respiratory or feeding problems or NNE) was substantially higher than had been anticipated, and an initial review of these cases (by PB and DF, masked to allocation) suggested that a number of cases were included in this outcome that were unrelated to perinatal hypoxia (*Table 16*). It was also recognised that, for many of these uncertain cases, the detail provided by the INFANT data collection forms was insufficient (*Figure 13*). All cases were included in this outcome if question 2 was answered 'Yes' and 'Yes' was also answered for one or more of questions 5, 6, 8 and/or 9 (*Figure 13*).

It was agreed that neonatal unit discharge summaries would be collected for all babies who were admitted to the neonatal unit within 48 hours of birth for ≥ 48 hours. A more formal process of review of a proportion of these cases would then be undertaken by Peter Brocklehurst, David Field, Keith Greene and

TABLE 16 The composite primary outcome event rate overall, and the relative contribution of its four components prior to the review

	Expected		Observed	
Component of primary outcome	Event rate (*n*/1000)	Number (*n* = 29,233[a])	Event rate (*n*/1000)	Number (*n* = 29,233[a])
Intrapartum stillbirth	0.35	10	0.07	2
Neonatal death up to 28 days after birth	0.70	20	0.48	14
Moderate or severe NNE	1.30	38	0.92	27
Admission to NICU within 48 hours of birth for ≥ 48 hours with evidence of respiratory or feeding problems or NNE	1.25	37	18.10	529
Overall (total)	3.60[b]	105	19.57	572

NICU, neonatal intensive care unit.
a Sample size at database lock on 6 November 2012.
b The actual sample size calculation was based on an incidence of the primary outcome in the no decision support group of 3/1000 to err on the side of caution.


2. **Was this baby admitted to Neonatal care/Neonatal Unit (whatever level) within 48 hours of birth for a period of ≥ 48 hours?** Yes ☐ No ☐

Conditions/diagnoses/treatments

5. **Did this baby receive any respiratory support (ventilator or CPAP)?** Yes ☐ No ☐
   If Yes, total number of days receiving respiratory support (ventilator or CPAP) (Include any part of a day as a day) ☐☐☐ days
6. **Did this baby receive any non mechanical supplemental oxygen (e.g. nasal specs/head box)?** Yes ☐ No ☐
   If Yes, total number of days receiving supplemental oxygen days (Include any part of a day as a day) ☐☐☐ days
7. **Did this baby have seizures whilst in this hospital?** Yes ☐ No ☐
   If Yes, were they treated? Yes ☐ No ☐
8. **Did this baby have neonatal encephalopathy (NNE)?** Yes ☐ No ☐
   If Yes, please complete a NNE chart for each day of the baby's higher level of care. Please state when this form is completed how many NNE assessments are included in this form ☐☐☐
9. **Did this baby have any feeding difficulties?** Yes ☐ No ☐
   If Yes, please indicate whether any of the following were used:
   Tube feeding . . . . . ☐
   Parenteral feeding . . . . . ☐
10. **Did the baby achieve full oral sucking feeds before discharge or transfer?** Yes ☐ No ☐
    If Yes, what date did the baby achieve full oral sucking feeds? D D / M M / Y Y

FIGURE 13 Definition of 'Admission to neonatal intensive care unit within 48 hours of birth for ≥ 48 hours with evidence of respiratory or feeding problems or NNE'. See *Appendix 5*.

Nikki Robertson (a neonatologist independent of the trial who is an expert on perinatal hypoxia in term babies) to devise a more structured way of assessing the classification of these babies. This system would then be implemented by David Field and Keith Greene for the purposes of data monitoring. There was also agreement that this process would be repeated by an independent panel of neonatologists at the end of the trial.

Peter Brocklehurst, David Field, Keith Greene and Nikki Robertson met on 16 January 2013 and reviewed approximately 40 sets of discharge summaries (masked to trial allocation) and devised a data extraction form, which included the key elements of the neonatal course which are most likely to be related to intrapartum hypoxia. This form was not an established or validated list of criteria, but the numeric scoring was devised to try and give some quantification of the severity of elements of the clinical course. A score of ≥ 3 points was agreed to be evidence that the condition of the baby was likely to be associated with intrapartum hypoxia, acknowledging that there remained uncertainty about this, as there is no absolute measure of intrapartum hypoxia. However, having reviewed the discharge summaries with the data extraction form, the criteria were felt to be a good reflection of the baby's clinical condition.

Process

David Field and Keith Greene then reviewed all the discharge forms independently to score the cases. A teleconference on 22 February 2012 resolved, by consensus with Peter Brocklehurst, the uncertain cases so that a decision could be made as to whether or not to include each baby as having evidence of the primary outcome (*Table 17*).

TABLE 17 The composite primary outcome event rate overall, and the relative contribution of its four components after the review

Component of primary outcome	Expected		Observed	
	Event rate (*n*/1000)	Number ($n = 29,233$[a])	Event rate (*n*/1000)	Number ($n = 29,233$[a])
Intrapartum stillbirth	0.35	10	0.07	2
Neonatal death up to 28 days after birth	0.70	20	0.48	14
Moderate or severe NNE	1.30	38	0.92	27
Admission to NICU within 48 hours of birth for ≥ 48 hours with evidence of respiratory or feeding problems or NNE	1.25	37	3.18	93
Overall (total) of those reviewed	3.60	105	4.65	136

NICU, neonatal intensive care unit.
a Sample size at database lock on 6 November 2012.

This produced a slightly revised definition of this component of the composite primary outcome:

- Admission to the neonatal unit within 48 hours of birth for ≥ 48 hours with evidence of respiratory or feeding problems or NNE (when there is evidence of compromise at birth).

This process and revised definition were reviewed and accepted by the TSC on 18 March 2013 and by the DMC on 21 March 2013.

Cases continued to be reviewed by David Field and Keith Greene on a monthly basis for the purposes of data monitoring. These data were entered into the INFANT database accordingly.

Independent review panel

An independent panel of neonatologists, to review all cases of the primary outcome (all stillbirths, early neonatal deaths, cases of NNE and babies admitted to the neonatal intensive care unit within 48 hours for ≥ 48 hours with evidence of respiratory or feeding difficulties), was assembled. An advertisement was placed in the British Association of Perinatal Medicine newsletter for prospective panel members. In order to ensure the independence of the panel, members could not be practising at any of the INFANT trial recruiting centres. Brief information of what would be expected as part of the review, how often they would be required to meet and details of payments to be made were included in the advertisement. The role was remunerated at £500 per day. Applicants were selected by the INFANT coinvestigators group.

After an initial face-to-face meeting to establish methods of working, panel members were sent a proportion of the cases once trial recruitment had finished. There was an overlap of cases so that every case was reviewed by at least two reviewers. When there was lack of agreement by two members of the panel, consensus was reached by discussion with the whole panel, at either a face-to-face meeting or teleconference.

Follow-up of deaths to age 2 years for entire trial cohort

After the initial analysis of the results of the trial, there was an unusual finding noted with the data from the 2-year follow-up.

In the original INFANT protocol, 46,000 women would be recruited and their babies would be followed up until hospital discharge, with a sample of 7000 of these babies being followed up at 2 years to assess longer-term outcomes, including neurodevelopmental outcomes. These 7000 babies were planned to be selected from the early phase of trial recruitment so that follow-up would not prolong the duration of the trial and the time to publication. We also initiated a system of 'flagging' with the NHS that notified the trial team of later deaths (after initial hospital discharge) to report deaths among all of the 46,000 babies by the time follow-up was completed. The duration of this mortality follow-up was intended to be dependent on when the baby was born and, for babies whose mothers were recruited later in the trial, would be < 2 years.

Once the planned follow-up was complete, the preliminary results from the INFANT trial were analysed and presented to the coinvestigators. There was an apparent difference in the number of longer-term deaths between groups. Given the lack of any difference in the primary outcome (early mortality and major morbidity), this result was surprising. At a joint meeting of the TSC and DMC in December 2014, it was suggested that the trial team should undertake a structured review of all the deaths, including obtaining as complete information about the later deaths as possible and, masked to allocation, ascribe cause-of-death classifications so that we could get some insight into whether this difference in deaths was likely to be real or spurious.

The distribution of all deaths between trial entry and follow-up at this time was 20 in one arm compared with 40 in the other arm. Masked to allocation, the cause of death was classified for babies for whom we had known cause-of-death data, and cause-of-death data were sought from the relevant national bodies (in England and Scotland) so that the later deaths could also be classified. Some cause-of-death data were still missing at this time. If an infant death is a coroner's case, there is often a delay in the cause-of-death data becoming available.

Once the coding was undertaken, the allocations were revealed and these data were presented to the coinvestigator group at its meeting on 4 February 2015. We compared the causes of death, including identifying deaths for congenital anomalies and lethal genetic conditions in which the decision support system could not be expected to make a difference. There were no differences in the numbers of deaths as a result of lethal congenital anomalies or lethal genetic conditions between the two groups. There appeared to be a possible difference between the two groups in terms of sudden unexplained death in infancy and other conditions, such as sepsis, in which there might potentially be a link between condition at birth and these later health outcomes. Although conditions might not be sufficient or severe enough to register as an event in the primary outcome, they might predispose the child to later morbidity and mortality.

The coinvestigator group decided that they could not conclude that this was a spurious result and agreed with the recommendations of the TSC/DMC that we should continue to follow up the remaining children until they reached age 2 years to determine the complete number of deaths by 2 years for the entire cohort.

The last baby was born in August 2013, resulting in a continuation of follow-up until after August 2015, allowing approximately 4 months for the majority of coroner's case cause-of-death data to be entered into the national systems.

During the further follow-up, it became apparent that an error had been made by the national authority in England when searching for cases of death. Despite the denominator of the trial growing each time the data were submitted for flagging, the search for deaths continued to be carried out for the initial submitted cohort, which was less than half of the entire trial population.

Once this error was recognised, a greater number of deaths were identified and, by the time the final child had reached age 2 years, the total numbers of deaths in each arm (excluding lethal congenital anomalies) were similar, with 29 in the decision support arm and 35 in the no decision support arm, adjusted risk ratio (aRR) 0.83 (99% CI 0.44 to 1.59).

Chapter 6 Results

Between 6 January 2010 and 31 August 2013, 47,062 women were randomised to the INFANT trial from the participating centres (*Table 18*). A total of 1020 women (2.2%) were excluded from the analysis of the primary outcome (*Figure 14*). The majority of these exclusions were because of missing or incomplete consent forms. Data at the time of birth were available for 100% of women and babies eligible to be analysed. Follow-up data at 2 years were available for 56% (7066/12,704) of those contacted, although data were sufficiently complete for the analysis for 6707 children.

A total of 30 women withdrew from the trial, 23 in the decision support group and seven in the no decision support group. The reasons given are in *Table 19*. A total of 1059 women were randomised in error, and the reasons for this are given in *Table 20*.

Baseline characteristics were similar between the two groups in the trial (*Table 21*). Mean maternal age was 29 years. The majority of women participating in the trial were of white ethnic origin and the median BMI at booking was 25 kg/m^2. Nearly 60% of women were having their first baby, and the majority of women in both groups had a gestational age of between 38 and 41 completed weeks, although 11% were < 38 weeks' gestation and 6.3% were 42 weeks or later. Very few women had experienced a previous stillbirth (1%) and approximately 6% had undergone a caesarean section in a previous birth. In almost 60% of women, labour was induced.

TABLE 18 List of participating centres

Centre	Trial arm, *n* (%)	
	Decision support (*N* = 22,987)	No decision support (*N* = 23,055)
Birmingham Women's Hospital	1131 (4.9)	1131 (4.9)
Burnley General Hospital	2058 (9.0)	2062 (8.9)
Chelsea and Westminster Hospital, London	441 (1.9)	449 (2.0)
Derriford Hospital, Plymouth	1641 (7.1)	1626 (7.1)
Homerton University Hospital, London	944 (4.1)	940 (4.1)
Liverpool Women's Hospital	1524 (6.6)	1559 (6.8)
Northwick Park Hospital, London	926 (4.0)	936 (4.1)
Nottingham City Hospital and Queens Medical Centre	902 (3.9)	903 (3.9)
Princess Anne Hospital, Southampton	585 (2.5)	581 (2.5)
Princess Royal Hospital and Southern General Hospital, Glasgow	2041 (8.9)	2033 (8.8)
Queen Alexandra Hospital, Portsmouth	1370 (6.0)	1372 (6.0)
Rotunda Hospital, Dublin	1735 (7.6)	1728 (7.5)
Royal Bolton Hospital	499 (2.2)	510 (2.2)
Royal Derby Hospital	421 (1.8)	425 (1.8)
St Mary's Hospital, Manchester	935 (4.1)	945 (4.1)
Stoke Mandeville Hospital	1214 (5.3)	1216 (5.3)
University College Hospital, London	196 (0.9)	192 (0.8)
University Hospital Coventry	600 (2.6)	607 (2.6)
University Hospital of North Staffordshire	1670 (7.3)	1679 (7.3)
Warrington Hospital	1730 (7.5)	1732 (7.5)
Warwick Hospital	424 (1.8)	429 (1.9)

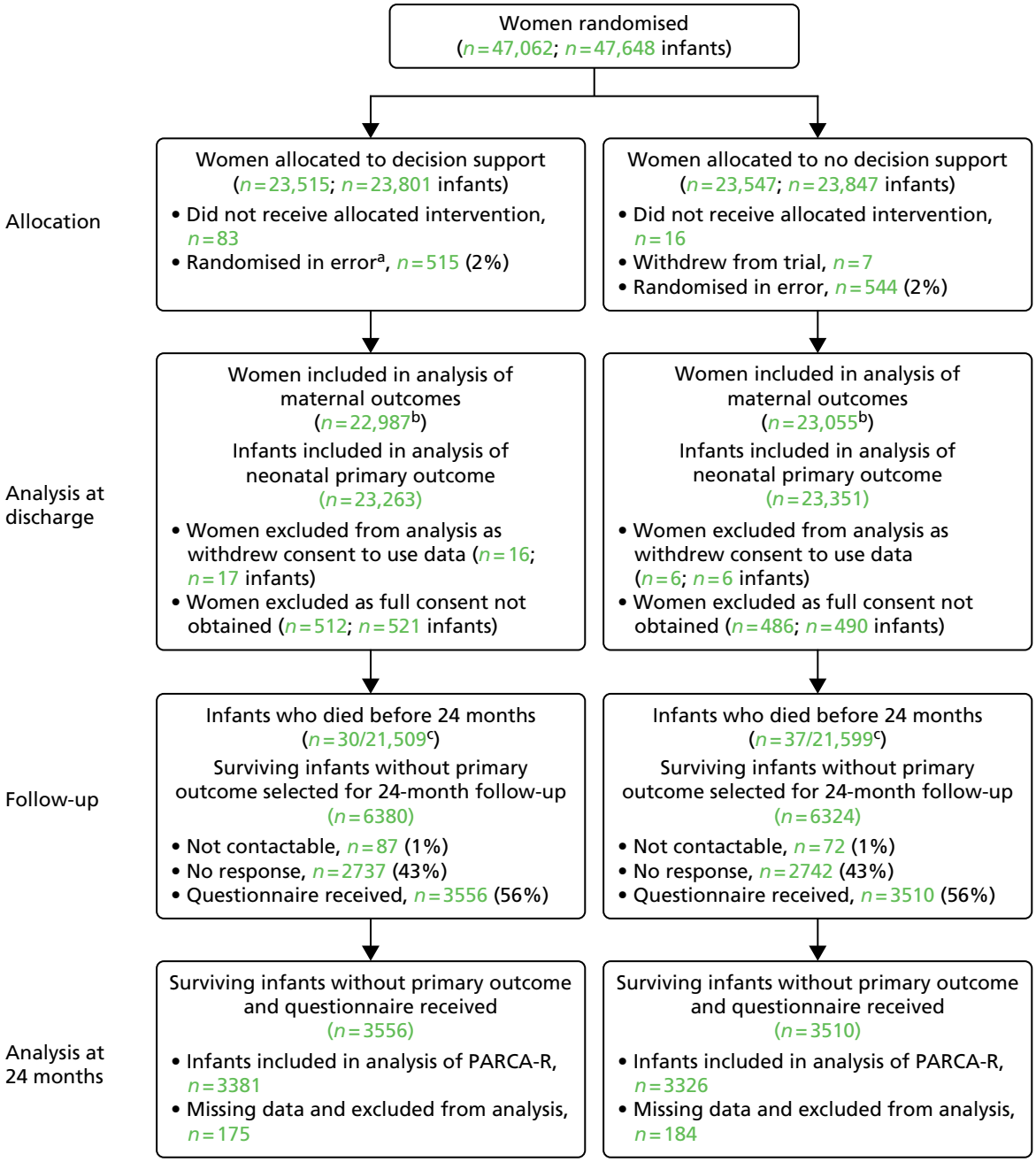


FIGURE 14 Consolidated Standards of Reporting Trials (CONSORT) flow of participants. a, One woman who withdrew (with consent to use of data) was also randomised in error; b, the 46,042 women included in the analysis includes 448 women (1%) with two singleton birth episodes and six women with one singleton and one twin birth episode in the study period and the allocation received for the subsequent delivery was independent of the first allocation received; and c, data from the Republic of Ireland not included in the numerator ($n = 1$ decision support) or denominator ($n = 1754$ in decision support and $n = 1752$ in no decision support) as data on deaths after discharge were not available. Deaths in the flow chart include stillbirths ($n = 1$ in decision support and $n = 2$ in no decision support).

There was no evidence of a difference in the incidence of the primary outcome of the composite of poor neonatal outcome between the groups, with 172 babies (0.7%) having a poor outcome in the decision support group compared with 171 babies (0.7%) in the no decision support group (aRR 1.01, 95% CI 0.82 to 1.25) (*Table 22*). Similarly, there was no evidence of a difference in any individual component of the composite primary outcome between the groups.

In a prespecified sensitivity analysis that used a different cut-off point for defining compromise at birth (a score of ≥ 7 points indicating a more severe compromise than a score of ≥ 3 points) this made no difference

TABLE 19 Reasons for withdrawal

Reason	Trial arm, number of participants	
	Decision support ($N = 23$)	No decision support ($N = 7$)
No longer wishes data to be collected/used	2	2
Did not like alerts	4	0
Twin baby died	1	0
No longer wishes to be followed up	1	0
Not happy with care/approach	1	2
Too distressed	1	0
Not happy with allocation	4	0
Not known/other	9	3

TABLE 20 Reasons for being randomised in error

Reason	Trial arm, number of participants	
	Decision support ($N = 515$)	No decision support ($N = 544$)
No labour/elective caesarean section	378	371
Date of randomisation after date of delivery	92	120
Fetal abnormality	18	19
Gestational age at entry of < 35 weeks or not known	10	15
Not CTG monitored	9	9
Not known/other	8	10

TABLE 21 Maternal characteristics at trial entry

Maternal characteristic	Trial arm	
	Decision support ($N = 22,987$)[a]	No decision support ($N = 23,055$)[a]
Maternal age at trial entry (years)		
Median (IQR)	29 (25–33)	29 (25–33)
Ethnic group, *n* (%)[b]		
White	17,234 (83.3)	17,213 (83.0)
Indian	743 (3.6)	724 (3.5)
Pakistani	736 (3.6)	802 (3.9)
Bangladeshi	98 (0.5)	113 (0.5)
Black Caribbean	116 (0.7)	135 (0.6)
Black African	461 (2.2)	505 (2.4)
Any other ethnic group	1296 (6.3)	1249 (6.0)
Unknown	2303	2314

continued

TABLE 21 Maternal characteristics at trial entry (*continued*)

Maternal characteristic	Trial arm	
	Decision support ($N = 22,987$)[a]	No decision support ($N = 23,055$)[a]
Twin pregnancy, *n* (%)	276 (1.2)	296 (1.3)
Gestational age at entry (completed weeks)		
Median (IQR)	40 (39–41)	40 (39–41)
$< 35^{+0}$, *n* (%)	4 (–[d])	6 (–[d])
35^{+0} to 37^{+6}, *n* (%)	2529 (11.0)	2522 (10.9)
38^{+0} to 39^{+6}, *n* (%)	7322 (31.9)	7266 (31.5)
40^{+0} to 41^{+6}, *n* (%)	11,688 (50.9)	11,795 (51.2)
$\geq 42^{+0}$, *n* (%)	1437 (6.3)	1457 (6.3)
BMI (kg/m^2), at booking visit		
Median (IQR)	25 (22–30)	25 (22–30)
< 18.5, *n* (%)	379 (2.5)	384 (2.6)
18.5 to 24.9, *n* (%)	6302 (42.1)	6225 (41.6)
25 to 29.9, *n* (%)	4531 (30.3)	4560 (30.5)
30 to 34.9, *n* (%)	2178 (14.5)	2237 (14.9)
35 to 39.9, *n* (%)	1024 (6.8)	1025 (6.8)
≥ 40, *n* (%)	565 (3.8)	544 (3.6)
Unknown, *n*	8008	8080
Smoking, at booking visit, *n* (%)		
Yes	2448 (14.3)	2536 (14.7)
No	14,724 (85.7)	14,722 (85.3)
Unknown	5815	5797
Parity, *n* (%)		
Nulliparous	13,736 (59.8)	13,650 (59.2)
Parous	9247 (40.2)	9390 (40.8)
Obstetric history, *n* (%)		
Previous stillbirth	273 (1.2)	223 (1.0)
Previous elective caesarean section	208 (0.9)	253 (1.1)
Previous emergency caesarean section	1240 (5.4)	1224 (5.3)
Previous neonatal death	80 (0.4)	95 (0.4)
Cervical dilatation at time of trial entry (cm)		
Median (IQR)	4 (2–6)	4 (2–5)
Unknown, *n*	16,184	16,339
Fetal growth restriction suspected at labour onset, *n* (%)	859 (3.7)	914 (4.0)
Labour induction, *n* (%)		
Induced	13,516 (59.2)	13,568 (59.2)
Spontaneous	8955 (39.2)	8967 (39.2)
No labour	376 (1.7)	367 (1.6)

TABLE 21 Maternal characteristics at trial entry (*continued*)

Maternal characteristic	Trial arm	
	Decision support ($N = 22,987$)[a]	No decision support ($N = 23,055$)[a]
Epidural analgesia, *n* (%)		
Yes	2682 (26.0)	2766 (26.8)
No	7628 (74.0)	7549 (73.2)
Unknown[a]	12,677	12,740
Presence of meconium, *n* (%)		
Yes	449 (4.5)	454 (4.5)
No	9454 (95.5)	9535 (95.5)
Unknown[c]	13,084	13,066

a Women with more than one birth episode in the study period are included more than once ($n = 454$).
b As coded by the NHS.
c Timing of epidural and presence of meconium in relation to trial entry only collected from 2013 for most centres.
d Negligible.
Note
Missing data are < 1% unless otherwise presented; there were no apparent differences in missing data between trial arms.

TABLE 22 Primary and neonatal outcomes

Outcome	Trial arm		
	Decision support ($N = 23,263$)	No decision support ($N = 23,351$)	Adjusted[a] RR (CI) unless otherwise indicated
Composite primary outcome (95% CI)			
Composite primary outcome 1–4, *n* (%)[b]	172 (0.7)	171 (0.7)	1.01 (0.82 to 1.25)
(1) Intrapartum stillbirths, *n* (%)[c]	1 (–)	2 (–)	0.50 (0.05 to 5.53)
(2) Neonatal deaths up to 28 days after birth, *n* (%)[d]	6 (–)	4 (–)	1.51 (0.42 to 5.33)
(3) Moderate or severe NNE (requiring cooling), *n* (%)	18 (0.1)	21 (0.1)	0.86 (0.46 to 1.61)
(4) Admission to neonatal unit within 48 hours of birth for ≥ 48 hours because of feeding difficulties, respiratory illness/symptoms or NNE and evidence of compromise at birth, *n* (%)	147 (0.6)	144 (0.6)	1.02 (0.81 to 1.29)
Other neonatal outcomes (99% CI)			
Admission to a higher level of care, *n* (%)	1389 (6.0)	1429 (6.1)	0.98 (0.89 to 1.08)
An Apgar score of < 4 at 5 minutes, *n* (%)	43 (0.2)	65 (0.3)	0.67 (0.40 to 1.11)
Cord artery pH, *n* (%)			
< 7.15	1625 (11.3)	1695 (11.8)	0.96 (0.88 to 1.04)
< 7.05	268 (1.9)	278 (1.9)	0.95 (0.77 to 1.19)
Mean (SD)	7.24 (0.08)	7.24 (0.08)	
Unknown	8829	8981	
Metabolic acidosis, *n* (%)[e]			
Yes	148 (1.1)	131 (1.0)	1.12 (0.82 to 1.52)
No	13,538 (98.9)	13,533 (99.0)	
Unknown	9577	9687	

continued

TABLE 22 Primary and neonatal outcomes (*continued*)

Outcome	Trial arm		
	Decision support (*N* = 23,263)	No decision support (*N* = 23,351)	Adjusted[a] RR (CI) unless otherwise indicated
Resuscitation, *n* (%)			
None	18,457 (87.3)	18,605 (87.6)	
One intervention	2139 (10.1)	2116 (10.0)	1.03[f] (0.96 to 1.09)
Two or more interventions	554 (2.6)	524 (2.5)	
Unknown	2113	2106	
Seizures while in hospital, *n* (%)	39 (0.2)	41 (0.2)	0.95 (0.54 to 1.70)
Destination of baby immediately after birth, *n* (%)			
Postnatal ward	21,571 (93.6)	21,664 (93.6)	
Home	467 (2.0)	485 (2.1)	1.00[g] (0.99 to 1.00)
Transitional care unit	277 (1.2)	235 (1.0)	
Neonatal unit	653 (2.8)	690 (3.0)	
Transferred hospital	4 (–)	7 (–)	
Stillbirth	1 (–)	2 (–)	
Other	69 (0.3)	53 (0.2)	
Length of hospital stay to discharge (days)			
Median (IQR)	2 (1–3)	2 (1–3)	Hazard ratio: 0.99 (99% CI 0.97 to 1.01)

a Adjusted for stratification factors used in the randomisation (centre and twin birth) and clustering because of twins and multiple-birth episodes. Minimisation factors not adjusted for in the analysis of intrapartum stillbirths, neonatal deaths and NNE because of the small number of events. Crude effect measures not presented as identical to one decimal place (two decimal places for most outcomes).
b The components of the primary outcome are mutually exclusive and outcomes listed higher take precedence over those listed lower down, for example if a baby with NNE died within 28 days, the outcome would be recorded as neonatal death.
c Excluding stillbirths as a result of congenital anomalies.
d Excluding deaths as a result of congenital anomalies. Deaths after hospital discharge not reported for the Republic of Ireland.
e A cord artery pH of < 7.05 and a base deficit of ≥ 12 mmol/l.
f RR of one or more interventions vs. none.
g RR of ward or home vs. all other destinations (if known).

Note
Missing data are < 1% unless otherwise presented; there were no apparent differences in missing data between trial arms.

to the interpretation of the measure of effect for the primary outcome (aRR 0.97, 95% CI 0.58 to 1.63; *Table 23*).

There was no evidence of any difference in any of the trial's secondary outcomes for the baby (see *Table 22*), including Apgar score, all admissions to the neonatal unit, metabolic acidosis of cord blood sample, the need for neonatal resuscitation and duration of hospital stay.

Just over half of all births were spontaneous vaginal births and there was no statistically significant difference between the two groups [11,823 women (50.8%) in the decision support group vs. 11,959 women (51.2%) in the no decision support group; aRR 0.99, 99% CI 0.97 to 1.01]. Of the operative births, half were by caesarean section and half were instrumental (*Table 24*). More women in the decision support group underwent fetal blood sampling: 2366 (10.3%) in the decision support group versus 2187 (9.5%) in the no decision support group (aRR 1.08, 99% CI 1.01 to 1.16). No other statistically significant differences were found between the two groups from trial entry to birth in clinical outcomes (see *Table 24*).

TABLE 23 Sensitivity analysis of composite primary outcome (panel review score of ≥ 7 vs. ≥ 3)

Outcome	Decision support (*N* = 23,263)	No decision support (*N* = 23,351)	Adjusted[a] relative risk (95% CI)
Composite primary outcome 1–4, *n* (%)[b]	28 (0.1)	29 (0.1)	0.97 (0.58 to 1.63)
Unknown	1	2	
(1) Intrapartum stillbirths, *n* (%)[c]	1 (–[d])	2 (–[d])	0.50 (0.05 to 5.53)
(2) Neonatal deaths up to 28 days after birth, *n* (%)[e]	6 (–[d])	4 (–[d])	1.51 (0.42 to 5.33)
(3) NNE (requiring cooling), *n* (%)	18 (0.1)	21 (0.1)	0.86 (0.46 to 1.61)
(4) Admission to neonatal unit within 48 hours of birth for ≥ 48 hours as a result of feeding difficulties, respiratory illness/ symptoms or NNE and evidence of compromise at birth with panel review score of ≥ 7, *n* (%)	3 (–[d])	2 (–[d])	1.51 (0.25 to 9.01)

a Adjusted for twin birth and clustering because of twins and multiple-birth episodes. Minimisation factors not adjusted for because of the small number of events.
b The components of the primary outcome are mutually exclusive and outcomes listed higher take precedence over those listed lower down, for example if a baby with NNE died within 28 days, the outcome would be recorded as neonatal death.
c Excluding stillbirths as a result of congenital anomalies.
d Negligible.
e Excluding deaths as a result of congenital anomalies. Deaths after hospital discharge not reported for the Republic of Ireland.

TABLE 24 Delivery outcomes

Outcome	Trial arm		Adjusted RR (99% CI)[a]
	Decision support	No decision support	
Number of infants in denominator	***23,263***	***23,351***	
Mode of delivery, *n* (%)			
Spontaneous cephalic vaginal	11,823 (50.8)	11,959 (51.2)	0.99 (0.97 to 1.01)
Caesarean section	5669 (24.4)	5555 (23.8)	
Instrumental	5698 (24.5)	5765 (24.7)	
Vaginal breech	73 (0.3)	72 (0.3)	
Indications for any operative intervention (caesarean section and instrumental delivery), *n* (%)			
Fetal distress	4278 (18.4)	4262 (18.3)	1.04[b] (1.00 to 1.08)
Failure to progress	5059 (21.8)	5175 (22.2)	1.01[b] (0.97 to 1.05)
Fetal distress and failure to progress	1774 (7.6)	1599 (6.9)	
Other reason	229 (1.0)	247 (1.1)	
Indication for instrumental vaginal deliveries, *n* (%)			
Fetal distress	2608 (11.2)	2559 (11.0)	1.03[b] (0.97 to 1.09)
Failure to progress	2262 (9.7)	2396 (10.3)	0.97[b] (0.91 to 1.03)
Fetal distress and failure to progress	700 (3.0)	660 (2.8)	
Other reason	117 (0.5)	134 (0.6)	

continued

TABLE 24 Delivery outcomes (*continued*)

Outcome	Trial arm		
	Decision support	No decision support	Adjusted RR (99% CI)[a]
Caesarean section, *n* (%)			
Grade 1 (immediate threat to life)	1138 (4.9)	1121 (4.8)	1.02[c] (0.92 to 1.13)
Grade 2 (some threat of compromise)	3754 (16.2)	3605 (15.5)	1.04[c] (0.99 to 1.09)
Grade 3 (no threat of compromise)	645 (2.8)	689 (3.0)	1.02[c] (0.98 to 1.07)
Grade 4 (elective – timing to suit)	12 (0.1)	12 (0.1)	
Number of women in denominator	***22,987***	***23,055***	
Episiotomy, *n* (%)	6396 (28.9)	6498 (29.3)	0.99 (0.95 to 1.03)
Unknown	826	840	
Any episode of fetal blood sampling, *n* (%)	2366 (10.3)	2187 (9.5)	1.08 (1.01 to 1.16)
Destination of mother immediately after birth, *n* (%)			
Ward	21,554 (94.6)	21,614 (94.5)	
Home	429 (1.9)	462 (2.0)	1.00[d] (0.99 to 1.00)
ICU	15 (0.1)	19 (0.1)	
High-dependency unit	793 (3.5)	768 (3.4)	
Theatre	0 (–)	0 (–)	
Other hospital	0 (–)	8 (–)	
Admission to a higher level of care, *n* (%)	1245 (5.4)	1193 (5.2)	1.05 (0.95 to 1.16)
Length of labour from trial entry (minutes)[e]			
Geometric mean and GMR	379	381	0.99 (0.98 to 1.01)
Median (IQR)	404 (234–638)	408 (236–640)	
Unknown	871	924	
Length of first stage from trial entry (minutes)[e]			
Geometric mean and GMR	169	168	1.01 (0.98 to 1.04)
Median (IQR)	200 (100–351)	201 (96–354)	
Unknown	6422	6292	
Length of second stage from trial entry (minutes)[e]			
Geometric mean and GMR	39	39	0.99 (0.96 to 1.03)
Median (IQR)	49 (15–113)	50 (16–114)	
Unknown	6036	5934	

a Adjusted for stratification factors used in the randomisation (centre and twin birth) and clustering because of twins and multiple-birth episodes. Crude effect measures not presented as identical to one decimal place (two decimal places for most outcomes).
b RR for fetal distress and RR for failure to progress include (in the numerator) deliveries in the third category in which both fetal distress and failure to progress were recorded.
c RRs based on cumulative totals for grade, i.e. grade 1 vs. all other deliveries, grade 1–2 vs. all other deliveries, and grade 1–3 vs. all other deliveries.
d RR of ward or home vs. all other destinations (if known).
e Denominators exclude women with no labour (1378 in the decision support arm and 371 in the no decision support arm) date of randomisation after date of delivery (92 in the decision support arm and 120 in the no decision support arm) and unknown length of labour.

Note
Missing data are < 1% unless otherwise presented; there were no apparent differences in missing data between trial arms.

Quality of care was assessed by an expert panel for all neonatal deaths and intrapartum stillbirths as well as for all babies with an adverse outcome (trial primary outcome plus a cord artery pH of < 7.05 with a base deficit of ≥ 12 mmol/l) (*Tables 25* and *26*). The addition of cord artery metabolic acidosis as a criterion for review substantially reduced the number of babies considered by the panel. The overall proportion of cases with poor outcome in which babies were judged to have suboptimal care likely to have affected the outcome was 38% (27/71), which is similar to that reported previously.[72] This included all instances of suboptimal care, regardless of whether this was related to CTG interpretation or subsequent management decisions. We could not investigate whether or not in all cases appropriate action was taken in response to recognised abnormality, although that aspect has been examined in cases with a composite adverse outcome and biochemical evidence of asphyxia (the analysis of suboptimal care will be reported separately).

TABLE 25 Quality-of-care outcomes

Levels of care[a]	Trial arm		
	Decision support	No decision support	Adjusted[b] RR (99% CI)
Babies with an adverse outcome[c]	*N* = 35	*N* = 36	
Babies with an adverse outcome for whom care has been judged not to be suboptimal (level 0), *n* (%)	11 (31.4)	15 (41.7)	
Babies with an adverse outcome for whom care has been judged to be suboptimal (levels 1, 2 and 3), *n* (%)	24 (68.6)	21 (58.3)	1.18 (0.82 to 1.68)
Level 1	7 (20.0)	2 (5.6)	
Level 2	3 (8.6)	6 (16.7)	
Level 3	14 (40.0)	13 (36.1)	

a Level 0, no suboptimal care; level 1, suboptimal care, but different management would have made no difference to outcome; level 2, suboptimal care, and different management might have made a difference to outcome; level 3, suboptimal care, and different management would reasonably be expected to have made a difference to the outcome.
b Adjusted for twin birth and clustering because of twins and multiple-birth episodes. Minimisation factors not adjusted for because of the small number of events.
c Neonatal death, stillbirth or trial primary outcome with metabolic acidosis (a cord artery pH of < 7.05 with a base deficit of ≥ 12 mmol/l).

TABLE 26 Quality-of-care outcomes (all babies in denominator)

Levels of care[a]	Trial arm		
	Decision support	No decision support	Adjusted[b] relative risk (99% CI)
All babies	*N* = 23,263	*N* = 23,351	
Babies with an adverse outcome[c] for whom care has been judged not to be suboptimal (level 0), *n* (%)	11 (0.05)	15 (0.06)	
Babies with an adverse outcome for whom care has been judged to be suboptimal (levels 1, 2 and 3), *n* (%)	24 (0.10)	21 (0.09)	1.15 (0.64 to 2.06)
Level 1	7 (0.03)	2 (0.01)	
Level 2	3 (0.01)	6 (0.03)	
Level 3	14 (0.06)	13 (0.06)	

a Level 0, no suboptimal care; level 1, suboptimal care, but different management would have made no difference to outcome; level 2, suboptimal care, and different management might have made a difference to outcome; level 3, suboptimal care, and different management would reasonably be expected to have made a difference to the outcome.
b Adjusted for twin birth and clustering because of twins and multiple-birth episodes. Minimisation factors not adjusted for because of the small number of events.
c Neonatal death, stillbirth or trial primary outcome with metabolic acidosis (a cord artery pH of < 7.05 with a base deficit of ≥ 12 mmol/l).

The process outcomes collected in the trial are shown in *Table 27*. For women in the no decision support group, the presence of alerts was calculated by the software during labour but not revealed to the woman or her caregivers. Using women with any level of concern as the denominator, blue levels of concern (the least severe alert) occurred most frequently, with a median of nine such alerts during these labours (a rate of just below 1.4 per hour). The next more severe alert – a yellow level of concern – occurred a median of twice per labour for both women in the decision support group and those in the no decision support group. There was evidence of a lower rate of yellow levels of concern in the decision support group (adjusted rate ratio 0.87, 99% CI 0.84 to 0.89; *Table 27*). The most severe alert, the red level of concern, occurred infrequently (a median of once per labour, with a rate of 0.14 per hour) and there was no evidence of a difference between the two groups (aRR 0.98, 99% CI 0.92 to 1.04).

TABLE 27 Process outcomes after trial entry

Outcome	Trial arm		
	Decision support (*N* = 22,987)	No decision support[a] (*N* = 23,055)	Adjusted[b] effect measure (99% CI)
No labour, *n*	378	371	
Date and time of randomisation after date and time of delivery, *n*	92	120	
Number of remaining participants	***22,517***	***22,564***	
Epidural analgesia, *n* (%)			
Yes	2770 (27.3)	2689 (26.5)	RR 1.03 (0.97 to 1.09)
No	7383 (72.7)	7453 (73.5)	
Unknown[c]	12,364	12,422	
Labour augmentation, *n* (%)			
Yes	2705 (30.9)	2750 (31.3)	RR 0.99 (0.93 to 1.04)
No	6047 (69.1)	6042 (68.7)	
Unknown[c]	13,765	13,772	
Presence of meconium, *n* (%)			
Yes	440 (4.5)	469 (4.8)	RR 0.94 (0.80 to 1.11)
No	9316 (95.5)	9346 (95.2)	
Unknown[c]	12,761	12,749	
Number of women with at least one blue, yellow or red level of concern, *n* (%)	21,950 (97.5)	22,021 (97.6)	RR 1.00 (1.00 to 1.00)
Number of women with at least one blue level of concern (mild abnormality), *n* (%)	21,863 (97.1)	21,913 (97.1)	RR 1.00 (1.00 to 1.00)
Number of women with at least one yellow level of concern (moderate abnormality), *n* (%)	16,765 (74.5)	16,722 (74.1)	RR 1.00 (0.99 to 1.02)
Number of women with at least one red level of concern (severe abnormality), *n* (%)	2335 (10.8)	2413 (11.1)	RR 0.97 (0.90 to 1.04)
Unknown[d]	822	833	
Number of blue, yellow or red levels of concern in women with at least one level of concern			
Median (IQR)	9 (5–15)	9 (5–15)	Rate ratio 0.98 (0.96 to 1.00)
Rate per hour	1.37	1.40	
Unknown[e]	765	824	

TABLE 27 Process outcomes after trial entry (*continued*)

Outcome	Trial arm		
	Decision support (*N* = 22,987)	No decision support[a] (*N* = 23,055)	Adjusted[b] effect measure (99% CI)
Number of blue levels of concern in women with a blue level			
Median (IQR)	7 (4–11)	7 (4–11)	Rate ratio 1.01 (0.99 to 1.03)
Rate per hour	1.06	1.05	
Unknown[e]	740	800	
Number of yellow levels of concern in women with a yellow level			
Median (IQR)	2 (1–4)	2 (1–5)	Rate ratio 0.87 (0.84 to 0.89)
Rate per hour	0.35	0.40	
Unknown[e]	354	421	
Number of red levels of concern in women with a red level			
Median (IQR)	1 (1–1)	1 (1–1)	Rate ratio 0.98 (0.92 to 1.04)
Rate per hour	0.14	0.14	
Unknown[d,e]	41	55	
Interaction with Guardian system via number of thumbprint entries from time of trial entry to first yellow level of concern, or until cervix fully dilated if no abnormality detected			
Median (IQR)	5 (0–16)	4 (0–15)	Rate ratio 0.99 (0.95 to 1.03)
Rate per hour	4.22	4.21	
Unknown	1723	1603	
Number of vaginal examinations			
Median (IQR)	2 (1–3)	2 (1–3)	Rate ratio 1.03 (1.00 to 1.05)
Rate per hour	0.28	0.27	
Unknown	877	929	
Time from last red level of concern to delivery (minutes)			
Median (IQR)	58 (13–279)	58 (13–264)	HR 0.99 (0.92 to 1.06)
Unknown[d]	822	823	

HR, hazard ratio; RR, risk ratio.
a For the control group with CTG monitoring only, decision support software was used retrospectively to determine when an alert would have sounded.
b Adjusted for stratification factors used in the randomisation (centre and twin birth) and clustering because of twins and multiple-birth episodes. Crude effect measures not presented as identical to one decimal place (two decimal places for most outcomes).
c Timing of epidural, labour augmentation and presence of meconium only recorded and uploaded for analysis from 2013 for most centres.
d Data on timing of red levels of concern not available for two centres: Warwick Hospital (*n* = 823) and Derby Hospital (*n* = 832).
e Women with missing length of labour data not included in calculation of rates and rate ratios.

Although there was a worry within the trial term that women in the decision support group would be left alone in labour more frequently because the decision support software was running, there was no evidence to suggest that caregivers interacted with the Guardian system less frequently in this group. The rate of thumbprint entries on the Guardian system was 4.22 per hour in the decision support group and 4.21 per hour in the no decision support group (aRR 0.99, 99% CI 0.95 to 1.03; see *Table 27*).

The time from the last red level of concern to birth was similar in both groups, with a median of 58 minutes. Although this appears lengthy, there were red levels of concern that did not prompt immediate delivery, for example when the CTG monitor was picking up the maternal heart rate. In a subgroup of 500 traces (with a similar number of consecutive cases from each contributing centre) containing at least one red level of concern, the last red level of concern was judged (by an expert coinvestigator, PS) to be a valid fetal concern for 55%. For the remainder of these traces, the maternal heart rate triggered the red level of concern in 70%, and it was triggered for other reasons in 30%.

Follow-up at 2 years

Families were contacted when the surviving child(ren) born in the INFANT trial reached age 2 years. A total of 7066 families returned a questionnaire. There were statistically significant differences in the characteristics of the mothers who responded and those of the entire trial cohort, as well as between mothers who did and did not respond to an invitation to complete the questionnaire (*Tables 28* and *29*). Many of these differences are very small, but, given the large number of participants in the trial, are statistically significant. In general, the questionnaire responders, when compared with the entire trial cohort, were more likely to be

TABLE 28 Maternal characteristics at trial entry by follow-up status: responders vs. non-responders or not followed up at 2 years (mothers of surviving infants without the trial primary outcome only)

Characteristic	Follow-up status		*p*-value[b]
	Non-responders or not followed up at 2 years (*N* = 38,669)[a]	Responders at 2 years (*N* = 6986)[a]	
Maternal age (years)			
Median (IQR)	29 (24–33)	30 (26–34)	< 0.001
Ethnic group, *n* (%)[c]			
White	28,714 (81.9)	5461 (90.9)	< 0.001
Indian	1318 (3.8)	130 (2.2)	
Pakistani	1356 (3.9)	166 (2.8)	
Bangladeshi	190 (0.5)	19 (0.3)	
Black Caribbean	231 (0.7)	19 (0.3)	
Black African	917 (2.6)	37 (0.6)	
Any other ethnic group	2354 (6.7)	176 (2.9)	
Unknown	3589	978	
Twin pregnancy, *n* (%)	486 (1.3)	80 (1.2)	0.44
Gestational age at entry (completed weeks)			
Median (IQR)	40 (38–41)	40 (39–41)	< 0.001
$< 35^{+0}$, *n* (%)	9 (–)	1 (–)	
35^{+0} to 37^{+6}, *n* (%)	4314 (11.2)	682 (9.8)	
38^{+0} to 39^{+6}, *n* (%)	12,467 (32.3)	2035 (29.1)	
40^{+0} to 41^{+6}, *n* (%)	19,584 (50.7)	3702 (53.0)	
$\geq 42^{+0}$, *n* (%)	2282 (5.9)	566 (8.1)	
BMI (kg/m^2), at booking visit			
Median (IQR)	25 (22–30)	25 (22–29)	0.64
< 18.5, *n* (%)	644 (2.6)	110 (2.2)	
18.5–24.9, *n* (%)	10,321 (41.8)	2125 (42.3)	

TABLE 28 Maternal characteristics at trial entry by follow-up status: responders vs. non-responders or not followed up at 2 years (mothers of surviving infants without the trial primary outcome only) (*continued*)

Characteristic	Follow-up status		*p*-value[b]
	Non-responders or not followed up at 2 years (*N* = 38,669)[a]	Responders at 2 years (*N* = 6986)[a]	
25–29.9, *n* (%)	7467 (30.2)	1563 (31.1)	
30–34.9, *n* (%)	3638 (14.7)	735 (14.6)	
35–39.9, *n* (%)	1703 (6.9)	319 (6.4)	
≥ 40, *n* (%)	936 (3.8)	169 (3.4)	
Unknown	13,960	1965	
Smoking (at booking visit), *n* (%)			
Yes	4198 (15.0)	747 (11.9)	< 0.001
No	23,681 (85.0)	5518 (88.1)	
Unknown	10,795	721	
Parity, *n* (%)			
Nulliparous	22,792 (59.0)	4317 (61.8)	< 0.001
Parous	15,858 (41.0)	2669 (38.2)	
Obstetric history, *n* (%)			
Previous stillbirth	425 (1.1)	70 (1.0)	0.47
Previous elective caesarean section	359 (0.9)	100 (1.4)	< 0.001
Previous emergency caesarean section	2028 (5.2)	413 (5.9)	0.02
Previous neonatal death	153 (0.4)	19 (0.3)	0.12
Cervical dilatation at time of trial entry (cm)			
Median (IQR)	4 (2–6)	4 (2–5)	0.09
Unknown	27,528	4750	
Fetal growth restriction suspected at labour onset, *n* (%)	1506 (3.9)	247 (3.5)	0.08
Labour induction, *n* (%):			
Induced	22,848 (59.5)	4022 (57.9)	0.01
Spontaneous	14,932 (38.9)	2829 (40.7)	
No labour	632 (1.7)	101 (1.5)	
Epidural analgesia, *n* (%)			
Yes	4966 (28.0)	425 (15.9)	< 0.001
No	12,798 (72.0)	2257 (84.2)	
Unknown[d]	20,905	4304	
Presence of meconium, *n* (%)			
Yes	771 (4.5)	113 (4.1)	0.30
No	16,202 (95.5)	2642 (95.9)	
Unknown[d]	21,696	4231	

a Women with more than one birth episode in the study period are included more than once.
b *p*-value from chi-squared test for categorical variables and Wilcoxon rank-sum test for continuous variables.
c As coded by the NHS.
d Timing of epidural and presence of meconium in relation to trial entry only collected from 2013 for most centres.

Note
Missing data are < 1% unless otherwise presented; there were no apparent differences in missing data between trial arms.

TABLE 29 Maternal characteristics at trial entry by follow-up status: responders vs. non-responders at 2 years (mothers of surviving infants without the trial primary outcome only)

Characteristic	Follow-up status		*p*-value[b]
	Non-responders at 2 years ($N = 5560$)[a]	Responders at 2 years ($N = 6986$)[a]	
Maternal age (years)			
Median (IQR)	27 (23–31)	30 (26–34)	< 0.001
Ethnic group, *n* (%)[c]			
White	4094 (86.8)	5461 (90.9)	< 0.001
Indian	140 (3.0)	130 (2.2)	
Pakistani	230 (4.9)	166 (2.8)	
Bangladeshi	18 (0.4)	19 (0.3)	
Black Caribbean	15 (0.3)	19 (0.3)	
Black African	54 (1.1)	37 (0.6)	
Any other ethnic group	167 (3.5)	176 (2.9)	
Unknown	842	978	
Twin pregnancy, *n* (%)	78 (1.4)	80 (1.2)	0.20
Gestational age at entry (completed weeks)			
Median (IQR)	40 (38–41)	40 (39–41)	< 0.001
$< 35^{+0}$, *n* (%)	2 (–)	1 (–)	
35^{+0} to 37^{+6}, *n* (%)	665 (12.0)	682 (9.8)	
38^{+0} to 39^{+6}, *n* (%)	1728 (31.1)	2035 (29.1)	
40^{+0} to 41^{+6}, *n* (%)	2787 (50.1)	3702 (53.0)	
$\geq 42^{0}$, *n* (%)	377 (6.8)	566 (8.1)	
BMI (kg/m^2), at booking visit			
Median (IQR)	26 (22–30)	25 (22–29)	0.01
< 18.5	130 (3.3)	110 (2.2)	
18.5–24.9	1559 (39.1)	2125 (42.3)	
25–29.9	1187 (29.8)	1563 (31.1)	
30–34.9	607 (15.2)	735 (14.6)	
35–39.9	313 (7.9)	319 (6.4)	
≥ 40	192 (4.8)	169 (3.4)	
Unknown	1572	1965	
Smoking (at booking visit), *n* (%)			
Yes	994 (20.7)	747 (11.9)	< 0.001
No	3807 (79.3)	5518 (88.1)	
Unknown	759	721	
Parity, *n* (%)			
Nulliparous	3043 (54.7)	4317 (61.8)	< 0.001
Parous	2517 (45.3)	2669 (38.2)	

TABLE 29 Maternal characteristics at trial entry by follow-up status: responders vs. non-responders at 2 years (mothers of surviving infants without the trial primary outcome only) (*continued*)

Characteristic	Follow-up status		
	Non-responders at 2 years ($N = 5560$)[a]	Responders at 2 years ($N = 6986$)[a]	*p*-value[b]
Obstetric history, *n* (%)			
Previous stillbirth	77 (1.4)	70 (1.0)	0.05
Previous elective caesarean section	61 (1.1)	100 (1.4)	0.10
Previous emergency caesarean section	345 (6.2)	413 (5.9)	0.49
Previous neonatal death	22 (0.4)	19 (0.3)	0.23
Cervical dilatation at time of trial entry (cm)			
Median (IQR)	4 (2–5)	4 (2–5)	0.53
Unknown	3730	4750	
Fetal growth restriction suspected at labour onset, *n* (%)	266 (4.8)	247 (3.5)	< 0.001
Labour induction, *n* (%)			
Induced	3108 (56.2)	4022 (57.9)	0.18
Spontaneous	2336 (42.2)	2829 (40.7)	
No labour	86 (1.6)	101 (1.5)	
Epidural analgesia, *n* (%)			
Yes	266 (13.8)	425 (15.9)	0.05
No	1665 (86.2)	2257 (84.2)	
Unknown[d]	3629	4304	
Presence of meconium, *n* (%)			
Yes	66 (3.1)	113 (4.1)	0.06
No	2085 (96.9)	2642 (95.9)	
Unknown[d]	3409	4231	

a Women with more than one birth episode in the study period are included more than once.
b From the chi-squared ftest for categorical variables and the Wilcoxon rank-sum test for continuous variables.
c As coded by the NHS.
d Timing of epidural and presence of meconium in relation to trial entry only collected from 2013 for most centres.
Note
Missing data are < 1% unless otherwise presented; there were no apparent differences in missing data between trial arms.

slightly older, to be of white ethnic origin, to have given birth at a later gestational age and to have been having their first baby and were less likely to smoke.

Data could be analysed for 6707 of the 7066 infants for whom a questionnaire was returned (95%). There was no evidence of a difference between the two groups in any of the 2-year outcomes, including the long-term primary outcome of the PARCA-R, with a mean composite score of 98.0 points (SD 33.8 points) in the decision support group and 97.2 points (SD 33.4 points) in the no decision support group (mean difference 0.63 95% CI –0.98 to 2.25) (*Table 30*).

Nearly 6% of children were classified as having major disability. The classification of disability used resulted in relatively large numbers of children being assigned a major disability as a consequence of poor growth (between 2.8% and 3% of all children) and cognitive difficulties (between 1.2 and 1.5% of all children).[60,61] Other major disabilities, such as physical disability, blindness and deafness, were all very uncommon (*Table 31*).

TABLE 30 Health and development outcomes at 2 years (in a sample of surviving infants without the primary outcome who were selected for follow-up)

Outcome	Trial arm		Adjusted[a] RR (99% CI) unless otherwise indicated[b]
	Decision support	No decision support	
Infant deaths at 2 years, *n/N* (%)[c]	29/21,508 (0.13)	35/21,597 (0.16)	0.83 (0.44 to 1.59)
Number of surviving infants without the primary outcome	***3556***	***3510***	
PARCA-R composite score[b]			
Mean score (points) (SD)	98.0 (33.8)	97.2 (33.4)	
Median score (points) (IQR)	98 (73–126)	97 (72–125)	Mean difference (95% CI): 0.63 (–0.98 to 2.25)
Unknown	175	184	
Components of the PARCA-R			
Non-verbal cognition scale			
• Mean score (points) (SD)	27.7 (3.7)	28.0 (3.6)	
• Median score (points) (IQR)	28 (26–30)	28 (26–31)	Mean difference (99% CI): –0.22 (–0.44 to 0.01)
Vocabulary subscale			
• Mean score (points) (SD)	57.4 (27.8)	56.5 (27.7)	
• Median score (points) (IQR)	58 (36–81)	56 (35–80)	Mean difference (99% CI): 0.82 (–0.91 to 2.54)
Sentence complexity subscale			
• Mean score (points) (SD)	12.4 (5.4)	12.3 (5.3)	
• Median score (points) (IQR)	12 (9–6)	12 (9–16)	Mean difference (99% CI): 0.07 (–0.26 to 0.41)
Cerebral palsy, *n* (%)	4 (0.12)	4 (0.12)	0.99 (0.16 to 6.1)
Unknown	111	114	
Non-major or major disability, *n* (%)[d]	942 (40.4)	840 (37.4)	1.08 (0.98 to 1.18)
Unknown	1225	1266	
Major disability, *n* (%)[d]	134 (5.8)	135 (6.0)	0.95 (0.70 to 1.29)
Unknown	1225	1266	

a Adjusted for stratification factors used in the randomisation (centre and twin birth) and clustering because of twins and multiple-birth episodes. Stratification factors not adjusted for in the analysis of infant deaths at 2 years and cerebral palsy because of the small number of events. Crude effect measures are not presented as identical to one decimal place (two decimal places for most outcomes).

b 95% CIs presented for the PARCA-R composite score (joint primary outcome).

c All deaths reported up to age 2 years excluding stillbirths ($n = 3$; 1 in the decision support group and 2 in the no decision support group). Data from the Republic of Ireland not included in the numerator ($n = 1$, decision support) or denominator ($n = 1754$ in the decision support grup and $n = 1752$ in no decision support group) as data on deaths after discharge were not available.

d Disability in any of the following domains: neuromotor function, seizures, auditory function, communication, visual function, cognitive function and other physical disability.

Note

Missing data are < 3% unless otherwise presented; there were no apparent differences in missing data between trial arms.

TABLE 31 Components of non-major and major disability at 2 years

Disability component	Trial arm	
	Decision support (*N* = 3556)	No decision support (*N* = 3510)
Cognition, *n* (%)		
None	3159 (93.4)	3134 (94.2)
Non-major	180 (5.3)	143 (4.3)
Major	42 (1.2)	49 (1.5)
Unknown	175	184
Communication, *n* (%)		
None	3132 (88.6)	3096 (88.7)
Non-major	394 (11.2)	392 (11.2)
Major	8 (0.2)	4 (0.1)
Unknown	22	18
Physical ability, *n* (%)		
None	3161 (92.3)	3166 (93.7)
Non-major	245 (7.2)	199 (5.9)
Major	19 (0.6)	15 (0.4)
Unknown	131	130
Vision, *n* (%)		
None	3409 (99.6)	3373 (99.7)
Non-major	14 (0.4)	8 (0.2)
Major	1 (–)	1 (–)
Unknown	132	128
Hearing, *n* (%)		
None	3307 (99.0)	3293 (99.2)
Non-major	30 (0.9)	25 (0.8)
Major	5 (0.2)	2 (0.1)
Unknown	214	190
Growth, *n* (%)		
None	1899 (90.5)	1882 (92.2)
Non-major	137 (6.5)	102 (5.0)
Major	63 (3.0)	58 (2.8)
Unknown	1457	1468
Seizures, *n* (%)		
None	3302 (99.0)	3259 (98.9)
Non-major	31 (0.9)	30 (0.9)
Major	4 (0.1)	5 (0.2)
Unknown	219	216

continued

TABLE 31 Components of non-major and major disability at 2 years (*continued*)

Disability component	Trial arm	
	Decision support (*N* = 3556)	No decision support (*N* = 3510)
Feeding, *n* (%)		
None	3385 (99.9)	3326 (99.9)
Non-major	0 (0.0)	0 (0.0)
Major	3 (0.1)	5 (0.2)
Unknown	168	179
Respiratory, *n* (%)		
None	3284 (97.0)	3266 (97.4)
Non-major	100 (3.0)	86 (2.6)
Major	0 (0.0)	0 (0.0)
Unknown	172	158
Other disability, *n* (%)		
None	3550 (99.9)	3501 (99.8)
Non-major	0 (0.0)	0 (0.0)
Major	3 (0.1)	6 (0.2)
Unknown	3	3

A number of subgroup analyses were prespecified (*Figures 15–40* and *Tables 32–35*). There was no evidence that the decision support software produced different outcomes in any of the subgroups (e.g. multiple pregnancy, suspected fetal growth restriction, BMI of the mother) for either the primary outcome or a limited range of prespecified secondary outcomes. There were also no differences in the distribution of cord blood pH measurements (*Figure 41*). The number of alerts in the analysis differed by centre (*Figures 33*, *35–39*). The reasons for this are unclear, particularly as there were no statistically significant differences in the other outcomes by centre.

Predefined subgroup analyses of short-term outcomes

Note: results are presented on forest plots showing the RR plus 95% CI for each subgroup, by treatment group, with the *p*-value for the statistical test of interaction. Subgroup analyses are not adjusted for the stratification factors used at randomisation because of the small number of events in some subgroup categories.

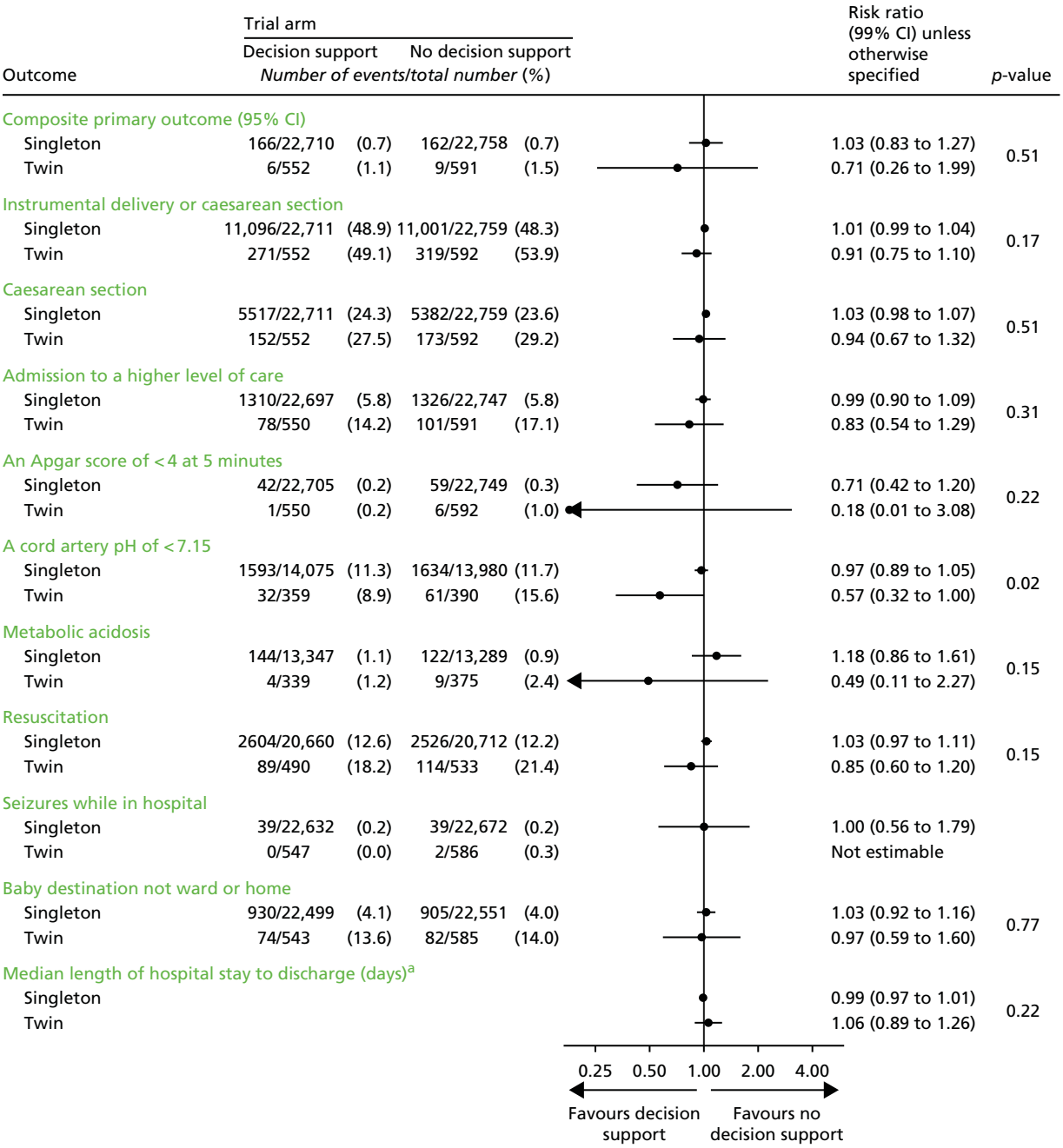


FIGURE 15 Maternal and neonatal outcomes, by twin pregnancy. a, Hazard ratios reported.

Outcome	Trial arm: Decision support *Number of events/total number* (%)		Trial arm: No decision support *Number of events/total number* (%)		Risk ratio (99% CI) unless otherwise specified	*p*-value
Composite primary outcome (95% CI)						
No FGR	166/22,384	(0.7)	164/22,407	(0.7)	1.01 (0.82 to 1.26)	0.87
FGR	6/878	(0.7)	7/942	(0.7)	0.92 (0.31 to 2.73)	
Instrumental delivery or caesarean section						
No FGR	11,085/22,385	(49.5)	11,051/22,409	(49.3)	1.00 (0.98 to 1.03)	0.12
FGR	282/878	(32.1)	269/942	(28.6)	1.12 (0.93 to 1.36)	
Caesarean section						
No FGR	5530/22,385	(24.7)	5432/22,409	(24.2)	1.02 (0.98 to 1.06)	0.15
FGR	139/878	(15.8)	123/942	(13.1)	1.21 (0.89 to 1.65)	
Admission to a higher level of care						
No FGR	1307/22,370	(5.8)	1330/22,401	(5.9)	0.98 (0.89 to 1.09)	0.52
FGR	81/877	(9.2)	97/937	(10.4)	0.89 (0.61 to 1.31)	
An Apgar score of < 4 at 5 minutes						
No FGR	42/22,377	(0.2)	62/22,399	(0.3)	0.68 (0.40 to 1.14)	0.58
FGR	1/878	(0.1)	3/942	(0.3)	0.36 (0.02 to 6.99)	
A cord artery pH of < 7.15						
No FGR	1586/13,938	(11.4)	1651/13,882	(11.9)	0.96 (0.88 to 1.04)	0.66
FGR	39/496	(7.9)	44/488	(9.0)	0.87 (0.51 to 1.50)	
Metabolic acidosis						
No FGR	144/13,205	(1.1)	129/13,188	(1.0)	1.11 (0.82 to 1.52)	0.51
FGR	4/481	(0.8)	2/476	(0.4)	1.98 (0.21 to 18.33)	
Resuscitation						
No FGR	2603/20,299	(12.8)	2546/20,336	(12.5)	1.02 (0.96 to 1.10)	0.99
FGR	90/851	(10.6)	94/909	(10.3)	1.02 (0.71 to 1.48)	
Seizures while in hospital						
No FGR	36/22,306	(0.2)	39/22,320	(0.2)	0.92 (0.51 to 1.67)	0.55
FGR	3/873	(0.3)	2/938	(0.2)	1.61 (0.15 to 16.88)	
Baby destination not ward or home						
No FGR	946/22,164	(4.3)	918/22,196	(4.1)	1.03 (0.92 to 1.16)	0.46
FGR	58/878	(6.6)	69/940	(7.3)	0.90 (0.57 to 1.42)	
Median length of hospital stay to discharge (days)[a]						
No FGR					0.99 (0.97 to 1.01)	0.79
FGR					0.98 (0.88 to 1.09)	

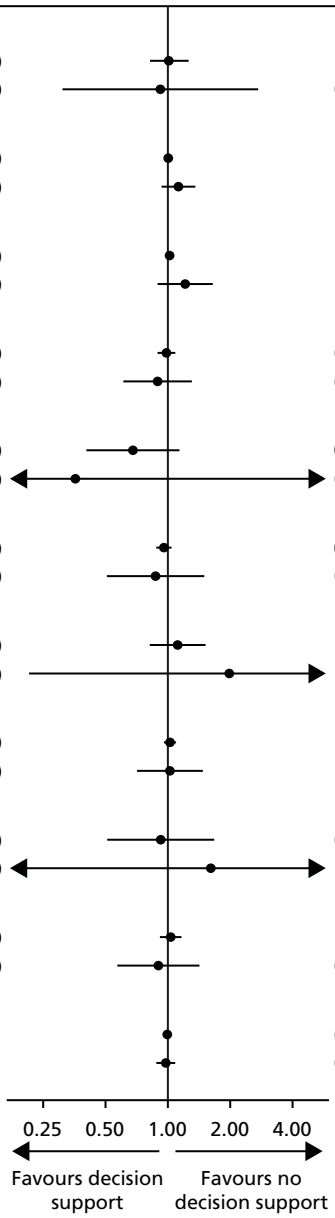


FIGURE 16 Maternal and neonatal outcomes, by suspected fetal growth restriction. a, Hazard ratios reported.

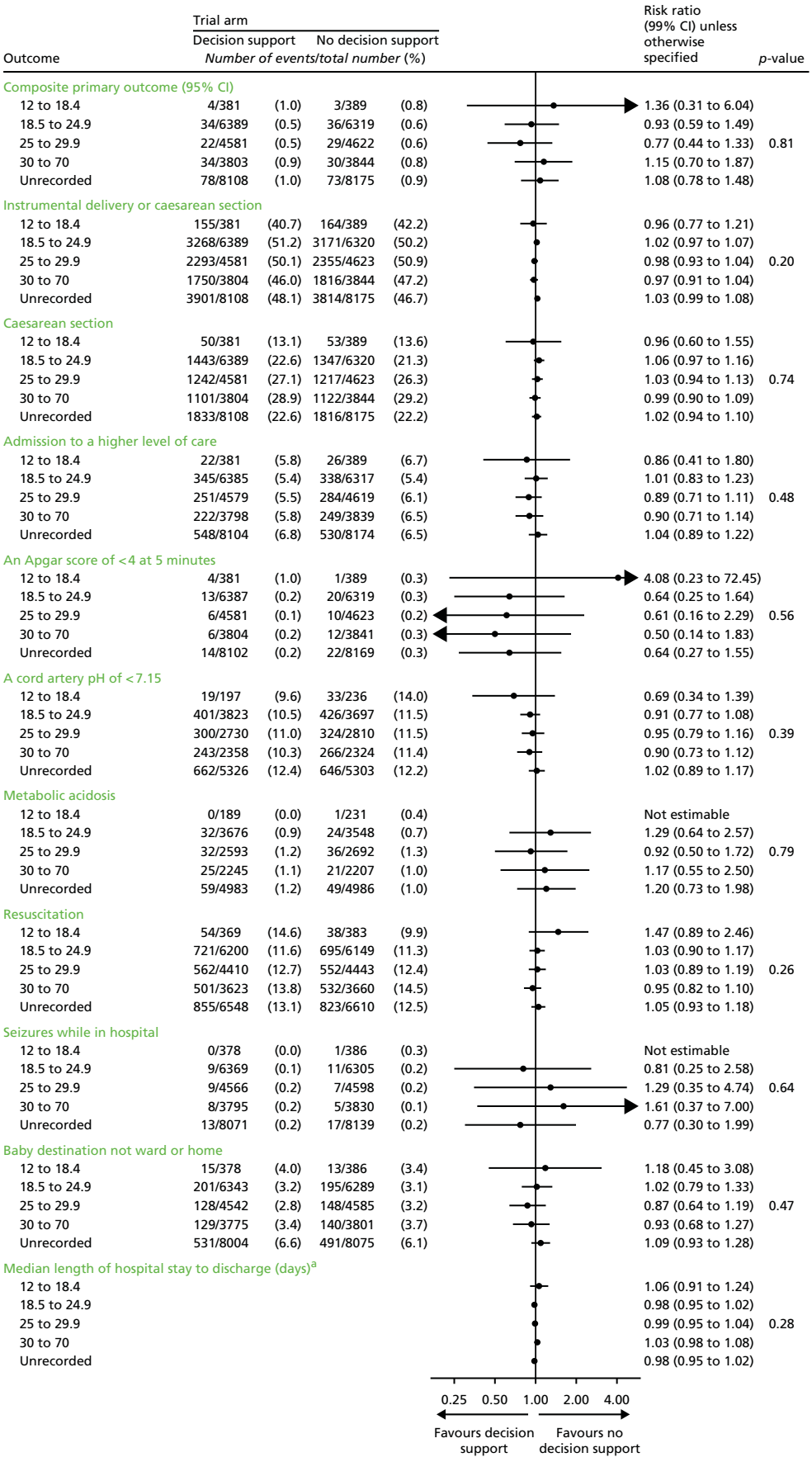


FIGURE 17 Maternal and neonatal outcomes, by BMI at booking visit. a, Hazard ratios reported.

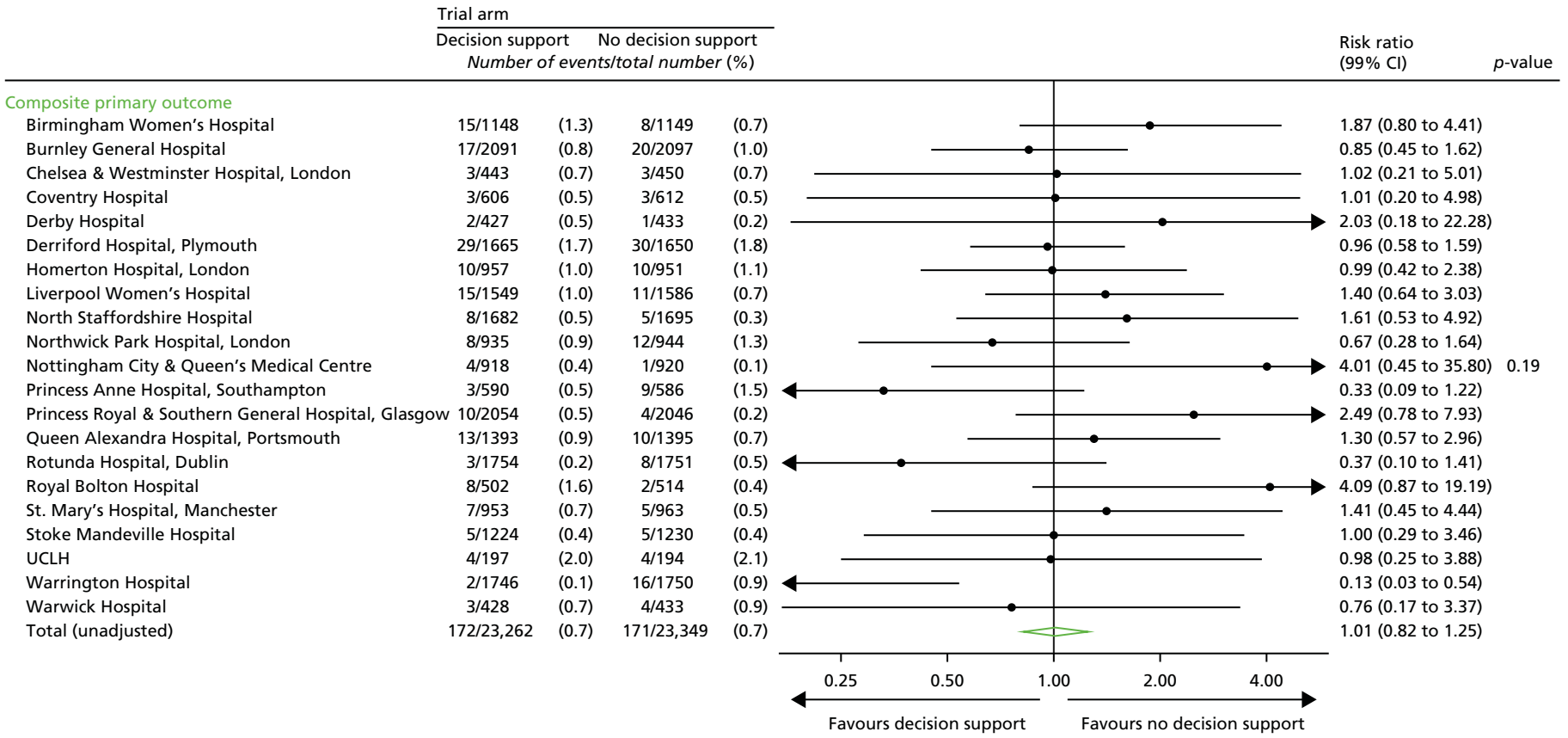


FIGURE 18 Composite primary outcome by centre.

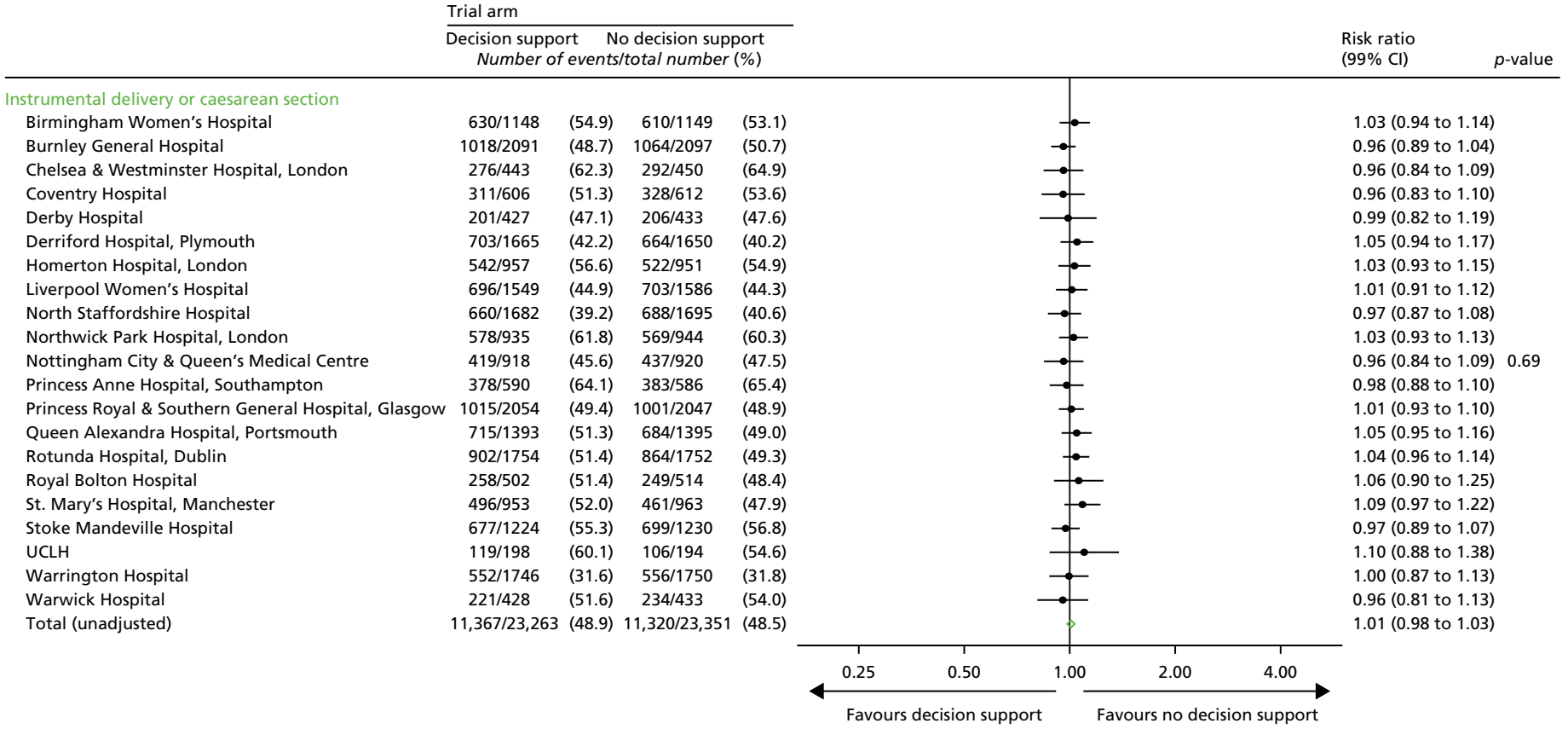


FIGURE 19 Instrumental delivery or caesarean section, by centre.

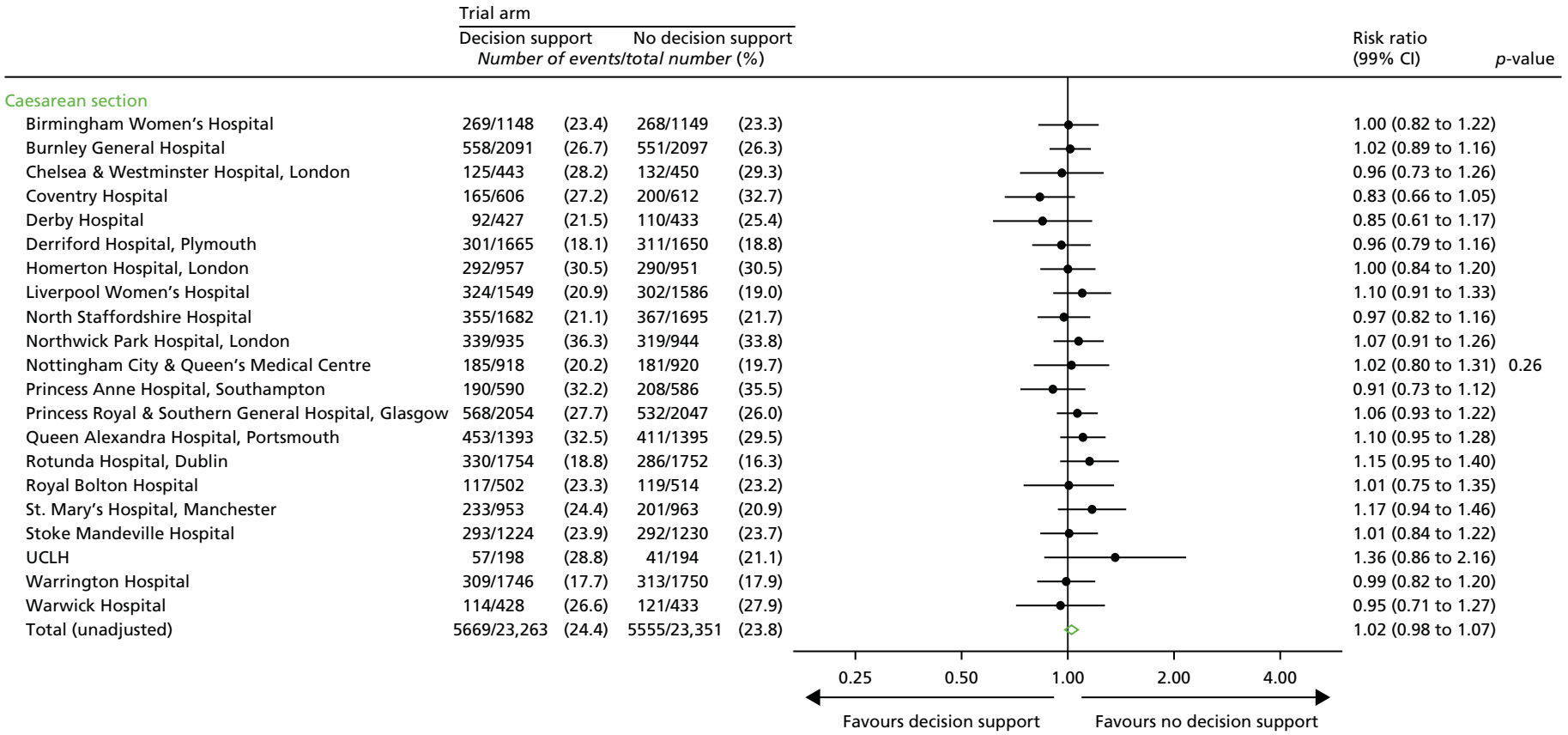


FIGURE 20 Caesarean section by centre.

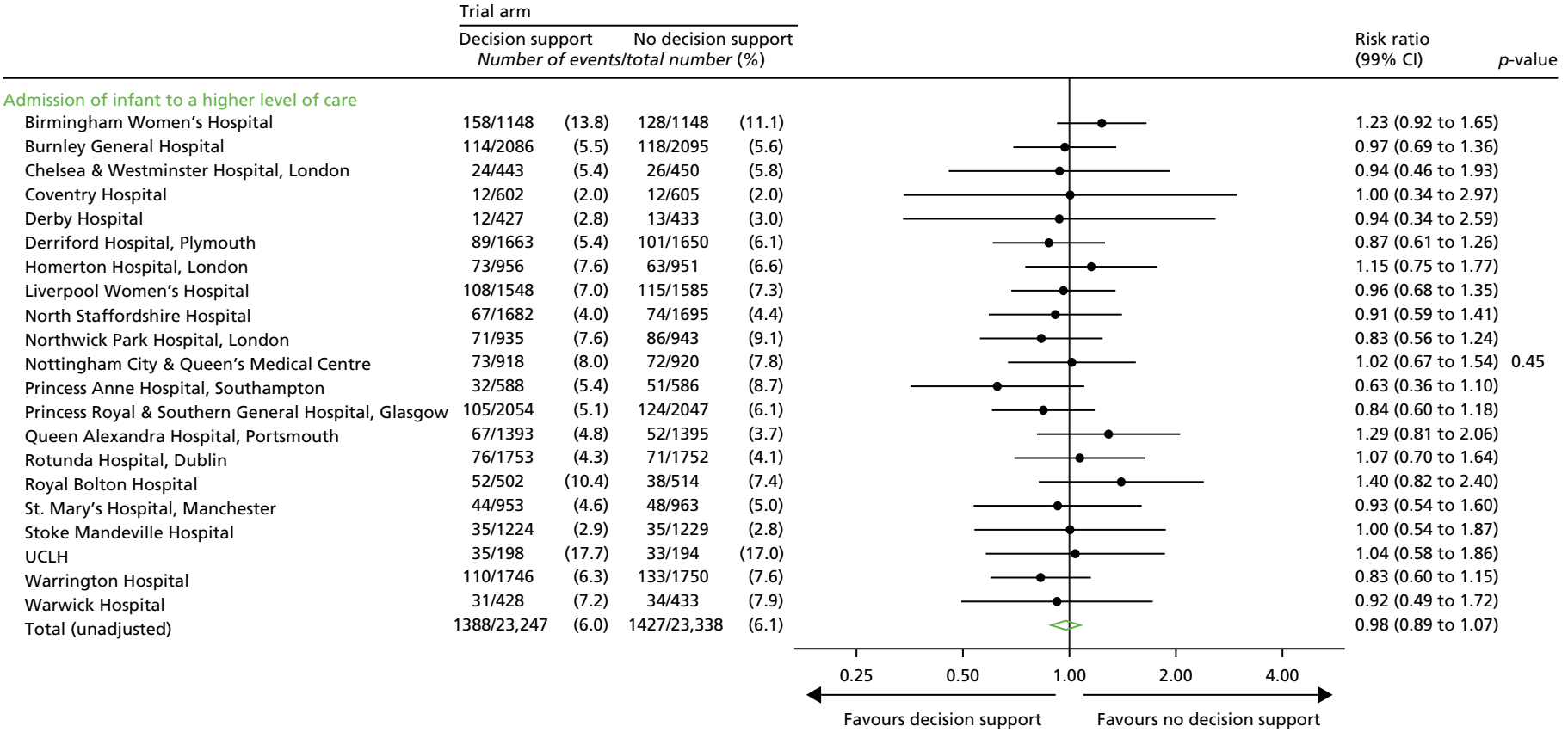


FIGURE 21 Admission of infant to a higher level of care, by centre.

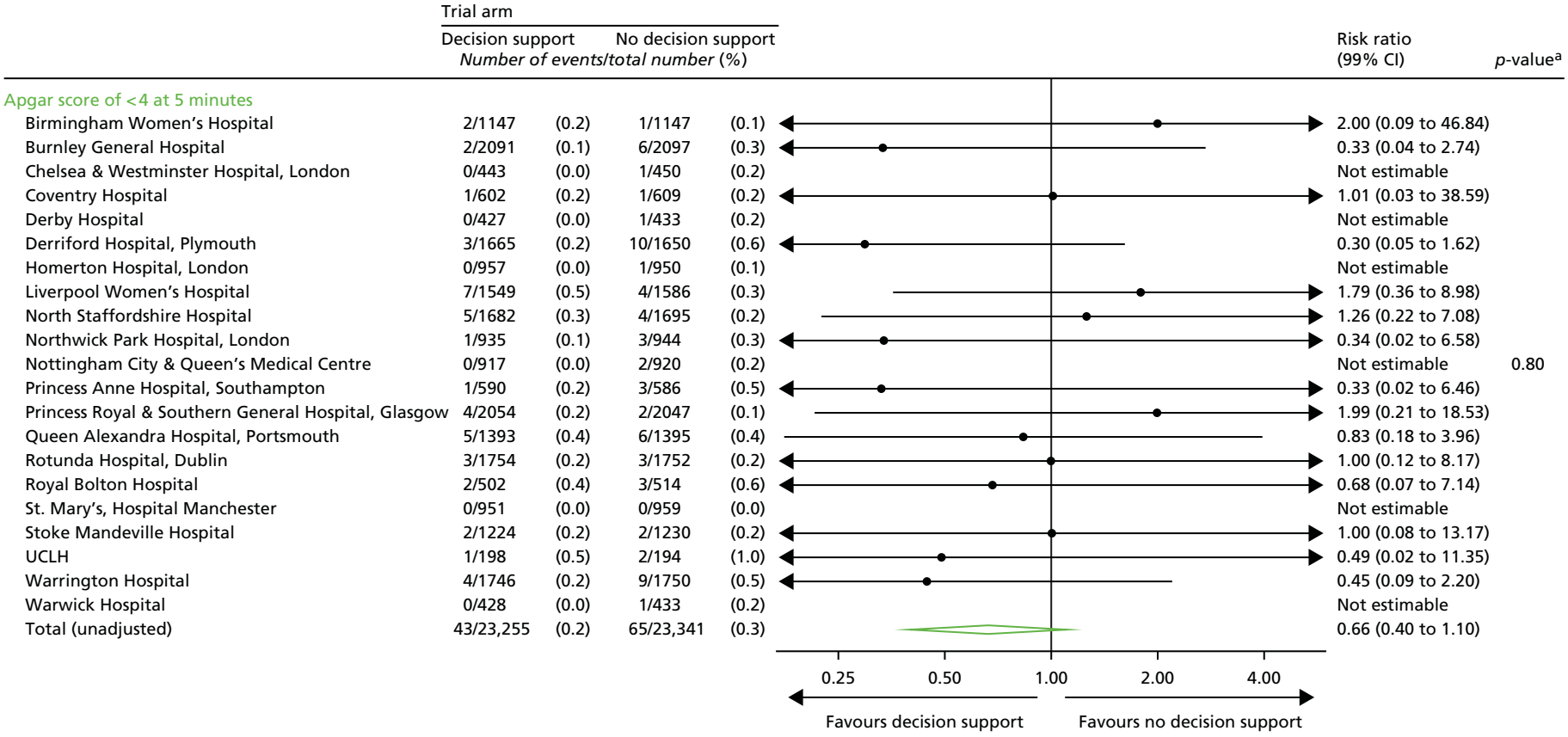


FIGURE 22 Apgar score by centre. a, *p*-value calculated using centres with estimable RRs.

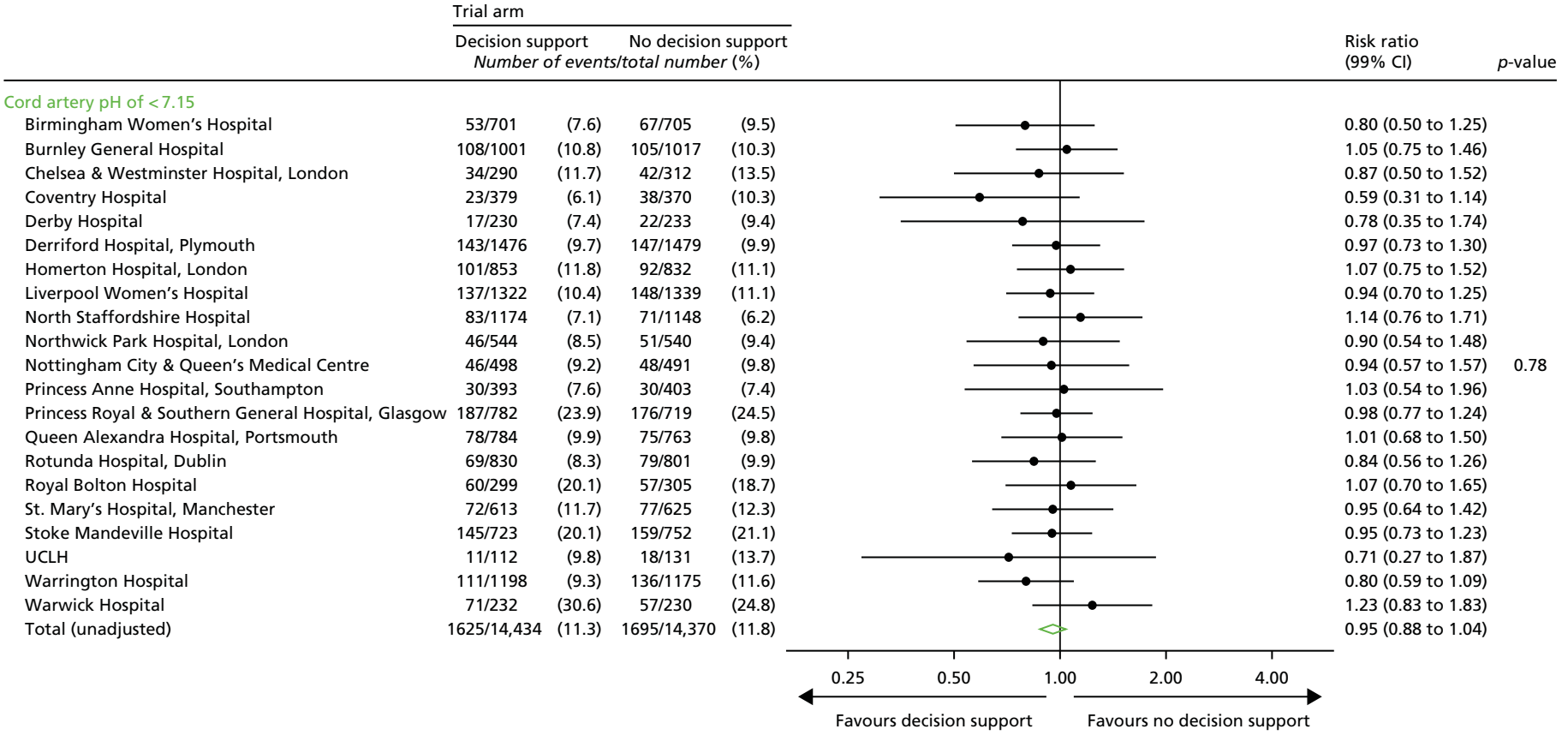


FIGURE 23 Cord artery pH by centre.

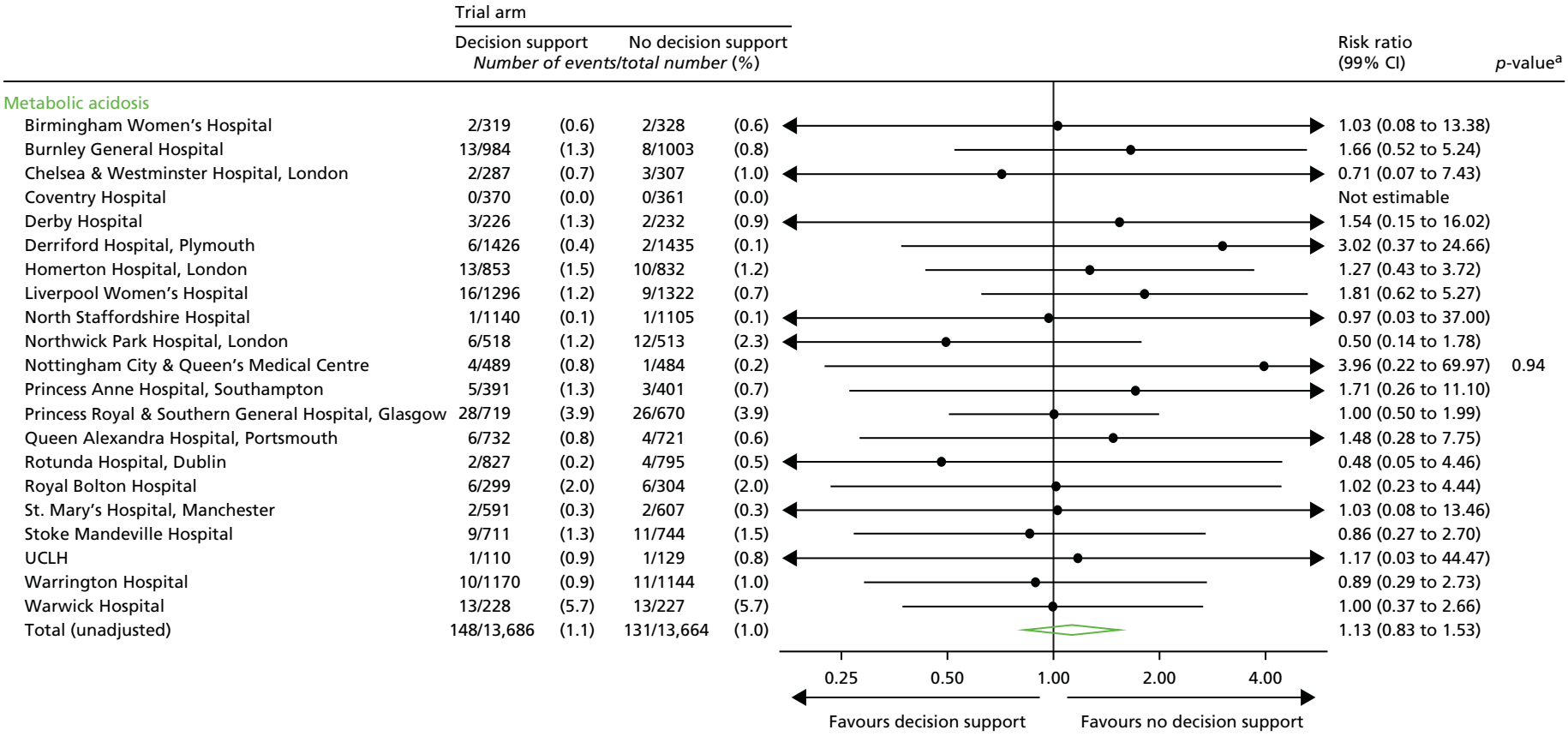


FIGURE 24 Metabolic acidosis by centre. a, *p*-value calculated using centres with estimable RRs.

	Trial arm: Decision support *Number of events/total number* (%)		Trial arm: No decision support *Number of events/total number* (%)		Risk ratio (99% CI)	*p*-value[a]
Resuscitation						
Birmingham Women's Hospital[b]	0/0		0/0		Not estimable	
Burnley General Hospital	303/2091	(14.5)	321/2097	(15.3)	0.95 (0.78 to 1.14)	
Chelsea & Westminster Hospital, London	30/443	(6.8)	30/449	(6.7)	1.01 (0.53 to 1.93)	
Coventry Hospital	47/602	(7.8)	45/609	(7.4)	1.06 (0.63 to 1.77)	
Derby Hospital	42/427	(9.8)	45/433	(10.4)	0.95 (0.56 to 1.60)	
Derriford Hospital, Plymouth	292/1665	(17.5)	279/1650	(16.9)	1.04 (0.85 to 1.26)	
Homerton Hospital, London[b]	0/0		0/0		Not estimable	
Liverpool Women's Hospital	224/1549	(14.5)	208/1586	(13.1)	1.10 (0.88 to 1.39)	
North Staffordshire Hospital	241/1682	(14.3)	229/1695	(13.5)	1.06 (0.85 to 1.32)	
Northwick Park Hospital, London	70/935	(7.5)	63/943	(6.7)	1.12 (0.73 to 1.72)	
Nottingham City & Queen's Medical Centre	107/917	(11.7)	128/920	(13.9)	0.84 (0.61 to 1.15)	0.96
Princess Anne Hospital, Southampton	118/590	(20.0)	98/586	(16.7)	1.20 (0.87 to 1.64)	
Princess Royal & Southern General Hospital, Glasgow	214/2054	(10.4)	205/2047	(10.0)	1.04 (0.82 to 1.32)	
Queen Alexandra Hospital, Portsmouth	163/1393	(11.7)	159/1395	(11.4)	1.03 (0.78 to 1.34)	
Rotunda Hospital, Dublin	282/1754	(16.1)	262/1752	(15.0)	1.08 (0.87 to 1.32)	
Royal Bolton Hospital	71/502	(14.1)	81/514	(15.8)	0.90 (0.61 to 1.32)	
St. Mary's Hospital, Manchester	99/951	(10.4)	109/962	(11.3)	0.92 (0.66 to 1.29)	
Stoke Mandeville Hospital	134/1224	(10.9)	131/1230	(10.7)	1.03 (0.76 to 1.39)	
UCLH	11/197	(5.6)	14/194	(7.2)	0.77 (0.27 to 2.18)	
Warrington Hospital	215/1746	(12.3)	204/1750	(11.7)	1.06 (0.83 to 1.34)	
Warwick Hospital	30/428	(7.0)	29/433	(6.7)	1.05 (0.55 to 2.00)	
Total (unadjusted)	2693/21,150	(12.7)	2640/21,245	(12.4)	1.02 (0.96 to 1.09)	

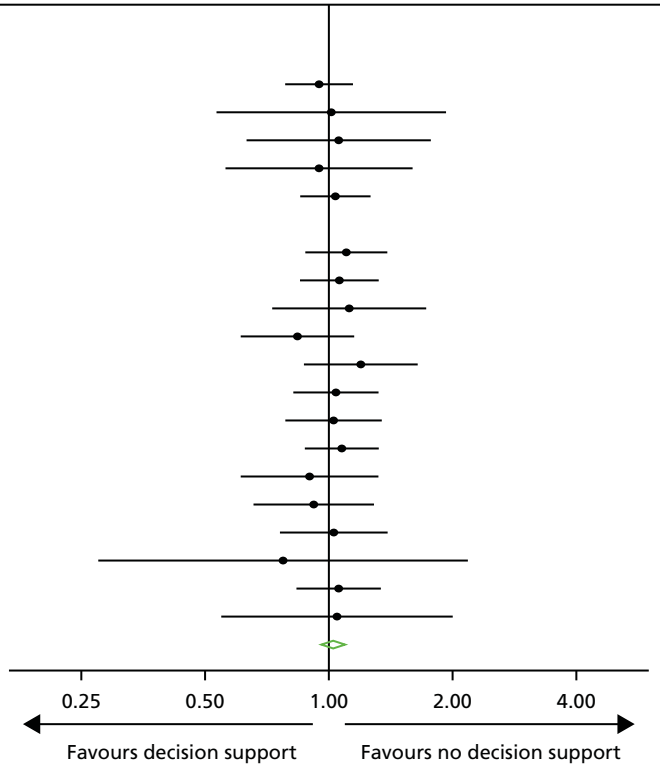


FIGURE 25 Resuscitation by centre. a, *p*-value calculated using centres with estimable RRs. b, Resuscitation data were not recorded in the Guardian system at Birmingham Women's Hospital and Homerton University Hospital.

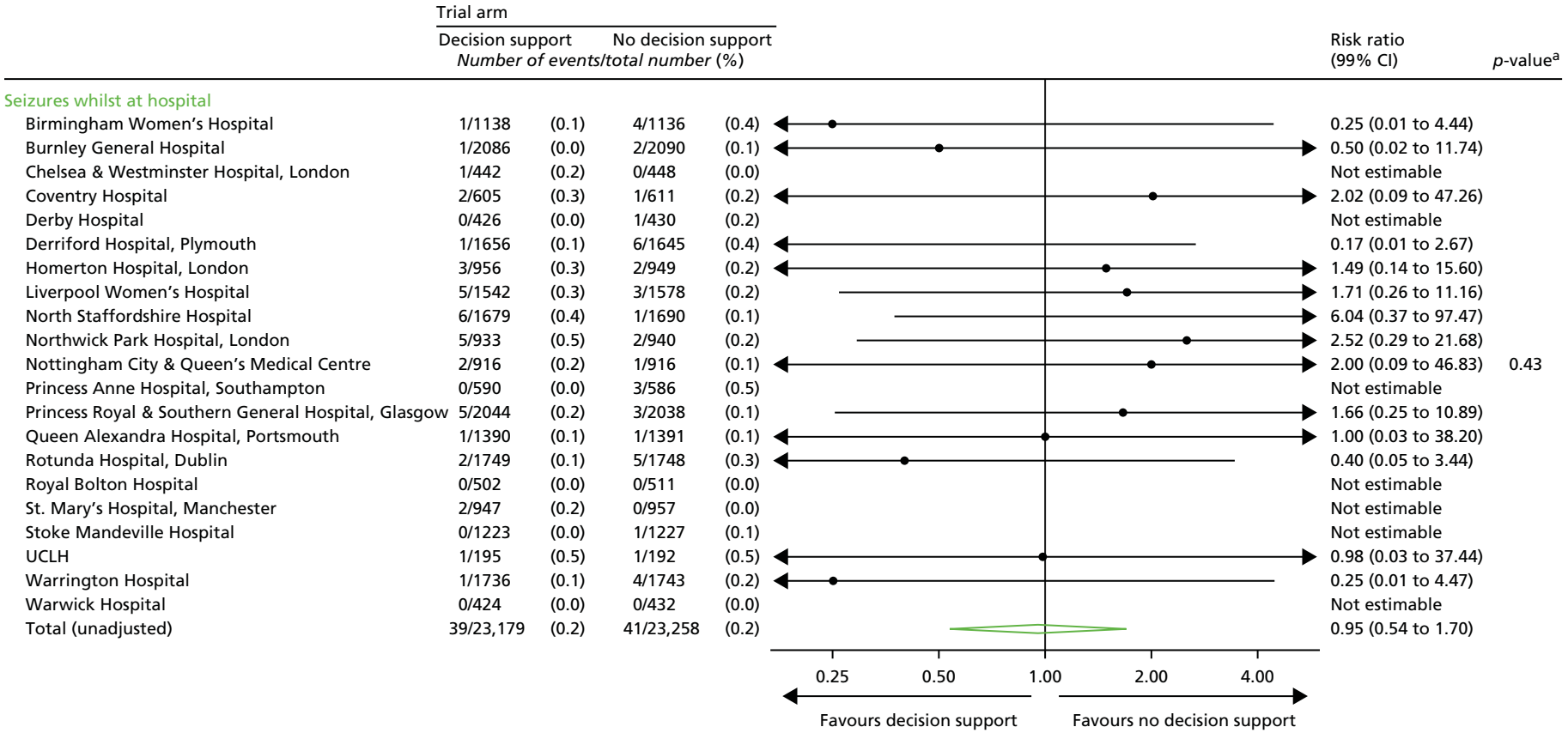


FIGURE 26 Seizures by centre. a, *p*-value calculated using centres with estimable RRs.

	Trial arm: Decision support *Number of events/total number* (%)		Trial arm: No decision support *Number of events/total number* (%)		Risk ratio (99% CI)	*p*-value
Baby destination ward or home						
Birmingham Women's Hospital	908/986	(92.1)	920/988	(93.1)	0.99 (0.96 to 1.02)	
Burnley General Hospital	2019/2089	(96.6)	2028/2092	(96.9)	1.00 (0.98 to 1.01)	
Chelsea & Westminster Hospital, London	426/442	(96.4)	440/450	(97.8)	0.99 (0.96 to 1.02)	
Coventry Hospital	583/599	(97.3)	588/605	(97.2)	1.00 (0.98 to 1.03)	
Derby Hospital	417/427	(97.7)	425/433	(98.2)	0.99 (0.97 to 1.02)	
Derriford Hospital, Plymouth	1382/1664	(83.1)	1398/1650	(84.7)	0.98 (0.94 to 1.02)	
Homerton Hospital, London	913/951	(96.0)	912/948	(96.2)	1.00 (0.97 to 1.02)	
Liverpool Women's Hospital	1505/1548	(97.2)	1525/1581	(96.5)	1.01 (0.99 to 1.02)	
North Staffordshire Hospital	1648/1682	(98.0)	1662/1695	(98.1)	1.00 (0.99 to 1.01)	
Northwick Park Hospital, London	886/929	(95.4)	882/939	(93.9)	1.02 (0.99 to 1.04)	
Nottingham City & Queen's Medical Centre	891/916	(97.3)	895/916	(97.7)	1.00 (0.98 to 1.01)	0.12
Princess Anne Hospital, Southampton	564/588	(95.9)	550/586	(93.9)	1.02 (0.99 to 1.06)	
Princess Royal & Southern General Hospital, Glasgow	2007/2048	(98.0)	1990/2040	(97.5)	1.00 (0.99 to 1.02)	
Queen Alexandra Hospital, Portsmouth	1351/1392	(97.1)	1369/1395	(98.1)	0.99 (0.97 to 1.00)	
Rotunda Hospital, Dublin	1700/1746	(97.4)	1699/1747	(97.3)	1.00 (0.99 to 1.02)	
Royal Bolton Hospital	434/502	(86.5)	453/513	(88.3)	0.98 (0.92 to 1.04)	
St. Mary's Hospital, Manchester	916/943	(97.1)	932/956	(97.5)	1.00 (0.98 to 1.02)	
Stoke Mandeville Hospital	1187/1221	(97.2)	1191/1227	(97.1)	1.00 (0.98 to 1.02)	
UCLH	189/197	(95.9)	192/194	(99.0)	0.97 (0.93 to 1.01)	
Warrington Hospital	1707/1745	(97.8)	1682/1748	(96.2)	1.02 (1.00 to 1.03)	
Warwick Hospital	405/427	(94.8)	416/433	(96.1)	0.99 (0.95 to 1.03)	
Total (unadjusted)	22,038/23,042	(95.6)	22,149/23,136	(95.7)	1.00 (0.99 to 1.00)	

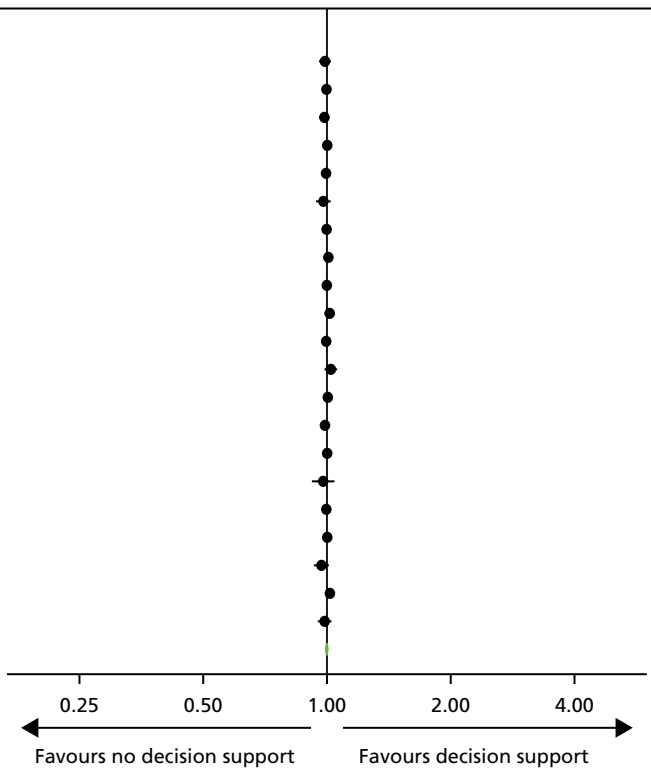


FIGURE 27 Infant destination immediately after birth, by centre.

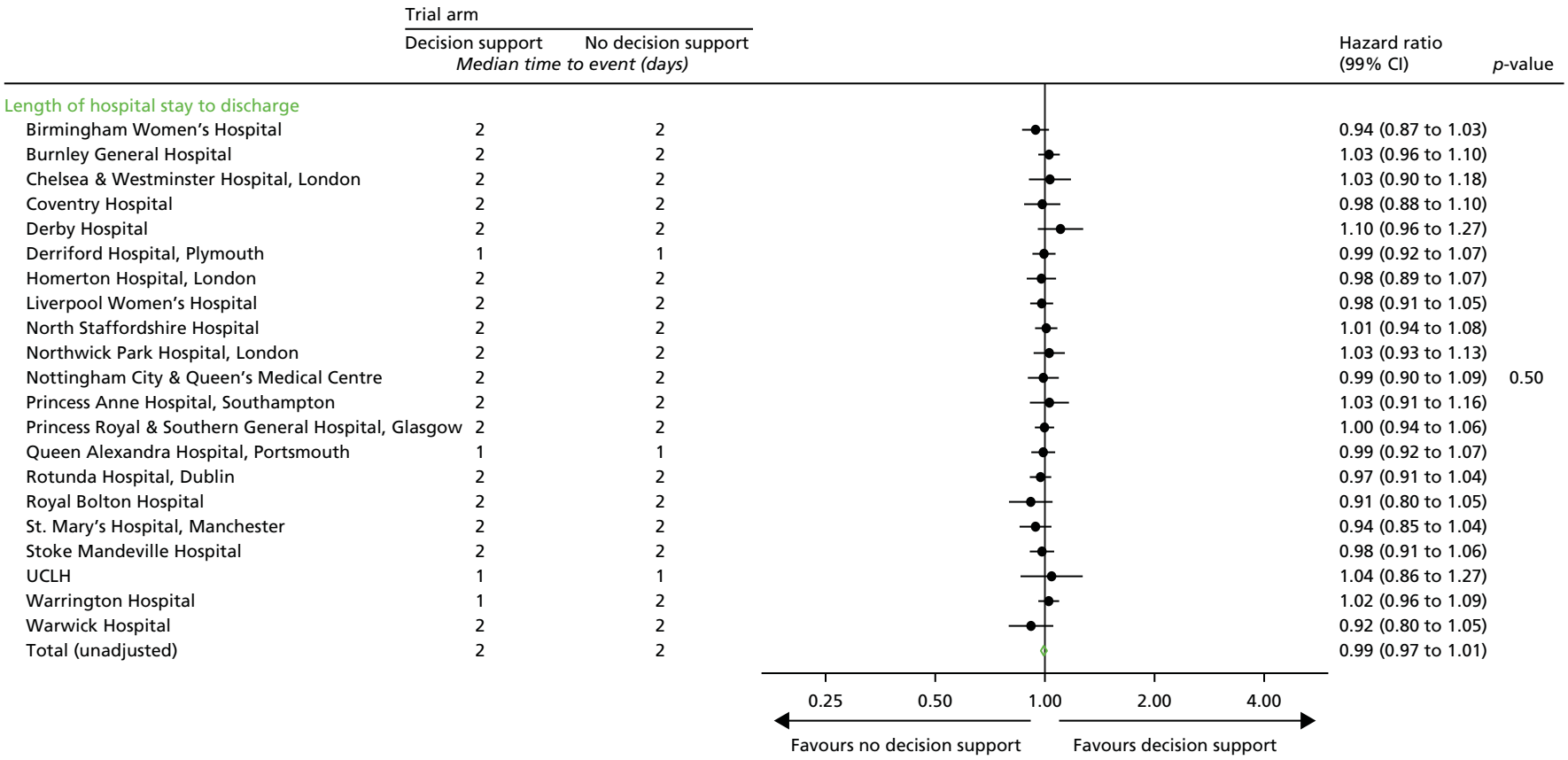


FIGURE 28 Length of hospital stay to discharge, by centre.

	Trial arm: Decision support *Number of events/total number* (%)		Trial arm: No decision support *Number of events/total number* (%)		Risk ratio (99% CI)	*p*-value[a]
Epidural analgesia after trial entry[b]						
Birmingham Women's Hospital	126/386	(32.6)	124/384	(32.3)	1.01 (0.77 to 1.32)	
Burnley General Hospital	149/541	(27.5)	154/533	(28.9)	0.95 (0.74 to 1.23)	
Chelsea & Westminster Hospital, London	151/418	(36.1)	169/417	(40.5)	0.89 (0.71 to 1.12)	
Coventry Hospital	1/25	(4.0)	0/17	(0.0)	Not estimable	
Derby Hospital	130/417	(31.2)	124/412	(30.1)	1.04 (0.79 to 1.36)	
Derriford Hospital, Plymouth	382/1048	(36.5)	399/1030	(38.7)	0.94 (0.81 to 1.09)	
Homerton Hospital, London	82/242	(33.9)	107/250	(42.8)	0.79 (0.59 to 1.07)	
Liverpool Women's Hospital	102/984	(10.4)	105/1000	(10.5)	0.99 (0.70 to 1.39)	
North Staffordshire Hospital	73/286	(25.5)	61/289	(21.1)	1.21 (0.82 to 1.79)	
Northwick Park Hospital, London	28/128	(21.9)	30/130	(23.1)	0.95 (0.52 to 1.72)	
Nottingham City & Queen's Medical Centre	2/3	(66.7)	2/4	(50.0)	1.33 (0.22 to 8.03)	0.37
Princess Anne Hospital, Southampton	5/46	(10.9)	6/46	(13.0)	0.83 (0.19 to 3.63)	
Princess Royal & Southern General Hospital, Glasgow	109/253	(43.1)	97/256	(37.9)	1.14 (0.86 to 1.50)	
Queen Alexandra Hospital, Portsmouth	254/1010	(25.1)	233/1011	(23.0)	1.09 (0.89 to 1.34)	
Rotunda Hospital, Dublin	380/1674	(22.7)	361/1665	(21.7)	1.05 (0.89 to 1.24)	
Royal Bolton Hospital	142/491	(28.9)	124/501	(24.8)	1.17 (0.89 to 1.53)	
St. Mary's Hospital, Manchester	96/226	(42.5)	90/236	(38.1)	1.11 (0.83 to 1.49)	
Stoke Mandeville Hospital	228/779	(29.3)	226/777	(29.1)	1.01 (0.82 to 1.23)	
UCLH	72/182	(39.6)	58/179	(32.4)	1.22 (0.85 to 1.76)	
Warrington Hospital	172/689	(25.0)	151/679	(22.2)	1.12 (0.87 to 1.44)	
Warwick Hospital	86/325	(26.5)	68/326	(20.9)	1.27 (0.88 to 1.83)	
Total (unadjusted)	2770/10,153	(27.3)	2689/10,142	(26.5)	1.03 (0.97 to 1.09)	

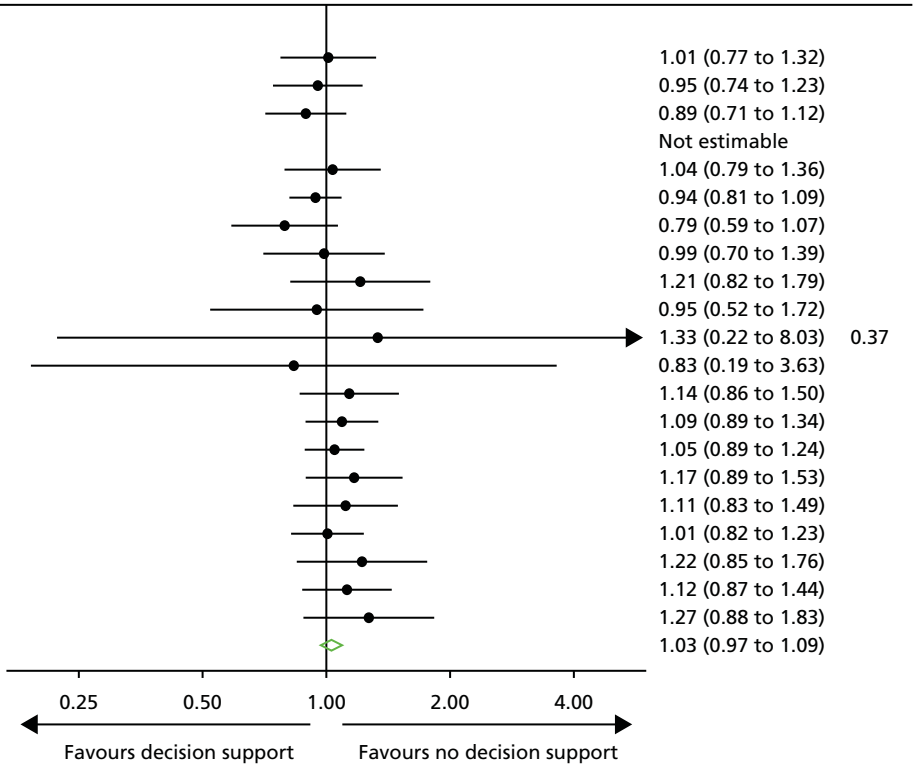


FIGURE 29 Epidural analgesia after trial entry, by centre. a, *p*-value calculated using centres with estimable RRs. b, Timing of epidural in relation to trial entry only collected from 2013 onwards for each centre.

	Trial arm: Decision support *Number of events/total number* (%)		Trial arm: No decision support *Number of events/total number* (%)		Risk ratio (99% CI)	*p*-value[a]
Labour augmentation after trial entry[b]						
Birmingham Women's Hospital	197/385	(51.2)	194/383	(50.7)	1.01 (0.84 to 1.21)	
Burnley General Hospital	196/534	(36.7)	230/527	(43.6)	0.84 (0.69 to 1.02)	
Chelsea & Westminster Hospital, London	119/375	(31.7)	123/383	(32.1)	0.99 (0.75 to 1.30)	
Coventry Hospital	7/29	(24.1)	6/27	(22.2)	1.09 (0.31 to 3.86)	
Derby Hospital	175/413	(42.4)	176/410	(42.9)	0.99 (0.80 to 1.22)	
Derriford Hospital, Plymouth	449/1036	(43.3)	439/1019	(43.1)	1.01 (0.88 to 1.15)	
Homerton Hospital, London	103/242	(42.6)	99/245	(40.4)	1.05 (0.80 to 1.39)	
Liverpool Women's Hospital	95/702	(13.5)	107/743	(14.4)	0.94 (0.67 to 1.32)	
North Staffordshire Hospital	68/271	(25.1)	79/274	(28.8)	0.87 (0.60 to 1.25)	
Northwick Park Hospital, London	24/152	(15.8)	30/156	(19.2)	0.82 (0.43 to 1.56)	
Nottingham City & Queen's Medical Centre	1/5	(20.0)	0/5	(0.0)	Not estimable	0.92
Princess Anne Hospital, Southampton	12/48	(25.0)	14/47	(29.8)	0.84 (0.35 to 2.00)	
Princess Royal & Southern General Hospital, Glasgow	123/253	(48.6)	114/254	(44.9)	1.08 (0.85 to 1.38)	
Queen Alexandra Hospital, Portsmouth	378/1246	(30.3)	362/1250	(29.0)	1.05 (0.89 to 1.23)	
Rotunda Hospital, Dublin	75/836	(9.0)	74/804	(9.2)	0.97 (0.65 to 1.46)	
Royal Bolton Hospital	189/492	(38.4)	201/498	(40.4)	0.95 (0.78 to 1.17)	
St. Mary's Hospital, Manchester	111/221	(50.2)	127/236	(53.8)	0.93 (0.74 to 1.18)	
Stoke Mandeville Hospital	71/528	(13.4)	73/526	(13.9)	0.97 (0.65 to 1.44)	
UCLH	88/184	(47.8)	75/180	(41.7)	1.15 (0.85 to 1.55)	
Warrington Hospital	124/479	(25.9)	128/502	(25.5)	1.02 (0.77 to 1.34)	
Warwick Hospital	100/321	(31.2)	99/323	(30.7)	1.02 (0.75 to 1.38)	
Total (unadjusted)	2705/8752	(30.9)	2750/8792	(31.3)	0.99 (0.93 to 1.05)	

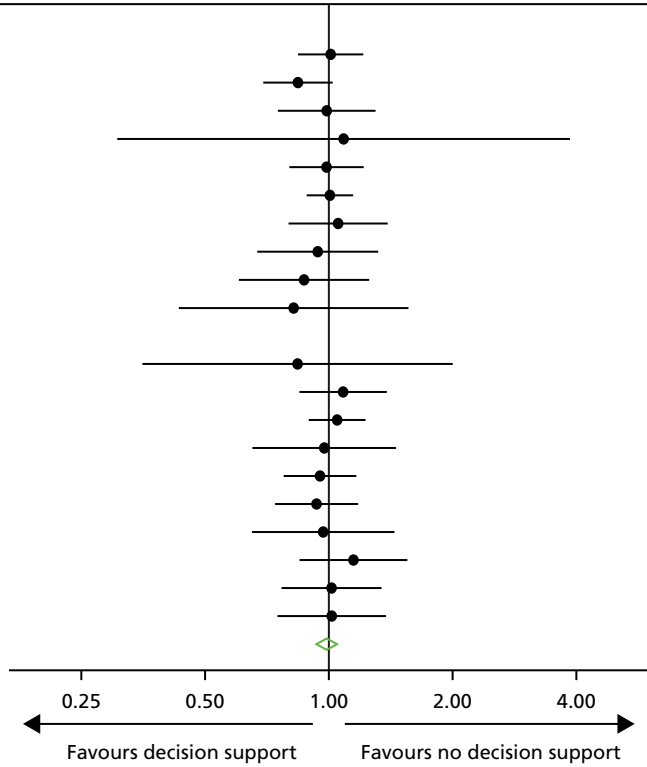


FIGURE 30 Labour augmentation after trial entry, by centre. a, *p*-value calculated using centres with estimable RRs. b, Timing of labour augmentation in relation to trial entry only collected from 2013 onwards for each centre.

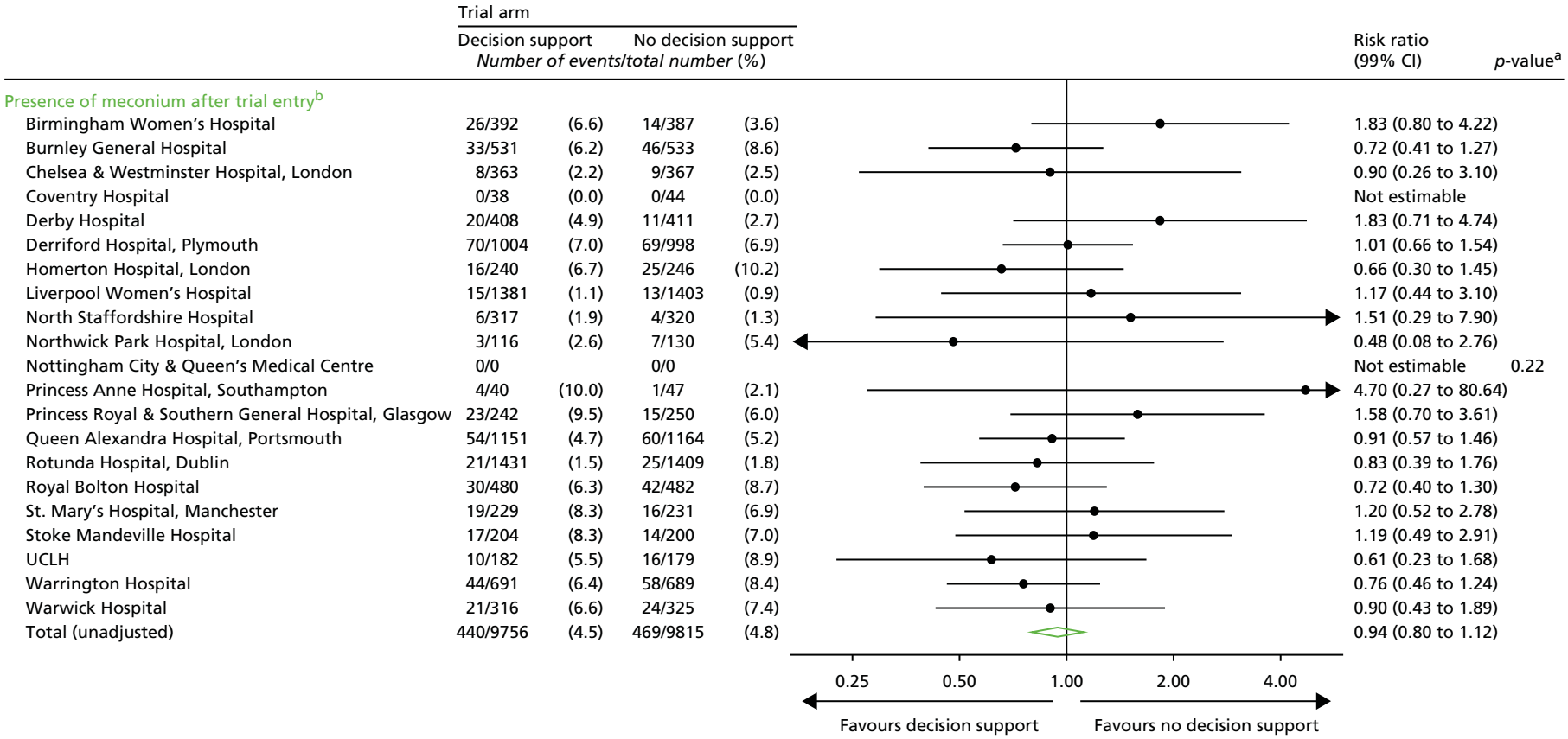


FIGURE 31 Presence of meconium after trial entry, by centre. a, *p*-value calculated using centres with estimable RRs. b, Timing of meconium in relation to trial entry only collected from 2013 onwards for each centre.

	Trial arm: Decision support *Number of events/total number* (%)		Trial arm: No decision support *Number of events/total number* (%)		Risk ratio (99% CI)	*p*-value
Number of women with at least one blue, yellow or red level of concern						
Birmingham Women's Hospital	1082/1114	(97.1)	1098/1117	(98.3)	0.99 (0.97 to 1.00)	
Burnley General Hospital	1990/2020	(98.5)	1985/2020	(98.3)	1.00 (0.99 to 1.01)	
Chelsea & Westminster Hospital, London	410/426	(96.2)	416/427	(97.4)	0.99 (0.96 to 1.02)	
Coventry Hospital	519/569	(91.2)	531/584	(90.9)	1.00 (0.96 to 1.05)	
Derby Hospital	400/417	(95.9)	401/415	(96.6)	0.99 (0.96 to 1.03)	
Derriford Hospital, Plymouth	1627/1638	(99.3)	1599/1616	(98.9)	1.00 (1.00 to 1.01)	
Homerton Hospital, London	887/905	(98.0)	879/898	(97.9)	1.00 (0.98 to 1.02)	
Liverpool Women's Hospital	1500/1511	(99.3)	1541/1550	(99.4)	1.00 (0.99 to 1.01)	
North Staffordshire Hospital	1485/1579	(94.0)	1478/1585	(93.2)	1.01 (0.98 to 1.03)	
Northwick Park Hospital, London	848/890	(95.3)	860/889	(96.7)	0.98 (0.96 to 1.01)	
Nottingham City & Queen's Medical Centre	873/895	(97.5)	885/901	(98.2)	0.99 (0.98 to 1.01)	0.62
Princess Anne Hospital, Southampton	563/573	(98.3)	560/568	(98.6)	1.00 (0.98 to 1.02)	
Princess Royal & Southern General Hospital, Glasgow	1992/2003	(99.5)	1986/1999	(99.3)	1.00 (0.99 to 1.01)	
Queen Alexandra Hospital, Portsmouth	1321/1365	(96.8)	1316/1363	(96.6)	1.00 (0.98 to 1.02)	
Rotunda Hospital, Dublin	1686/1726	(97.7)	1676/1719	(97.5)	1.00 (0.99 to 1.02)	
Royal Bolton Hospital	483/496	(97.4)	496/504	(98.4)	0.99 (0.97 to 1.01)	
St. Mary's Hospital, Manchester	899/924	(97.3)	925/938	(98.6)	0.99 (0.97 to 1.00)	
Stoke Mandeville Hospital	1180/1208	(97.7)	1183/1212	(97.6)	1.00 (0.98 to 1.02)	
UCLH	180/190	(94.7)	172/184	(93.5)	1.01 (0.95 to 1.08)	
Warrington Hospital	1633/1663	(98.2)	1626/1657	(98.1)	1.00 (0.99 to 1.01)	
Warwick Hospital	392/405	(96.8)	408/418	(97.6)	0.99 (0.96 to 1.02)	
Total (unadjusted)	21,950/22,517	(97.5)	22,021/22,564	(97.6)	1.00 (1.00 to 1.00)	

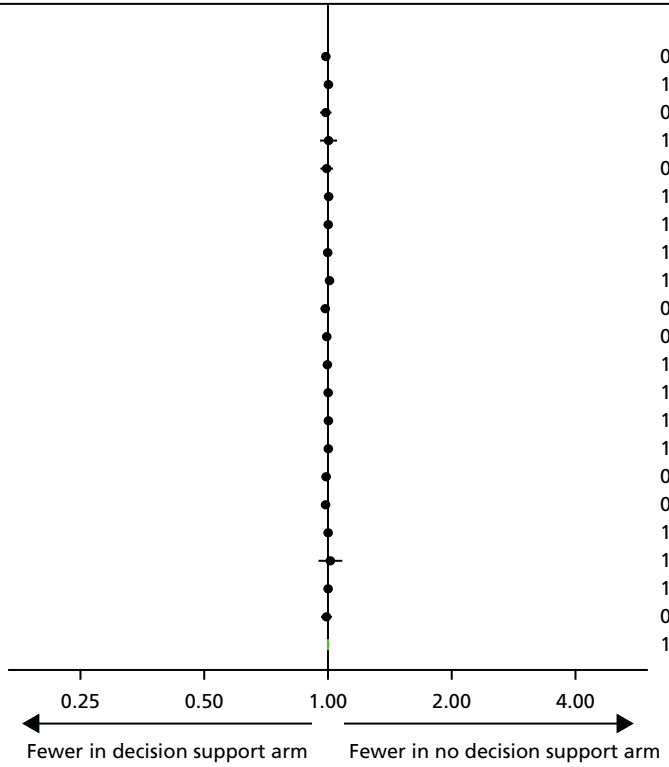


FIGURE 32 Number of women with at least one blue, yellow or red level of concern, by centre.

	Trial arm: Decision support		Trial arm: Number decision support		Risk ratio (99% CI)	*p*-value
	Number of events/total number (%)					
Number of women with at least one blue level of concern (mild abnormality)						
Birmingham Women's Hospital	1079/1114	(96.9)	1096/1117	(98.1)	0.99 (0.97 to 1.00)	
Burnley General Hospital	1987/2020	(98.4)	1982/2020	(98.1)	1.00 (0.99 to 1.01)	
Chelsea and Westminster Hospital, London	410/426	(96.2)	414/427	(97.0)	0.99 (0.96 to 1.03)	
University Hospital Coventry	510/569	(89.6)	526/584	(90.1)	1.00 (0.95 to 1.05)	
Royal Derby Hospital	394/417	(94.5)	395/415	(95.2)	0.99 (0.95 to 1.03)	
Derriford Hospital, Plymouth	1626/1638	(99.3)	1592/1616	(98.5)	1.01 (1.00 to 1.02)	
Homerton University Hospital, London	882/905	(97.5)	874/898	(97.3)	1.00 (0.98 to 1.02)	
Liverpool Women's Hospital	1500/1511	(99.3)	1541/1550	(99.4)	1.00 (0.99 to 1.01)	
North Staffordshire University Hospital	1462/1579	(92.6)	1455/1585	(91.8)	1.01 (0.98 to 1.04)	
Northwick Park Hospital, London	842/890	(94.6)	851/889	(95.7)	0.99 (0.96 to 1.02)	
Nottingham City Hospital and Queen's Medical Centre	873/895	(97.5)	885/901	(98.2)	0.99 (0.98 to 1.01)	0.39
Princess Anne Hospital, Southampton	563/573	(98.3)	559/568	(98.4)	1.00 (0.98 to 1.02)	
Princess Royal Hospital and Southern General Hospital, Glasgow	1988/2003	(99.3)	1984/1999	(99.2)	1.00 (0.99 to 1.01)	
Queen Alexandra, Portsmouth	1318/1365	(96.6)	1307/1363	(95.9)	1.01 (0.99 to 1.03)	
Rotunda Hospital, Dublin	1676/1726	(97.1)	1658/1719	(96.5)	1.01 (0.99 to 1.02)	
Royal Bolton Hospital	482/496	(97.2)	496/504	(98.4)	0.99 (0.96 to 1.01)	
St. Mary's Hospital, Manchester	895/924	(96.9)	922/938	(98.3)	0.99 (0.97 to 1.00)	
Stoke Mandeville Hospital	1178/1208	(97.5)	1180/1212	(97.4)	1.00 (0.98 to 1.02)	
University College Hospital, London	180/190	(94.7)	170/184	(92.4)	1.03 (0.96 to 1.10)	
Warrington Hospital	1629/1663	(98.0)	1621/1657	(97.8)	1.00 (0.99 to 1.01)	
Warwick Hospital	389/405	(96.0)	405/418	(96.9)	0.99 (0.96 to 1.03)	
Total (unadjusted)	21,863/22,517	(97.1)	21,913/22,564	(97.1)	1.00 (1.00 to 1.00)	

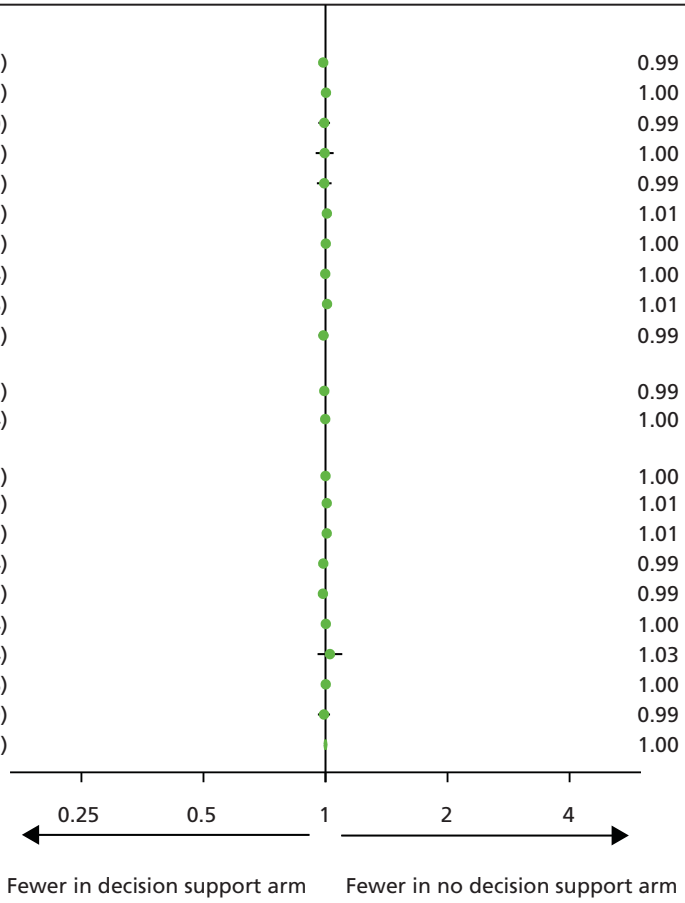


FIGURE 33 Number of women with at least one blue level of concern, by centre.

	Trial arm: Decision support *Number of events/total number* (%)		Trial arm: No decision support *Number of events/total number* (%)		Risk ratio (99% CI)	*p*-value
Number of women with at least one yellow level of concern (moderate abnormality)						
Birmingham Women's Hospital	880/1114	(79.0)	912/1117	(81.6)	0.97 (0.92 to 1.02)	
Burnley General Hospital	1423/2020	(70.4)	1452/2020	(71.9)	0.98 (0.93 to 1.03)	
Chelsea & Westminster Hospital, London	324/426	(76.1)	326/427	(76.3)	1.00 (0.90 to 1.10)	
Coventry Hospital	390/569	(68.5)	401/584	(68.7)	1.00 (0.90 to 1.11)	
Derby Hospital	303/417	(72.7)	302/415	(72.8)	1.00 (0.89 to 1.11)	
Derriford Hospital, Plymouth	1228/1638	(75.0)	1221/1616	(75.6)	0.99 (0.94 to 1.04)	
Homerton Hospital, London	752/905	(83.1)	761/898	(84.7)	0.98 (0.93 to 1.03)	
Liverpool Women's Hospital	1149/1511	(76.0)	1157/1550	(74.6)	1.02 (0.97 to 1.07)	
North Staffordshire Hospital	1018/1579	(64.5)	1035/1585	(65.3)	0.99 (0.92 to 1.06)	
Northwick Park Hospital, London	649/890	(72.9)	636/889	(71.5)	1.02 (0.94 to 1.10)	
Nottingham City & Queen's Medical Centre	661/895	(73.9)	655/901	(72.7)	1.02 (0.94 to 1.09)	0.73
Princess Anne Hospital, Southampton	433/573	(75.6)	431/568	(75.9)	1.00 (0.91 to 1.09)	
Princess Royal & Southern General Hospital, Glasgow	1418/2003	(70.8)	1363/1999	(68.2)	1.04 (0.98 to 1.10)	
Queen Alexandra Hospital, Portsmouth	939/1365	(68.8)	895/1363	(65.7)	1.05 (0.98 to 1.12)	
Rotunda Hospital, Dublin	1295/1726	(75.0)	1277/1719	(74.3)	1.01 (0.96 to 1.06)	
Royal Bolton Hospital	411/496	(82.9)	405/504	(80.4)	1.03 (0.95 to 1.11)	
St. Mary's Hospital, Manchester	706/924	(76.4)	735/938	(78.4)	0.98 (0.91 to 1.04)	
Stoke Mandeville Hospital	894/1208	(74.0)	883/1212	(72.9)	1.02 (0.95 to 1.08)	
UCLH	157/190	(82.6)	148/184	(80.4)	1.03 (0.90 to 1.17)	
Warrington Hospital	1446/1663	(87.0)	1425/1657	(86.0)	1.01 (0.98 to 1.04)	
Warwick Hospital	289/405	(71.4)	302/418	(72.2)	0.99 (0.88 to 1.11)	
Total (unadjusted)	16,765/22,517	(74.5)	16,722/22,564	(74.1)	1.00 (0.99 to 1.02)	

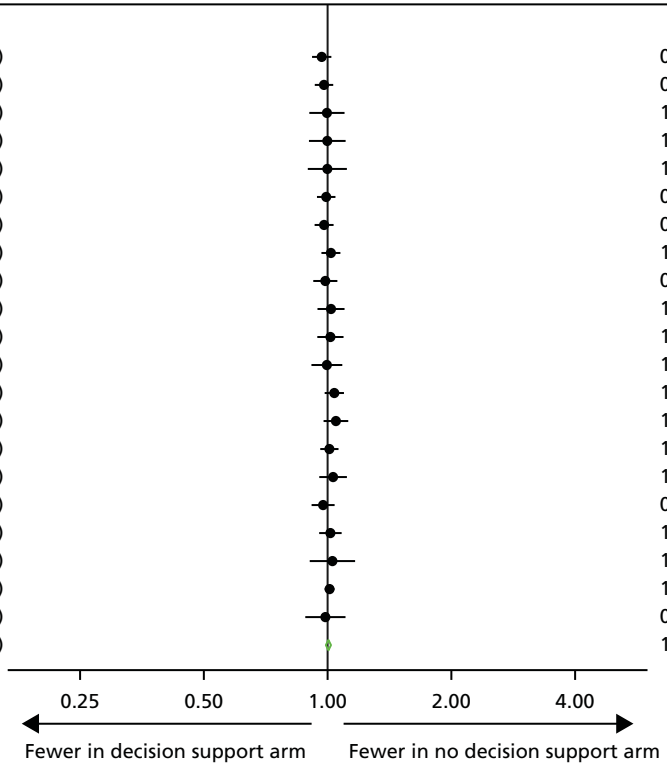


FIGURE 34 Number of women with at least one yellow level of concern, by centre.

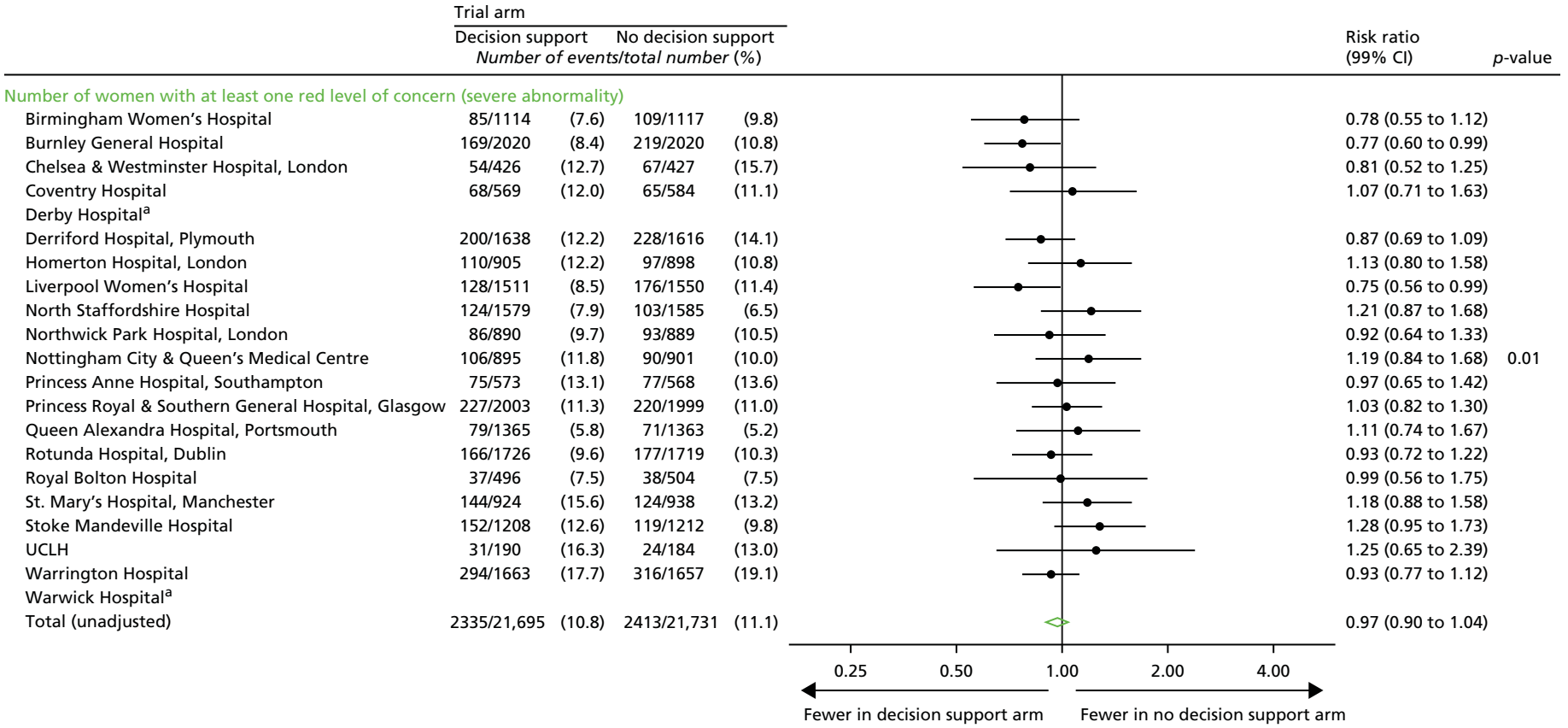


FIGURE 35 Number of women with at least one red level of concern, by centre. a, Data on timing of red level of concern are not available for two centres: Warwick Hospital ($n = 823$) and Derby Hospital ($n = 832$).

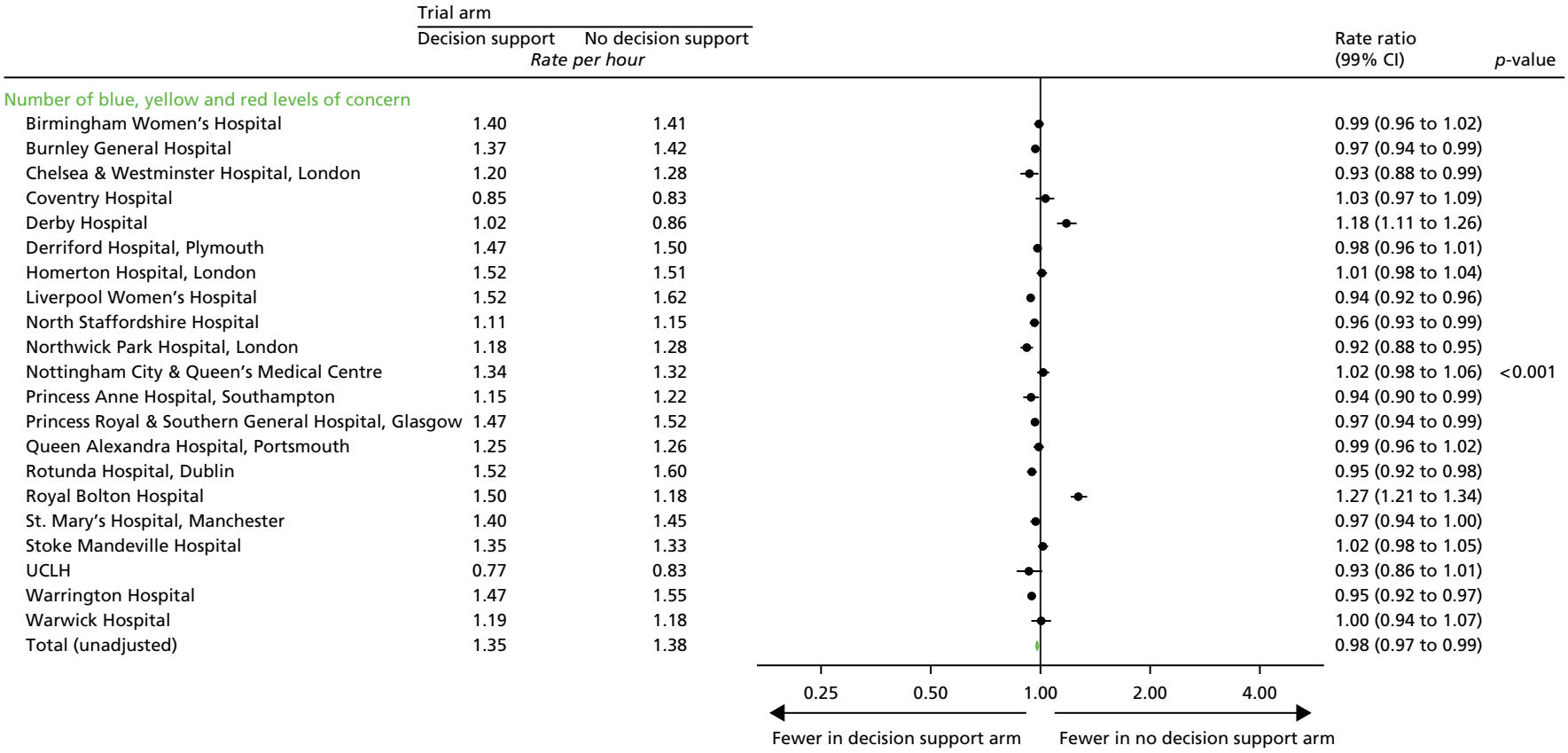


FIGURE 36 Number of blue, yellow and red levels of concern, by centre.

	Trial arm: Decision support (*Rate per hour*)	Trial arm: No decision support (*Rate per hour*)	Rate ratio (99% CI)	*p*-value
Number of blue levels of concern				
Birmingham Women's Hospital	1.02	0.98	1.04 (1.00 to 1.08)	
Burnley General Hospital	1.10	1.10	1.00 (0.97 to 1.03)	
Chelsea & Westminster Hospital, London	0.93	0.96	0.96 (0.90 to 1.03)	
Coventry Hospital	0.63	0.60	1.05 (0.98 to 1.12)	
Derby Hospital	0.73	0.59	1.23 (1.14 to 1.33)	
Derriford Hospital, Plymouth	1.19	1.16	1.02 (0.99 to 1.06)	
Homerton Hospital, London	1.07	1.03	1.05 (1.01 to 1.09)	
Liverpool Women's Hospital	1.23	1.25	0.98 (0.96 to 1.01)	
North Staffordshire Hospital	0.87	0.87	1.01 (0.98 to 1.04)	
Northwick Park Hospital, London	0.86	0.89	0.97 (0.92 to 1.01)	
Nottingham City & Queen's Medical Centre	1.09	1.06	1.03 (0.99 to 1.08)	<0.001
Princess Anne Hospital, Southampton	0.87	0.89	0.98 (0.92 to 1.03)	
Princess Royal & Southern General Hospital, Glasgow	1.21	1.23	0.99 (0.96 to 1.02)	
Queen Alexandra Hospital, Portsmouth	0.98	0.97	1.01 (0.97 to 1.05)	
Rotunda Hospital, Dublin	1.13	1.14	0.99 (0.96 to 1.03)	
Royal Bolton Hospital	0.99	0.78	1.26 (1.19 to 1.35)	
St. Mary's Hospital, Manchester	1.13	1.15	0.99 (0.95 to 1.03)	
Stoke Mandeville Hospital	1.07	1.03	1.04 (1.00 to 1.08)	
UCLH	0.50	0.52	0.96 (0.86 to 1.07)	
Warrington Hospital	1.09	1.10	0.99 (0.96 to 1.02)	
Warwick Hospital	0.92	0.88	1.04 (0.97 to 1.12)	
Total (unadjusted)	1.04	1.03	1.01 (1.00 to 1.02)	

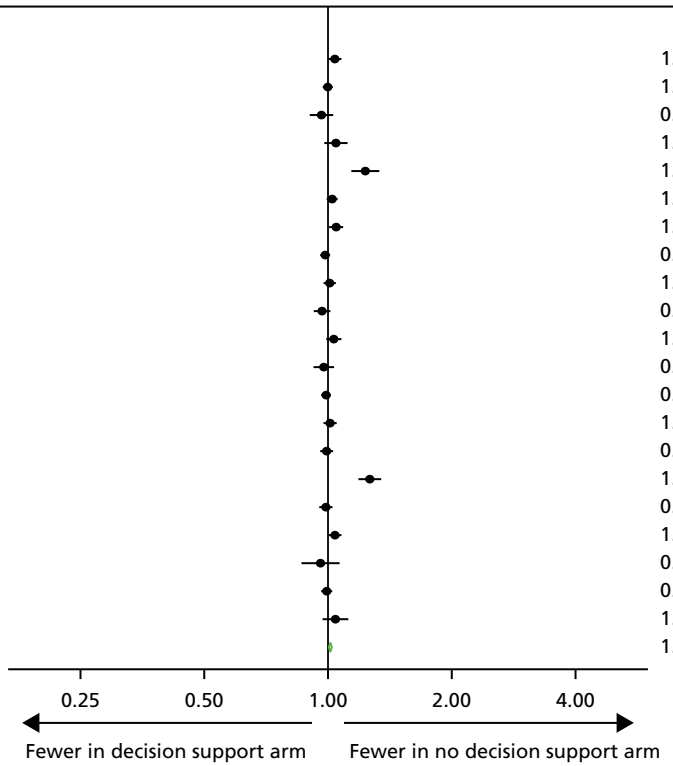


FIGURE 37 Number of blue levels of concern, by centre.

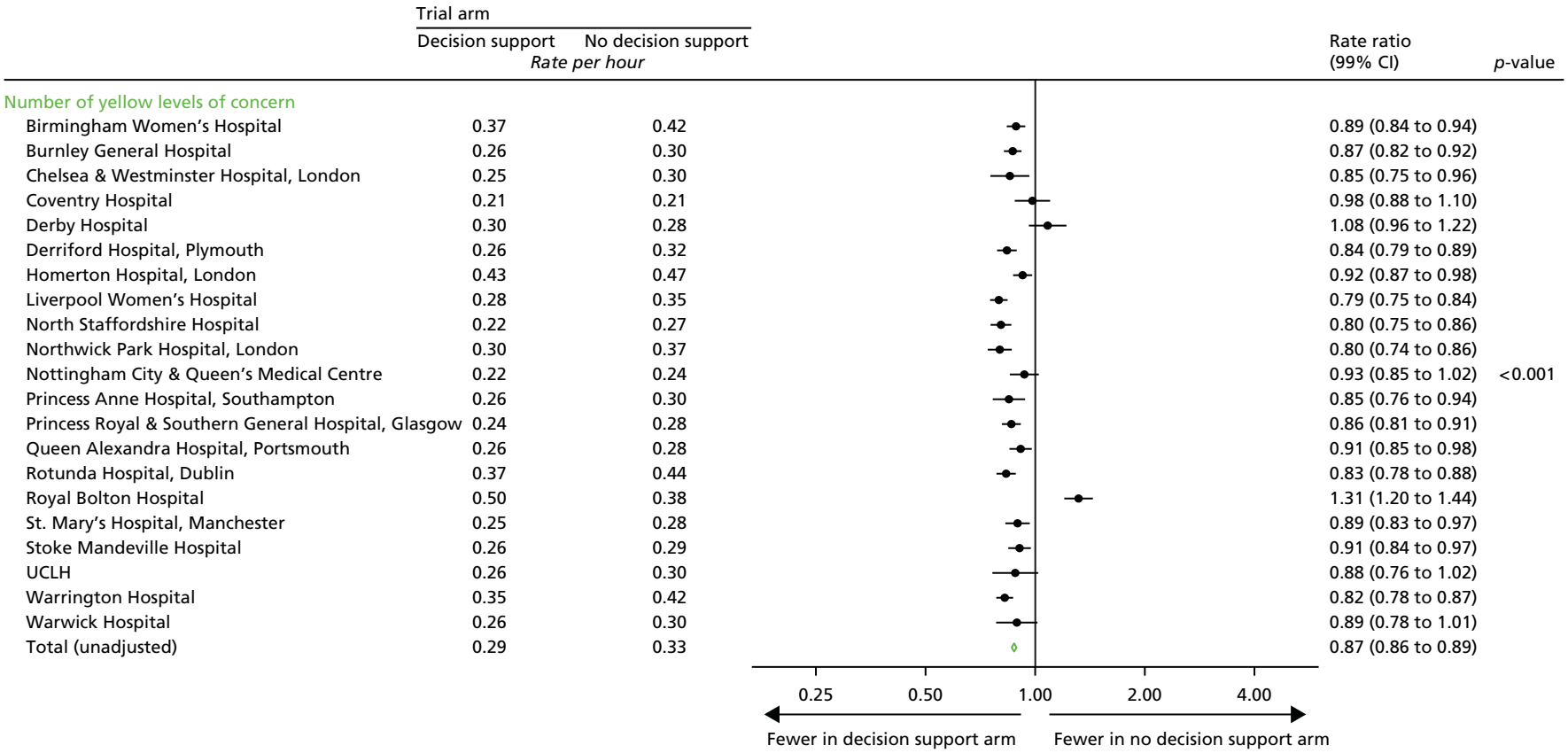


FIGURE 38 Number of yellow levels of concern, by centre.

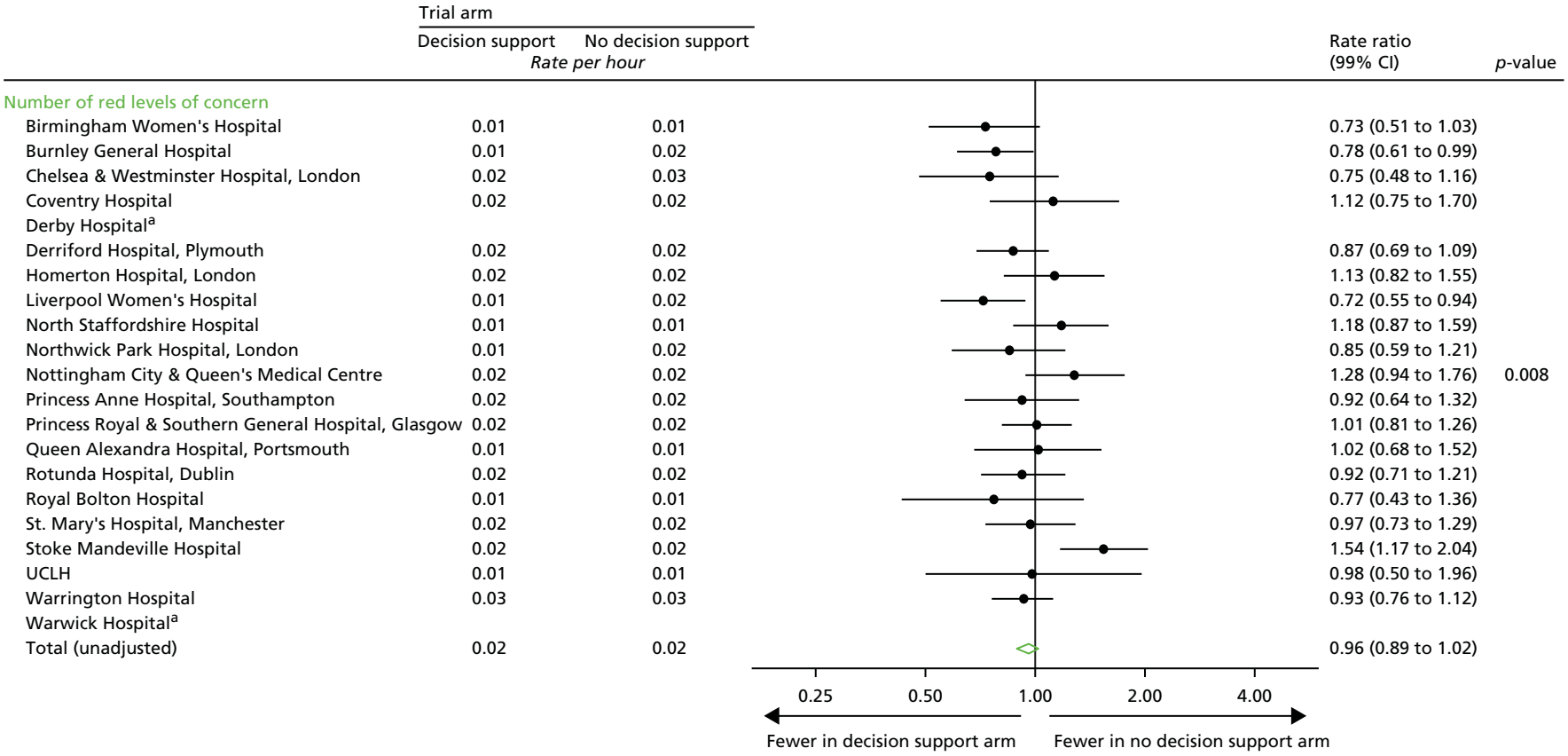


FIGURE 39 Number of red levels of concern, by centre. a, Data on timing of red level of concern are not available for two centres: Warwick Hospital ($n = 823$) and Derby Hospital ($n = 832$).

	Trial arm			
	Decision support	No decision support	Hazard ratio (99% CI)	*p*-value
	Median time to event (minutes)			
Time from last red level of concern to delivery[a]				
Birmingham Women's Hospital	47	51	0.98 (0.68 to 1.42)	
Burnley General Hospital	42	35	0.94 (0.72 to 1.22)	
Chelsea & Westminster Hospital, London	74	45	1.03 (0.65 to 1.65)	
Coventry Hospital	89	93	1.01 (0.64 to 1.58)	
Derby Hospital[b]				
Derriford Hospital, Plymouth	52	43	1.01 (0.79 to 1.30)	
Homerton Hospital, London	58.5	135	1.08 (0.75 to 1.54)	
Liverpool Women's Hospital	105.5	123	1.05 (0.78 to 1.42)	
North Staffordshire Hospital	72.5	132	1.16 (0.82 to 1.63)	
Northwick Park Hospital, London	45	58	1.05 (0.72 to 1.54)	
Nottingham City & Queen's Medical Centre	84.5	64.5	1.02 (0.71 to 1.48)	0.50
Princess Anne Hospital, Southampton	283	123	0.80 (0.52 to 1.24)	
Princess Royal & Southern General Hospital, Glasgow	84	111	1.07 (0.84 to 1.37)	
Queen Alexandra Hospital, Portsmouth	67	49	0.79 (0.51 to 1.21)	
Rotunda Hospital, Dublin	31	21	0.78 (0.59 to 1.04)	
Royal Bolton Hospital	24	55	0.90 (0.50 to 1.62)	
St. Mary's Hospital, Manchester	55	74.5	1.13 (0.83 to 1.54)	
Stoke Mandeville Hospital	97	134	1.17 (0.85 to 1.61)	
UCLH	50	19	0.87 (0.41 to 1.81)	
Warrington Hospital	35	38.5	0.93 (0.75 to 1.14)	
Warwick Hospital[b]				
Total (unadjusted)	58	58	0.99 (0.92 to 1.07)	

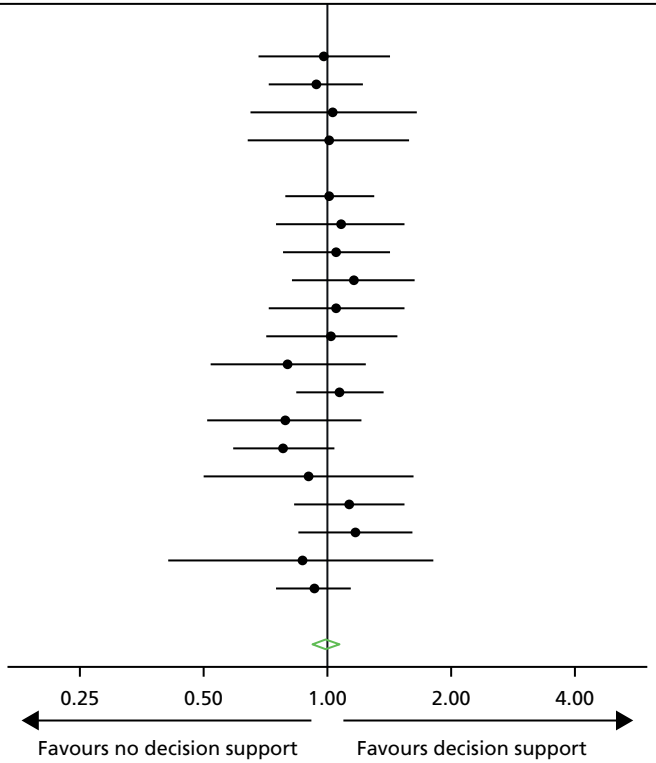


FIGURE 40 Time from last red level of concern to delivery. a, Hazard ratio of > 1 favours decision support as this implies that time to delivery (from last red level of concern) was reached more quickly than with no decision support. b, Data on timing of red level of concern are not available for two centres: Warwick Hospital ($n = 823$) and Derby Hospital ($n = 832$).

Predefined subgroup analyses of long-term outcomes

TABLE 32 Parent Report of Children's Abilities-Revised composite score, by twin pregnancy

		Trial arm, mean score (points) (SD)		
Singleton vs. twins	*n* (%)	Decision support	No decision support	Mean difference (95% CI)
Singleton	6555 (98)	98.2 (33.7)	97.4 (33.4)	0.82 (–0.81 to 2.44)
Twin	152 (2)	85.7 (37.3)	89.7 (32.4)	–3.95 (–19.4 to 11.5)
Total (unadjusted)	6707 (100)	98.0 (33.8)	97.2 (33.4)	0.73 (–0.88 to 2.34)
Unknown	359			

Note
p-value from the test of interaction = 0.54.

TABLE 33 Parent Report of Children's Abilities-Revised composite score, by suspected fetal growth restriction

		Trial arm, mean score (points) (SD)		
FGR	*n* (%)	Decision support	No decision support	Mean difference (95% CI)
No FGR	6472 (96)	98.3 (33.7)	97.5 (33.4)	0.77 (–0.89 to 2.42)
FGR	235 (4)	89.4 (35.0)	90.9 (34.1)	–1.50 (–10.5 to 7.54)
Total (unadjusted)	6707 (100)	98.0 (33.8)	97.2 (33.4)	0.73 (–0.88 to 2.34)
Unknown	359			

FGR, fetal growth restriction.
Note
p-value from the test of interaction = 0.63.

TABLE 34 Parent Report of Children's Abilities-Revised composite score, by BMI

		Trial arm, mean score (points) (SD)		
BMI (kg/m^2)	*n* (%)	Decision support	No decision support	Mean difference (95% CI)
12 to 18.4	104 (2)	94.6 (37.5)	99.9 (37.9)	–5.27 (–20.0 to 9.41)
18.5 to 24.9	2039 (30)	98.2 (33.7)	97.4 (32.8)	0.86 (–2.07 to 3.78)
25 to 29.9	1508 (23)	98.3 (34.8)	98.6 (33.3)	–0.34 (–3.82 to 3.14)
30 to 70	1157 (17)	96.7 (34.8)	95.3 (33.1)	1.43 (–2.53 to 5.39)
Unrecorded	1899 (28)	98.3 (32.4)	97.1 (34.0)	1.27 (–1.76 to 4.30)
Total (unadjusted)	6707 (100)	98.0 (33.8)	97.2 (33.4)	0.73 (–0.88 to 2.34)
Unknown	359			

Note
p-value from the test of interaction = 0.86.

TABLE 35 Parent Report of Children's Abilities-Revised composite score, by centre

Centre[a]	*n* (%)	Trial arm, mean score (points) (SD)		Mean difference (95% CI)
		Decision support	No decision support	
Birmingham Women's Hospital	262 (4)	95.1 (32.0)	96.8 (31.0)	–1.74 (–9.54 to 6.06)
Burnley General Hospital	832 (12)	94.0 (35.7)	94.0 (33.4)	0.02 (–4.73 to 4.78)
Derriford Hospital, Plymouth	814 (12)	95.6 (33.0)	94.7 (34.3)	0.84 (–3.85 to 5.53)
Liverpool Women's Hospital	725 (11)	102.4 (33.4)	97.6 (34.6)	4.79 (–0.28 to 9.85)
Northwick Park Hospital, London	146 (2)	86.3 (34.8)	88.4 (31.4)	–2.19 (–13.3 to 8.87)
Nottingham City Hospital and Queens Medical Centre	135 (2)	98.1 (33.2)	104.4 (30.0)	–6.30 (–17.1 to 4.50)
Princess Anne Hospital, Southampton	205 (3)	99.1 (32.0)	100.9 (32.0)	–1.77 (–10.7 to 7.15)
Princess Royal Hospital and Southern General Hospital, Glasgow	333 (5)	106.1 (31.9)	105.4 (32.4)	0.69 (–6.27 to 7.65)
Queen Alexandra Hospital, Portsmouth	693 (10)	98.2 (33.7)	97.7 (32.4)	0.56 (–4.44 to 5.56)
Rotunda Hospital, Dublin	161 (2)	109.8 (32.2)	110.0 (34.9)	–0.19 (–10.7 to 10.3)
St Mary's Hospital, Manchester	208 (3)	100.0 (34.8)	96.2 (32.4)	3.73 (–5.73 to 13.2)
Stoke Mandeville Hospital	462 (7)	98.3 (32.4)	96.4 (32.0)	1.86 (–4.08 to 7.80)
University Hospital of North Staffordshire	826 (12)	97.1 (34.3)	97.9 (33.3)	–0.75 (–5.37 to 3.88)
Warwick Hospital	905 (14)	97.4 (33.6)	96.8 (34.4)	0.61 (–3.88 to 5.10)
Total (unadjusted)	6707 (100)	98.0 (33.8)	97.2 (33.4)	0.73 (–0.88 to 2.34)
Unknown	359			

a Seven centres joining the trial at a later stage did not have infants included in the 2-year follow-up sample.

Note

p-value from the test of interaction = 0.94.

Chapter 7 Economic evaluation

In previous chapters we showed that the use of decision support software for the management of labour did not translate into statistically significant differences in the two primary outcomes in this trial. In addition, we reported that other neonatal secondary outcomes at hospital discharge and at 2 years' follow-up were similar between the two groups.

This chapter adds an additional layer of relevant information to the clinical outcomes and includes a cost–consequences analysis conducted alongside INFANT. It was originally intended to be presented as a cost-effectiveness analysis and a health economics analysis plan had been developed to support this (see *Appendix 10*). Given the trial findings, a cost–consequences approach was deemed more appropriate and helpful, as is discussed in detail later in this chapter.

The cost–consequences analysis was conducted from a NHS perspective and included direct costs to mothers and their babies. A detailed overview of the analysis conducted from trial entry to hospital discharge and up to 2 years' follow-up is provided in this chapter. In addition to the composite primary outcome at discharge, PARCA-R composite scores for a subset of surviving infants without the composite primary outcome at 2 years and maternal health-related quality of life (HRQoL) at 12 and 24 months post birth are presented.

Methods

NHS health-care resource use

A comprehensive list of health-care resource use information for mothers and their babies was collected for the study. Data collection began when women arrived in hospital in labour and ended when postnatal care for both mother and baby was complete. For most women, this was following hospital discharge. A subset of women who consented to be followed up post birth were sent a questionnaire regarding health-care resource use and maternal HRQoL information at 12 and 24 months' follow-up.

Labour-related resource use data included procedures undertaken for mothers and infants before discharge and were collected using the Guardian system. Additional information, such as maternal transfers after birth, whether or not babies or mothers had been admitted to a higher level of care unit and neonatal deaths, was collected using bespoke data collection forms. These were overseen by the trial's co-ordinating research midwife, who ensured that all care was documented. The forms were then posted to the INFANT trial administrative centre for data entry.

Health-care utilisation at 12- and 24-month follow-up was identified using a postal questionnaire that collected information about acute and community care, secondary care and maternal HRQoL. It included outpatient appointments and inpatient stays (e.g. for operations), follow-up care and numbers of visits to relevant health-care professionals. The questionnaires were sent to a subsample of mothers of surviving infants who consented to follow-up and who gave birth in the first year of the trial. The 12-month follow-up questionnaire collected resource use data between post-birth discharge and 1 year, and the 24-month questionnaire asked about resources consumed in the previous 12 months. Two postal reminders were sent by the trial management team for questionnaires not returned. All data collected using the postal questionnaire were double data entered and cleaned prior to analysis. *Table 36* presents categories of NHS health-care resource use collected during the study.

To estimate whether or not the use of decision support software in INFANT would incur additional NHS resources beyond the implementation of the Guardian system, the health economics team met with a representative from K2 Medical Systems to identify a base-case cost for the software. All sites (and hence all women) participating in the trial used the Guardian system, but we identified three additional aspects to cost for the decision support tool.

TABLE 36 Categories of resource use and associated unit costs used in the cost analysis (expressed in 2014–15 GBP)

Resource use item	Unit cost (GBP)	Source	Notes
Maternal			
Birth related			
Induction	173	Schroeder *et al.*, 2012[73]	
Episiotomy	27	Schroeder *et al.*, 2012[73]	
Perineal tear			
First- and second-degree tears	23	Schroeder *et al.*, 2012[73]	
Third- and fourth-degree tears	649	Schroeder *et al.*, 2012[73]	
Manual removal of the placenta	752	Schroeder *et al.*, 2012[73]	
Blood transfusion	158	Schroeder *et al.*, 2012[73]	Per blood pack
Higher level of care admissions			
Level of care, per day			
Special care	898	*NHS Reference Costs 2014 to 2015*, 2015[74]	
High-dependency care	1278	*NHS Reference Costs 2014 to 2015*, 2015[74]	
Intensive care	1432	*NHS Reference Costs 2014 to 2015*, 2015[74]	
Surgery/post-birth procedures			
Management of post-partum haemorrhage using the Bakri technique	987	*NHS Reference Costs 2014 to 2015*, 2015[74]	
Management of post-partum haemorrhage using EUA	1201	*NHS Reference Costs 2014 to 2015*, 2015[74]	
Hysterectomy	1388	*NHS Reference Costs 2014 to 2015*, 2015[74]	
Perineal haematoma	987	*NHS Reference Costs 2014 to 2015*, 2015[74]	
Transfer to another hospital	439	Schroeder *et al.*, 2012[73]	
Follow-up			
Secondary care			
Hospital inpatient (per day)	492	*NHS Reference Costs 2014 to 2015*, 2015[74]	Weighted average by data submissions of regular day or night admissions
Postnatal ward stay (per day)	104	Schroeder *et al.*, 2012[73]	
A&E department (per visit)	169	*NHS Reference Costs 2014 to 2015*, 2015[74]	Weighted average by data submissions of non-admitted to emergency medicine
Outpatient clinic	111	*NHS Reference Costs 2014 to 2015*, 2015[74]	Weighted average by activity of non-paediatric outpatient attendances
Day case	1078	*NHS Reference Costs 2014 to 2015*, 2015[74]	Weighted average by data submissions of non-paediatric day cases
Community care			
GP appointment	45	Curtis and Burns, 2015[75]	Per patient contact lasting 11.7 minutes
Practice nurse appointment	15	Curtis and Burns, 2015[75]	Per surgery consultation lasting 15.5 minutes

TABLE 36 Categories of resource use and associated unit costs used in the cost analysis (expressed in 2014–15 GBP) (*continued*)

Resource use item	Unit cost (GBP)	Source	Notes
Community nurse appointment	67	Curtis and Burns, 2015[75]	Per visit lasting 60 minutes
Physiotherapy appointment	38	Curtis and Burns, 2015[75]	Per visit lasting 60 minutes
Hospital community counselling	51	Curtis and Burns, 2015[75]	Per visit lasting 60 minutes
Other	43		Average of community care visits
Infant			
Birth related: mode of birth			
Vaginal delivery	1724	*NHS Reference Costs 2014 to 2015*, 2015[74]	Normal delivery, cc = 0 (HRG data)
Breech delivery	2311	*NHS Reference Costs 2014 to 2015*, 2015[74]	Normal delivery, cc = 1 (HRG data)
Assisted delivery	2046	*NHS Reference Costs 2014 to 2015*, 2015[74]	Assisted delivery, cc = 0 (HRG data)
Caesarean section delivery	3895	*NHS Reference Costs 2014 to 2015*, 2015[74]	Emergency C-section
Resuscitation	177	Schroeder *et al.*, 2012[73]	
Higher level of care admissions			
Level of care, per day			
Special care	486	*NHS Reference Costs 2014 to 2015*, 2015[74]	
High-dependency care	847	*NHS Reference Costs 2014 to 2015*, 2015[74]	
Intensive care	1176	*NHS Reference Costs 2014 to 2015*, 2015[74]	
Transfer to another hospital	1101	*NHS Reference Costs 2014 to 2015*, 2015[74]	Neonatal critical care, transportation
Neonatal death	703	Schroeder *et al.*, 2012[73]	
Consultations			
General	167	*NHS Reference Costs 2014 to 2015*, 2015[74]	
Orthopaedic	279	*NHS Reference Costs 2014 to 2015*, 2015[74]	
Surgery			
Paediatric cardiology	3895	*NHS Reference Costs 2014 to 2015*, 2015[74]	
Plastic surgery	1828	*NHS Reference Costs 2014 to 2015*, 2015[74]	
Gastrointestinal surgery	3706	*NHS Reference Costs 2014 to 2015*, 2015[74]	
Paediatric neurosurgery	1105	*NHS Reference Costs 2014 to 2015*, 2015[74]	
Total body cooling	6424	Regier *et al.*, 2009[76]	
Follow-up			
Secondary care			
Hospital inpatient (per day)	757	*NHS Reference Costs 2014 to 2015*, 2015[74]	Paediatric high-dependency ward
Postnatal ward stay (per day)	104	Schroeder *et al.*, 2012[73]	

continued

TABLE 36 Categories of resource use and associated unit costs used in the cost analysis (expressed in 2014–15 GBP) (*continued*)

Resource use item	Unit cost (GBP)	Source	Notes
A&E department (per visit)	169	*NHS Reference Costs 2014 to 2015*, 2015[74]	Weighted average by data submissions of non-admitted to emergency medicine
Outpatient clinic	180	*NHS Reference Costs 2014 to 2015*, 2015[74]	Weighted average by activity of paediatric outpatient attendances
Day case	661	*NHS Reference Costs 2014 to 2015*, 2015[74]	Weighted average by data submissions of paediatric day cases
Community care			
GP appointment	45	Curtis and Burns, 2015[75]	Per patient contact lasting 11.7 minutes
Practice nurse appointment	15	Curtis and Burns, 2015[75]	Per surgery consultation lasting 15.5 minutes
Health visitor	76	Curtis and Burns, 2015[75]	Per visit lasting 60 minutes
Community nurse appointment	67	Curtis and Burns, 2015[75]	Per visit lasting 60 minutes
Community paediatrician	274	*NHS Reference Costs 2014 to 2015,* 2015[74]	Non-admitted face-to-face attendance
Physiotherapy appointment	80	*NHS Reference Costs 2014 to 2015*, 2015[74]	Per one-to-one child session
Other	93		Average of community care visits

A&E, accident and emergency; cc, complication score; EUA, examination under anaesthetic; HRG, Healthcare Resource Group.

The first was the price to be paid by the NHS for the new software. A price for the decision support software had not been determined at the time the study was concluded. We understand that this price would be determined using a particular commercial strategy by K2 Medical Systems and would probably be selected in view of the trial results. Therefore, for the base-case scenario it was initially assumed that the software would be made available free of charge to the NHS. Scenarios to address this were identified for a multiway sensitivity analysis, to include any cost shifting in actual practice.

Second, an annual maintenance fee would be needed for software updates and other related information technology issues. A maintenance fee for the whole Guardian system had already been paid by the trial sites so it was assumed that further maintenance needed for the software would be included. Although the fee could potentially increase as a result of the installation of the decision support software, in the base case it was assumed that the fee would not change.

Finally, training of NHS staff members to develop familiarity and technical competence with the software was reviewed. All training received by staff during the preparation of the trial was delivered during working hours and was fitted into regular working patterns. Therefore, staff did not have to take additional time off work to learn how to use the decision support tool. It was assumed that a similar model would be used across the NHS and that no separate training costs were required. Consequently, in our base case, none of the three identified elements would incur additional NHS resource use, so no specific costs for the use of decision support software in INFANT were assigned. Scenarios to address this were identified for a multiway sensitivity analysis, to include any cost shifting in actual practice.

Unit costs

Sources and associated estimates of unit costs for the different categories of health-care resource use are presented in *Table 36*. Information was primarily extracted from secondary national sources including the Personal Social Services Research Unit[75] and *NHS Reference Costs*.[74] The unit costs associated with induction, episiotomy, perineal tear, manual removal of the placenta, blood transfusion and neonatal death

were not available in any of the secondary data sources consulted. Therefore, we replicated the 'bottom-up' costing survey conducted in a recent cost-effectiveness analysis of the Birthplace in England programme to estimate the unit costs for these items.[73] A bottom-up costing proforma was circulated to all trial midwives to complete. These were then followed up with face-to-face interviews. The proformas represented a detailed approach to capturing all possible NHS resources used in the care of the mother and baby during the period between admission and discharge. A working document was generated to capture the generalisability and variability of the procedures. For each scenario, the trial midwife was asked to describe in detail the 'standard procedures' that would be undertaken for labour and birth events and, when possible, the typical ratios of 'staff-to-woman' care. Scenarios were then varied between the least and the most complex, and included a description of the associated change in activity, staffing level and related resource use. Each of the interviews included approximately 1.5 hours of structured time. The data were then compiled into comparative resource use spreadsheets and were cross-referenced. The original unit costs (calculated for the Birthplace in England study) were then revised to be trial specific. The cost associated with total body cooling was not available in the Personal Social Services Research Unit or NHS reference costs data and was extracted from a study investigating the cost-effectiveness of total-body hypothermia plus intensive care versus intensive care alone to treat NNE.[76]

All costs were expressed in 2014–15 GBP inflated to this base using the most up-to-date Hospital and Community Health Service inflation index.[77] Costs incurred between 12 and 24 months' follow-up were discounted at an annual rate of 3.5%, as recommended by current guidance.[78]

Cost analysis

Categories of resource use and associated costs are presented separately for mothers and their babies. Quantities of resource use in each category were multiplied by the corresponding unit cost to estimate the cost in a particular category. This was then averaged across each trial arm to obtain a mean cost per mother or baby. Costs from post-birth discharge to 12 months, and then from 12 to 24 months' follow-up, were combined to estimate the overall costs at 2 years post birth. The total costs for the following categories are presented separately for the mother–baby dyad: trial entry to hospital discharge, community professional visits and secondary care. Given that we present the economic evaluation as a cost–consequences analysis, and that the numbers of participants used to estimate costs to hospital discharge and to 2 years' follow-up were different, an overall total cost over the trial period was not calculated. Analyses were by 'intention to treat', indicating that the costs incurred were attributed to the original trial arm.

A conditional two-stage top-down costing approach was designed to cost prescribed medications for mothers or their babies. In the first stage, the proportion of mothers or babies with prescribed medications and the number of courses received were compared between trial arms. Were statistically significant differences to be observed between the groups, a microcosting method would be followed to cost the type of medication and the number of courses received on an individual basis. No statistically significant differences in the medications or the number of courses prescribed were observed between the groups and the cost of medication was excluded from the analysis.

Health outcome measures

The two primary outcomes of the trial were a composite of poor neonatal outcome and the PARCA-R composite score at age 2 years. These were used for the cost–consequences analysis. PARCA-R information was collected on a subset of infants selected from those without the composite primary outcome at birth. The parents of all babies born without the primary outcome in the first and second years of the trial were sent follow-up questionnaires. This was to maximise the effort to reach the sample size of approximately 7000 at 24 months' follow-up by the end of the recruitment period for the larger trial. The subset of participants completing PARCA-R questionnaires and those completing the questionnaires collecting health-care resource use and maternal HRQoL data overlapped, with some women receiving both questionnaires.

The maternal HRQoL information was collected using the EuroQol-5 Dimensions, three-level version (EQ-5D-3L), at 12 and 24 months' follow-up.[79] The EQ-5D-3L is a multiattribute generic instrument widely used in the conduct of cost–utility analysis of competing technologies and is recommended by reimbursement organisations such as NICE.[78] It has two components: a descriptive system and a 'feeling thermometer' using a visual analogue scale. The descriptive system covers five dimensions (mobility, self-care, usual activity, pain/discomfort and anxiety/depression), with each dimension including three levels (no problem, some problems and extreme problems). The EQ-5D-3L identifies 243 different health states that can be converted into a preference-based score using a value set obtained from a representative sample of the UK general population.[80]

Statistical analysis

Health-care resource use between treatment arms was compared using RRs for binomial variables and mean differences for continuous covariates. Costs and EQ-5D-3L scores were compared using mean differences between treatment arms. Parametric and non-parametric methods accurately estimate the true SEs of means when large sample sizes for continuous variables are used even when the data are highly skewed.[81] Hence, mean resource use, cost and EQ-5D-3L score differences, and their associated uncertainty between the INFANT decision support and no decision support groups were estimated using parametric methods. In line with the statistical analysis of the primary outcomes, differences between treatment arms were adjusted using a random intercept binomial (for RRs) or linear (for mean differences) model adjusting for the stratification factors at randomisation (centre and twin birth) and clustering because of twins and multiple-birth episodes. A 95% significance level was used in all the comparisons made.

In all categories except for two health-care resource categories (manual removal of the placenta and infant resuscitation), the level of missing data was < 5%. Therefore, the cost analysis to the point of hospital discharge was conducted using a complete case analysis. Nevertheless, the 12- and 24-month follow-ups suffered from a larger number of missing data (specifically for resource use and EQ-5D-3L) and a multiple imputation framework with a chained equation was implemented.[82] This was developed using recent guidance for handling missing data in cost-effectiveness analysis.[83] We constructed an imputation model that included covariates with complete data on trial entry characteristics (maternal age at trial entry, twin pregnancy, gestational age at trial entry, whether the mother was nulliparous or multiparous, the baby's birth weight and mode of delivery), EQ-5D-3L scores and all individual categories of resource use variables at 12 and 24 months' follow-up. We used prediction mean matching, estimated 50 different imputations and the imputation model was implemented separately by trial allocation. Mean estimates and estimates of SEs were combined between imputed data sets using Rubin's rule[84] and were also adjusted using a random intercept binomial (for RRs) or linear (for mean differences) model adjusting for the stratification factors at randomisation (centre and twin birth) and clustering because of twins and multiple-birth episodes.

Results

Figure 41 presents the flow of participants and the sources of information used in each component of the cost–consequences analysis. For completeness, the numbers of participants for the two primary outcomes already reported in the CONSORT diagram in *Figure 14* are also included in this flow chart. The totals of 46,042 women and 46,614 infants are those included in the analysis (i.e. excluding women with missing consent forms and those who withdrew consent to use their data). Estimating the cost analysis to the point of hospital discharge used all women and infants participating in the trial although there were more missing data given the number of categories used for the calculation of costs up to this point. A subset of 12,704 women with surviving babies without the composite primary outcome were sent a questionnaire that included the PARCA-R at the 24-month follow-up. A total of 7066 questionnaires (56%) were received, resulting in 6707 infants with complete PARCA-R information. The health-care resource use and maternal HRQoL follow-up questionnaire at 12- and 24-month follow-ups was circulated to a subset of 3875 women with surviving babies in the trial. A total of 2389 questionnaires (62%) were received and multiple imputation was used to handle missing data and to present the cost analysis over the 24-month follow-up period on 3798 women and 3875 babies.

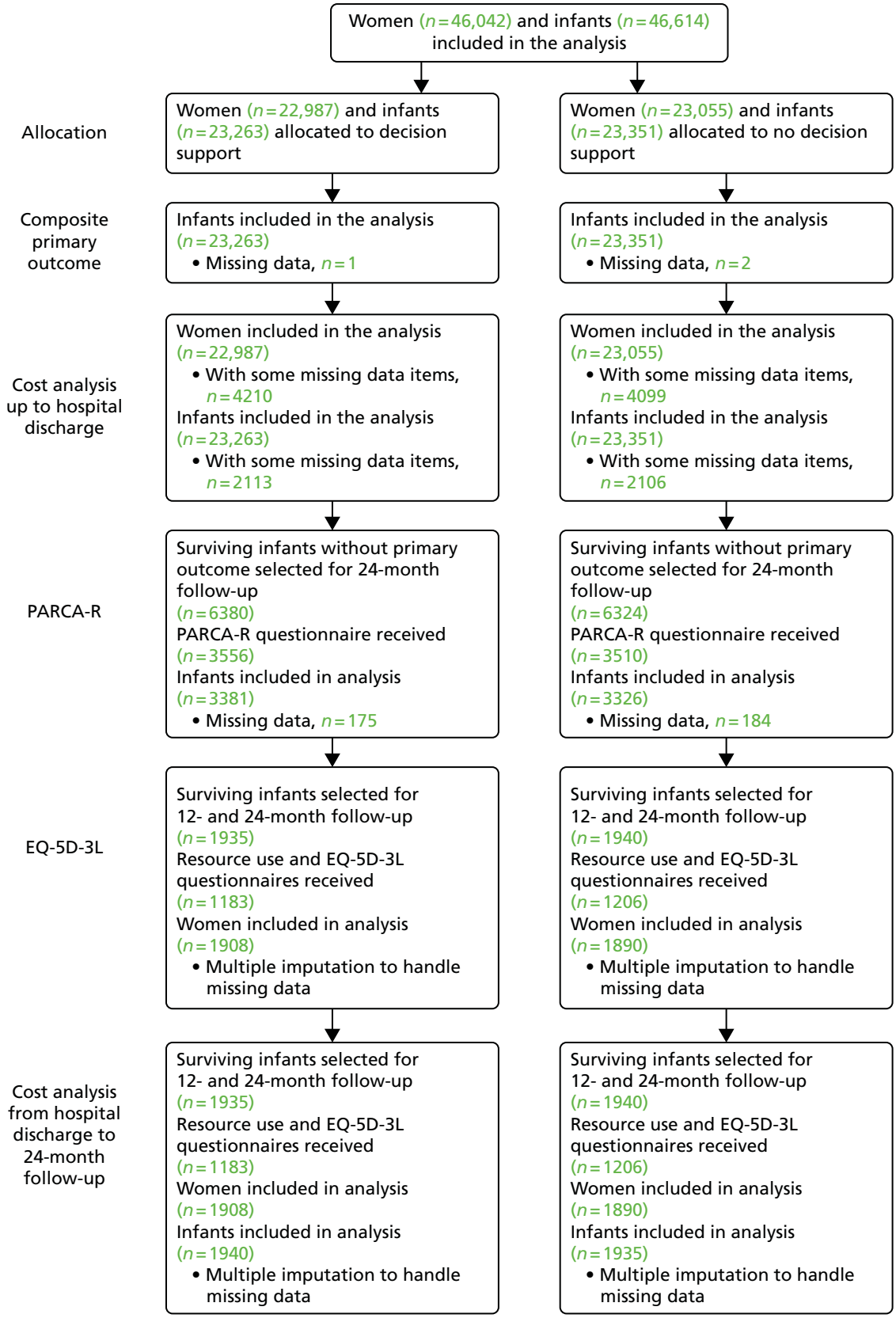


FIGURE 41 Flow of participants and data availability included in each component of the cost–consequences analysis.

Tables 37 and *38* present the maternal and infant health-care resource use from trial entry to postnatal hospital discharge. No statistically significant differences were detected in any category of resource use assessed.

TABLE 37 Maternal health-care resource use from trial entry to hospital discharge

Resource	Trial arm		
	Decision support (*N* = 22,987)	No decision support (*N* = 23,055)	RR/mean difference (95% CI)[a]
Induction, *n* (%)	13,516 (59.16)	13,568 (59.24)	1.00 (0.99 to 1.02)
Unknown	140	153	
Episiotomy, *n* (%)	6396 (28.86)	6498 (29.25)	0.99 (0.96 to 1.02)
Unknown	826	840	
Perineal tear, *n* (%)			
First- and second-degree tear	8105 (36.26)	8226 (37.13)	0.98 (0.95 to 1.00)
Third- and fourth-degree tear	652 (2.95)	697 (3.15)	0.94 (0.84 to 1.04)
Unknown	881	902	
Manual removal of the placenta, *n* (%)	396 (1.72)	421 (1.83)	0.93 (0.81 to 1.06)
Unknown	3703	3626	
Medical and surgical management post birth, *n* (%)			
Management of postpartum haemorrhage using the Bakri technique	18 (< 0.1)	23 (< 0.1)	0.78 (0.42 to 1.45)
Management of postpartum haemorrhage using EUA	44 (< 0.1)	49 (< 0.1)	0.90 (0.60 to 1.36)
Hysterectomy	8 (< 0.1)	5 (< 0.1)	1.61 (0.53 to 4.91)
Perineal haematoma	19 (< 0.1)	10 (< 0.1)	1.90 (0.88 to 4.09)
PPH with blood transfusion	1 (< 0.1)	2 (< 0.1)	0.50 (0.045 to 5.50)
Hospital length of stay, *n* (%)			
Length of stay (days), mean (SD)	2 (8.87)	2 (8.33)	–0.01 (–0.17 to 0.14)
Unknown	42	32	
Higher level of care admissions (days), mean (SD)			
High-dependency care	0.04 (0.32)	0.04 (0.24)	0.003 (–0.002 to 0.008)
Intensive care	0.00 (0.29)	0.00 (0.07)	0.001 (–0.002 to 0.005)

EUA, examination under anaesthetic.
a Adjusted for stratification factors used in the randomisation (centre and twin birth) and clustering because of twins and multiple-birth episodes with 95% CIs used.

TABLE 38 Infant health-care resource use from trial entry to hospital discharge

Resource	Trial arm		
	Decision support (*N* = 23,263)	No decision support (*N* = 23,351)	RR/mean difference (95% CI)[a]
Mode of birth, *n* (%)			
Spontaneous vaginal birth	11,823 (50.82)	11,959 (51.21)	0.99 (0.97 to 1.01)
Breech birth	73 (0.31)	72 (0.31)	1.06 (0.78 to 1.43)
Ventouse vaginal birth	2522 (10.84)	2509 (10.74)	1.01 (0.96 to 1.06)
Forceps vaginal birth	3176 (13.65)	3256 (13.94)	0.98 (0.93 to 1.02)
Caesarean section	5669 (24.37)	5555 (23.79)	1.02 (0.99 to 1.06)
Resuscitation, *n* (%)			
Initial	2139 (10.11)	2116 (9.96)	1.02 (0.96 to 1.07)
Intensive	554 (2.62)	524 (2.47)	1.07 (0.94 to 1.20)
Unknown	2113	2106	
Higher level of care admissions (days), mean (SD)			
Special care	0.21 (1.61)	0.23 (2.86)	–0.029 (–0.07 to 0.013)
High-dependency care	0.04 (0.75)	0.04 (0.91)	–0.006 (–0.021 to 0.009)
Intensive care	0.05 (0.85)	0.04 (0.64)	0.007 (–0.007 to 0.021)
Neonatal surgery, *n* (%)	23 (0.10)	26 (0.11)	
Paediatric cardiology	7 (0.03)	5 (0.02)	1.41 (0.45 to 4.43)
Plastic surgery	5 (0.02)	10 (0.04)	0.50 (0.17 to 1.47)
Gastrointestinal surgery	10 (0.04)	11 (0.05)	0.85 (0.34 to 2.11)
Paediatric neurosurgery	2 (0.01)	0	–
Total body cooling	19 (0.1)	21 (0.1)	0.90 (0.48 to 1.69)
Intrapartum stillbirth, *n* (%)	1 (–)	2 (–)	0.46 (0.04 to 6.05)
Neonatal death, *n* (%)	6 (–)	4 (–)	1.51 (0.42 to 5.33)

a Adjusted for stratification factors used in the randomisation (centre and twin birth) and clustering because of twins and multiple-birth episodes with 95% CIs used.

Tables 39 and *40* show the results of the maternal and infant cost analysis from trial entry to hospital discharge. The total mean maternal costs from trial entry to hospital discharge were estimated to be £431 (SE £7) and £433 (SE £6) in the decision support and no decision support groups, respectively; the non-significant mean-adjusted cost difference was –£2 (95% CI –£28 to £24). The total mean infant costs from trial entry to hospital discharge were estimated to be £2539 (SE £12) and £2541 (SE £15) in the decision support and no decision support groups, respectively; the non-significant mean-adjusted cost difference was £1 (95% CI –£37 to £39).

TABLE 39 Cost analysis of maternal health-care resource use from trial entry to hospital discharge (expressed in 2014–15 GBP)

Resource	Trial arm: Decision support (*N* = 22,987)		Trial arm: No decision support (*N* = 23,055)		Mean difference (95% CI)[b]
	n[a]	Mean (SE)	*n*[a]	Mean (SE)	
Induction	22,847	102 (0.56)	22,902	102 (0.56)	
Episiotomy	22,161	8 (0.08)	22,215	8 (0.08)	
Perineal tear	22,106	27 (0.71)	22,153	28 (0.73)	
Manual removal of the placenta	19,284	12 (0.65)	19,429	14 (0.66)	
Medical and surgical management	22,987	4 (0.46)	23,055	4 (0.46)	
Blood transfusion	22,987	2 (1.3)	23,055	3 (1.3)	
Maternal transfer	22,987	0.22 (0.06)	23,055	0.13 (0.05)	
Hospital length of stay	22,945	226 (6.07)	23,023	227 (5.69)	
Higher level of care admissions					
High-dependency care	22,987	49 (2.68)	23,055	45 (2.01)	
Intensive care	22,987	4 (2.72)	23,055	2 (0.62)	
Total maternal cost from trial entry to hospital discharge	18,777	431.3 (6.8)	18,956	432.6 (6.4)	–2 (–28 to 24)

a The sample size used for calculation of means and SEs, which comprises the number of mothers with relevant data.
b Adjusted for stratification factors used in the randomisation (centre and twin birth) and clustering because of twins and multiple-birth episodes with 95% CIs used.

TABLE 40 Cost analysis of infant health-care resource use from trial entry to hospital discharge (expressed in 2014–15 GBP)

Resource	Trial arm: Decision support (*N* = 23,263)		Trial arm: No decision support (*N* = 23,351)		Mean difference (95% CI)[b]
	n[a]	Mean (SE)	*n*[a]	Mean (SE)	
Mode of birth	23,263	2334 (5.88)	23,351	2322 (5.82)	
Resuscitation	21,150	8 (0.19)	21,245	8 (0.19)	
Neonatal surgery					
Paediatric cardiology	23,263	1 (0.44)	23,351	0.83 (0.37)	
Plastic surgery	23,263	0.39 (0.18)	23,351	0.78 (0.25)	
Gastrointestinal surgery	23,263	1.6 (0.50)	23,351	2 (0.50)	
Paediatric neurosurgery	23,263	0.09 (0.07)	23,351	0	
Total body cooling	23,263	5 (1.20)	23,351	6 (1.26)	
Neonatal death	23,263	0.18 (0.07)	23,351	0.12 (0.06)	
Higher level of care admissions					
Special care	23,263	99 (5.13)	23,351	114 (9.11)	
High-dependency care	23,263	36 (4.21)	23,351	41 (5.05)	
Intensive care	23,263	54 (6.61)	23,351	46 (5.00)	
Total infant cost from trial entry to hospital discharge	21,150	2539.3 (12.4)	21,245	2540.9 (14.9)	1 (–37 to 39)

a The sample size used for calculation of means and SEs, which comprises the number of mothers with relevant data.
b Adjusted for stratification factors used in the randomisation (centre and twin birth) and clustering because of twins and multiple-birth episodes with 95% CIs used.

Table 41 presents the results of the maternal health-care resource use and associated costs over 24 months since hospital discharge. A significant adjusted mean cost difference of –£166 (95% CI –£319 to –£12) was observed in secondary care admissions for mothers, favouring the decision support group. Such difference was driven by slightly more admissions to all units in the no decision support group since hospital discharge. However, when adding up all categories of costs (community plus secondary care), the total mean (SE) maternal follow-up costs were estimated to be £753 (SE £35) and £904 (SE £77) in the decision support and no decision support groups, respectively; the non-significant mean-adjusted cost difference was –£149 (95% CI –£314 to £16). *Table 42* reports similar information for the infants. None of the categories of costs or overall costs resulted in any statistically significant difference between the groups of infants.

Maternal HRQoL EQ-5D-3L scores at 12 and 24 months' follow-up are presented in *Table 43*. Mothers reported scores similar to the population norm for English females aged 25–34 years (currently a mean of 0.925 using the EuroQoL EQ-5D-3L index[85]) in both groups and, therefore, no statistically significant mean differences in scores were observed at any follow-up point.

TABLE 41 Maternal health-care resource use and associated costs (expressed in 2014–15 GBP) from hospital discharge to 2 years' follow-up using multiple imputation

	Trial arm				
	Decision support ($n = 1908$)		No decision support ($n = 1890$)		
Resource	Mean resource use (SE)	Mean cost (SE)	Mean resource use (SE)	Mean cost (SE)	Mean cost difference (95% CI)[a]
Community professional visits					
General practice	5.30 (0.16)	234 (7)	5.01 (0.12)	222 (5)	12 (–6 to 30)
Practice nurse	1.48 (0.08)	21 (1)	1.23 (0.06)	18 (1)	4 (1 to 6)*
Community nurse	0.16 (0.04)	11 (2)	0.25 (0.06)	17 (4)	–5 (–14 to 3)
Physiotherapy	0.61 (0.07)	23 (2)	0.67 (0.08)	25 (3)	–2 (–9 to 6)
Hospital community counselling	0.12 (0.03)	6 (2)	0.12 (0.03)	6 (1)	–0.09 (–5 to 4)
Other community professionals	1.09 (0.10)	46 (4)	0.90 (0.10)	38 (4)	8 (–3 to 20)
Total community professional visits		341 (11)		325 (10)	171 (–14 to 48)
Secondary care					
Outpatient visits	0.98 (0.06)	107 (7)	0.88 (0.07)	96 (8)	11 (–9 to 31)
A&E visits	0.35 (0.03)	58 (5)	0.35 (0.03)	57 (5)	1 (–13 to 14)
Intensive care unit (nights)	0.00 (0.00)	0 (0)	0.04 (0.02)	59 (34)	–60 (–128 to 9)
High-dependency ward/unit (nights)	0.05 (0.02)	58 (19)	0.11 (0.04)	120 (41)	–61 (–147 to 25)
General ward (nights)	0.42 (0.05)	43 (5)	0.47 (0.05)	48 (5)	–4 (–20 to 11)
Other admissions	0.18 (0.03)	87 (14)	0.29 (0.06)	140 (28)	–52 (–114 to 10)
Day case	0.06 (0.01)	59 (8)	0.06 (0.01)	59 (8)	0 (–23 to 23)
Total secondary care		412 (30)		580 (73)	–166 (–319 to –12)*
Total maternal follow-up		753 (35)		904 (77)	–149 (–314 to 16)

*$p < 0.05$.
A&E, accident and emergency.
a Adjusted for stratification factors used in the randomisation (centre and twin birth) and clustering because of twins and multiple-birth episodes with 95% CIs used.

TABLE 42 Infant health-care resource use and associated costs (expressed in 2014–15 GBP) from hospital discharge to 2 years' follow-up using multiple imputation

Resource use	Trial arm: Decision support ($n = 1940$) Mean resource use (SE)	Decision support ($n = 1940$) Mean cost (SE)	No decision support ($n = 1935$) Mean resource use (SE)	No decision support ($n = 1935$) Mean cost (SE)	Mean cost difference (95% CI)[a]
Community professional visits					
General practice	6.72 (0.16)	297 (7)	6.86 (0.16)	303 (7)	–6 (–25 to 14)
Practice nurse	0.88 (0.06)	12 (0.81)	0.81 (0.04)	12 (0.63)	0.99 (–1 to 3)
Health visitor	1.44 (0.11)	107 (8)	1.48 (0.10)	110 (7)	–2 (–23 to 19)
Community nurse	0.20 (0.03)	13 (2)	0.18 (0.04)	12 (2)	2 (–4 to 8)
Community paediatrician	0.31 (0.03)	84 (9)	0.31 (0.03)	84 (9)	3 (–23 to 28)
Physiotherapy	0.14 (0.03)	11 (2)	0.32 (0.07)	25 (5)	–14 (–26 to –2)
Other community professionals	0.54 (0.06)	49 (5)	0.63 (0.08)	58 (7)	–8 (–24 to 9)
Total community professional visits		575 (20)		603 (21)	–24 (–82 to 34)
Secondary care					
Outpatient visits	1.36 (0.08)	242 (15)	1.25 (0.07)	223 (12)	24 (–14 to 62)
A&E visits	1.14 (0.05)	188 (9)	1.01 (0.04)	167 (7)	21 (–2 to 44)
Intensive care unit (nights)	0.17 (0.05)	201 (58)	0.18 (0.06)	205 (69)	–3 (–187 to 181)
High-dependency ward/unit (nights)	0.20 (0.05)	131 (35)	0.12 (0.03)	78 (21)	53 (–29 to 134)
General ward (nights)	0.61 (0.06)	63 (6)	0.56 (0.05)	58 (6)	4 (–12 to 21)
Other admissions	0.12 (0.03)	88 (21)	0.07 (0.02)	51 (14)	37 (–14 to 87)
Day case	0.05 (0.01)	32 (5)	0.06 (0.01)	40 (6)	–8 (–23 to 7)
Total secondary care		945 (90)		822 (80)	128 (–120 to 375)
Total infant follow-up		1520 (100)		1425 (92)	104 (–174 to 382)

A&E, accident and emergency.
a Adjusted for stratification factors used in the randomisation (centre and twin birth) and clustering because of twins and multiple-birth episodes with 95% CIs used.

TABLE 43 Maternal HRQoL using EQ-5D-3L scores at 12- and 24-month follow-up using multiple imputation analysis

EQ-5D-3L follow-up point	Trial arm: Decision support ($n = 1908$) Mean score	Decision support ($n = 1908$) SE	No decision support ($n = 1890$) Mean score	No decision support ($n = 1890$) SE	Mean difference (95% CI)[a]
12 months	0.908	0.005	0.913	0.005	–0.005 (–0.020 to 0.012)
24 months	0.909	0.006	0.919	0.005	–0.008 (–0.023 to 0.007)

a Adjusted for stratification factors used in the randomisation (centre and twin birth) and clustering because of twins and multiple-birth episodes with 95% CIs used.

A summary of the different components included in the cost–consequences analysis is reported in *Table 44*. For each of the maternal and infant total mean cost components from trial entry to hospital discharge and over 24 months' follow-up since hospital discharge, no statistically significant differences were observed between the groups. Similarly, no statistically significant mean differences were observed between the groups in any of the consequences evaluated; the composite primary outcome, PARCA-R and maternal quality-of-life scores.

Discussion

Presentation of the results

The findings of the clinical study in *Chapter 6* showed no differences in the composite primary outcomes at birth, or in PARCA-R composite scores at 2 years. Given these findings, we chose to present the results of our economic evaluation (using the clinical outcomes reported previously) with a cost–consequences analysis. Our statistical analysis plan refers to the estimation of a cost-effectiveness analysis, but with no differences in costs or effects between the groups, there was no evidence of differences between the groups to generate this. A cost–utility analysis could not be conducted, owing to the lack of HRQoL data at baseline and postnatally, to derive quality-adjusted life-years. Given the overall trial results, we considered that presenting the data in a disaggregated manner to show the costs and benefits (consequences) for different time periods provides the most useful information to complement the clinical findings.

The study was conducted at multiple labour ward sites across England, Scotland and the Republic of Ireland, with differing configurations of care and economies of scale strengthening the generalisability of our results. A useful ancillary benefit of this study is that it provides detailed costs of intrapartum care, which contributes to the broader field of evidence available for health economic evaluations in the perinatal research arena.

TABLE 44 Summary of the different components included in the cost–consequences analysis alongside the INFANT study (2014–15 GBP)

Component	Trial arm, mean estimate		Mean difference (unless otherwise stated) (95% CI)[a]
	Decision support	No decision support	
Costs (2014–15 GBP)			
Total maternal from trial entry to hospital discharge	431	432	–2 (–28 to 24)
Total infant from trial entry to hospital discharge	2539	2540	1 (–37 to 39)
Total maternal follow-up	753	904	–149 (–314 to 16)
Total infant follow-up	1520	1425	104 (–174 to 382)
Consequences: infant			
Composite primary outcome, *n* (%)	172 (0.7)	171 (0.7)	RR: 1.01 (0.82 to 1.25)
PARCA-R score	98.0	97.2	0.63 (–0.98 to 2.25)
Consequences: maternal			
EQ-5D-3L 12 months	0.908	0.913	–0.005 (–0.020 to 0.012)
EQ-5D-3L 24 months	0.909	0.919	–0.008 (–0.023 to 0.007)

a Adjusted for stratification factors used in the randomisation (centre and twin birth) and clustering because of twins and multiple-birth episodes with 95% CIs used.

Findings

Both the clinical and cost–consequences analyses did not identify statistically significant differences between the trial arms. There were also no differences in the direction of costs, namely a consistent pattern of cost increase in one trial arm compared with the other. Within the cost categories there were small differences, such as secondary care for mothers post birth, but, overall, the differences between groups did not reflect a direction. We had anticipated that a decision support tool to prevent poor perinatal outcomes might have lifelong effects, that these could be modelled using decision-analytic or Markov models, and that 'obstetric litigation costs averted' would have been a key cost driver. Nevertheless, there were no differences in cost or effectiveness to model between the arms of the trial to 24 months post birth and for the longer term. Research was undertaken during the study to identify a composite 'quality of care' variable that would identify substandard (and potentially negligent) clinical care during birth. The consistent and methodical documentation of birth information captured in the Guardian system and decision support software (INFANT) might assist an interrogation of the 'quality-of-care' for clinical staff and may be useful in future studies. The software did not assist research for a longer-term cost-effectiveness study here but it has the potential to shorten an obstetric litigation process and even potentially to alter the outcome of some cases. This hypothesis is currently untested and may be relevant for future research.

The trial was not designed to assess the cost and benefit of the Guardian system and the value it provides for labour ward staff. No research was undertaken to explicitly cost Guardian separately from the decision support tool (INFANT). However, we did probe whether or not the combined information display (at the patient's bedside, centrally or remotely) and the interaction with the decision support tool caused a cost shifting or change to practice for staff for efficiency purposes. We conducted informal interviews at 11 out of 23 sites, which were all sites where research midwives agreed to discuss the health economics component including whether or not the sites had:

- installed Guardian for the study and had changed to be wholly paper-free, using it for all births since the start of the trial
- installed Guardian for the study, but did not use it consistently in the ward
- used Guardian prior to and after the trial for all births.

In summary, feedback from the interviews was consistent across the sites. Interactions with Guardian and the decision support (INFANT) system produced negligible changes and affected clinical staff differently. Midwives generally reported no change to practice but stated that the alarms during the second stage of labour sometimes distressed patients and might require additional checks or review, or even the option to switch off the software. There were a few reports of increased visits to the ward by clinical staff, querying yellow and red alerts. Most midwifery co-ordinators reported that the convenience and accessibility of the display platforms increased time efficiency for staff co-ordination and allocation. Clinicians reported that, although the duration of their staff shift did not change, they had greater flexibility around location (with an increased freedom to be desk based, enabling work time to be more productive). Central hospital information technology staff identified an increase in their staff time dedicated to the labour ward, providing technical support to the midwifery and medical staff. It was difficult to separate out the impact of Guardian and decision support (INFANT) for this particular activity, as both collect and display information. However, there did not seem to be a striking change to the workload models for clinical staff, for cost shifting or efficiency. Having documented the findings of this research question, we did not attribute a cost impact.

Limitations

As discussed, the economic evaluation presented here was originally intended to be a cost-effectiveness analysis. The incremental cost-effectiveness ratio (ICER) was to be expressed as an incremental cost per poor perinatal outcome prevented (at hospital discharge following birth). Two longer-term cost-effectiveness analyses were planned: (1) to estimate the cost-effectiveness of the decision support software (INFANT) when surviving children reached 2 years of age and (2) to incorporate lifetime cost and health consequences of the decision support software (INFANT) for the mother and child within an economic modelling framework. Given that there were no statistically significant differences between costs and outcomes at post-birth

discharge or at 24 months, we would not add value to this research with a longer-term framework. A cost-effectiveness analysis in the short term to include the cost of the software would only make the INFANT software more expensive and, thus, less cost-effective. Our original plan to perform multiway sensitivity analyses, to estimate and value the initial and annual maintenance fees for the decision support tool (INFANT), would make the decision support arm more expensive. As stated earlier, several strategies had been developed to estimate the additional software costs (apportioned per birth) via estimates of installation and maintenance fees or via a commercial strategy by K2 Medical Systems, but given the findings in the trial, we did not pursue a final cost estimate for the INFANT software.

The study is limited by different components of missing data. The trial suffered a large loss to follow-up; 46% of women contacted at 12-month follow-up and 38% of women contacted at 24-month follow-up returned questionnaires. Although numerous methods and substantial effort was invested to increase the response rate, it was an unsurprising outcome. Labour is a life-changing but acute event, and the majority of the women in this study had uncomplicated pregnancies and a fairly straightforward labour (albeit requiring EFM during the event). Most also had healthy babies so we surmise that they would not have felt an innate need to personally 'invest' in the study, in a manner equivalent to suffering a severe long-term illness. We also identified women pregnant with their second baby while completing questionnaires about their first, reflecting a progression in their life stage from the original birth event. Our only contact with the women was via postal address and, with limited resources, once this connection was lost as a result of residential change, we were not able to trace them further. Finally, conversations with research midwives revealed that, although recruitment into the trial was explicitly and clearly communicated to women and their partners, and consent was required for participation, many would not have identified the use of the decision support software (INFANT) separately from their overall birth experience. It was primarily used by midwives and would have been associated with other clinical activity, such as documenting patient information into the system.

As described throughout this chapter, we resolved the issue of missing data in different ways. We ensured that missing data are noted in detail throughout, in the flow chart (see *Figure 41*), in each table of resource use and in the final cost analyses (see *Tables 37* and *38*). For the 12- and 24-month follow-ups, we account for missing data using multiple imputation techniques.

Value of this research

This cost–consequences analysis fills an evidence gap regarding the use of computerised interpretation of the CTG in women receiving EFM during labour. It identifies and presents all the key resource use associated with the intervention. It also adds evidence to a growing body of unit cost information collected through primary sources for perinatal care.

Economic evaluation adds value to research by providing decision-makers with information that systematically considers all the evidence, balances trade-offs to ensure that health care provides value for money and explores uncertainty around key cost drivers and health outcomes. We have captured and combined the key clinical and cost impacts of the decision support software (INFANT). Based on the results presented in this chapter and previous chapters, there is no evidence to support the use of computerised interpretation of the CTG in women in the UK and the Republic of Ireland.

Chapter 8 Discussion and conclusion

In this trial of 46,000 women, there is no evidence of a difference in the risk of a poor neonatal outcome using CTG interpretation software to support decision-making. Another randomised trial (of 7730 women), which evaluated the use of decision support in women who were monitored during labour using fetal ECG monitoring, also found no evidence that CTG interpretation decision support improved the primary outcome of cord blood metabolic acidosis.[86]

Using a composite primary outcome is not always helpful if different components of the outcome respond differently to the intervention. If one component of the composite dominates the others, then effectively the trial results reflect any differences detected within this dominant component.[87] We initially hypothesised that the indicence of components of the composite outcome (extended perinatal mortality, NNE and prolonged admission to a neonatal unit following birth in a poor condition) would be similar, with each component likely to contribute approximately one-third to the composite.

Estimates of the incidence of the components of the primary outcome for the eligible study population were difficult to find before the trial commenced.[1] The observed perinatal mortality in the study (stillbirth and neonatal death, excluding lethal congenital anomalies) was lower than the prior estimate (13/46,614 births or 0.3 per 1000 births vs. 1.05 per 1000 births), and the incidence of NNE requiring cooling was also lower (39/46,614 births or 0.8 births per 1000 births vs. 1.3 births per 1000 births see *Chapter 2*). However, prolonged neonatal unit admission with evidence of compromise at birth, for which we had no good data at the time the trial was planned, occurred more frequently than expected (291/46,614 births or 6 per 1000 births), contributing substantially to the higher than anticipated overall primary event rate of 7 per 1000 births, compared with our estimated 3 per 1000 births. This allowed us to have the power to detect more modest differences in the composite outcome than we had originally planned.

The very low numbers of perinatal deaths and longer-term adverse outcomes, such as cerebral palsy, mean that this trial is unable to rule out even large differences in these individual outcomes. However, given this very low event rate, the numbers needed to treat to prevent one perinatal death would be very substantial even if the intervention was effective.

The strength of this study lies in its contemporaneous data collection and its size, the latter being designed to detect differences in substantive perinatal outcomes, as well as in more frequent outcomes such as cord metabolic acidosis and operative delivery. Potential weaknesses include the potential for staff to learn from exposure to the decision support arm of the trial, resulting in improved outcomes in the control arm. This potential weakness was identified when the trial was being planned. We acknowledged that passive learning from the decision support system was possible and the only way to completely rule out this effect would be to conduct a cluster randomised trial. Such a design was unfeasible given the limited number of centres with the Guardian system in the UK and Republic of Ireland and the very low incidence of the primary outcome measure. Moreover, part of our prior hypothesis was that, although some poor CTG interpretation is as a result of a lack of training, some clinicians have a poor intrinsic pattern recognition ability that is not susceptible to improvement by training. Such an intrinsic disability would, by definition, not be affected by training, and the performance of such clinicians would be particularly improved by assistance from automatic interpretation. Therefore, we collected a range of process outcomes to measure the impact on clinician behaviour during the trial. There was some evidence that clinical behaviour was changed in the decision support arm of the trial: the incidence of fetal blood sampling was higher in the decision support group (10.3% vs. 9.5% in the no decision support group) and the incidence of repeated yellow alerts was lower (0.35 per hour vs. 0.40 per hour in the no decision support group). It may be that different action was taken in response to the alerts in the decision support arm of the trial, for example the clinicians might have reduced the dose of an oxytocin infusion in women having their labour augmented if this was leading to very frequent contractions, or changed maternal position if the CTG abnormality resulted from vena caval compression. Such actions could have prevented further yellow alerts,

leading to a decrease in this group, but we do not have any direct evidence showing that this was the case. Even if it was, it did not result in any significant change in clinical outcomes. Another potential weakness is that the UK and Republic of Ireland setting, where EFM is not routine,[21] makes generalisability of the findings to settings where EFM is routine more uncertain.

Detecting abnormalities in the fetal heart rate can only improve outcome if caregivers respond appropriately to the alerts. An expert panel reviewed all severe adverse outcomes in the trial and found no evidence that there were differences in suboptimal care between the two groups. Therefore, we conclude that our hypothesis, that substandard care is largely related to failure to identify pathological fetal heart rate patterns, is not supported. It appears that most adverse outcomes associated with preventable substandard care involved a failure to take appropriate management decisions once the CTG abnormality had been recognised. This aspect will be reported on in detail in a follow-up paper. Our hypothesis that unnecessary intervention would be reduced was also not supported.

The decision support software used in this trial clearly identifies most fetal heart rate abnormalities.[35–37] However, the alerts do not take into account other information about the labour, such as the duration of labour, the rate of labour progress, presence of meconium, whether or not the woman has an elevated temperature and whether or not there is suspected fetal growth restriction, all of which may modify the way a clinician interprets the fetal heart rate and acts on this information. Further development of decision support software to include these variables may improve the quality of the feedback the system provides to clinicians and therefore may make a positive difference to outcomes. Given the importance of the consequences of intrapartum hypoxia for parents, clinicians and health services, there continues to be an urgent need to improve knowledge and training about the appropriate response to CTG abnormalities, including timely intervention.

Currently, there is no evidence to support the use of computerised interpretation of the CTG in women who have EFM in labour to improve clinical outcomes for mothers or babies.

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Contributions of others

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- Tracey Johnston, Principal Investigator
- Gemma Barnfield, Recruiting Midwife
- Karen Davies, Recruiting Midwife.

Chelsea and Westminster Hospital, London

- Mark Johnson, Principal Investigator
- Holly Patterson, Recruiting Midwife.

Derriford Hospital, Plymouth

- Imogen Montague, Principal Investigator
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Publications

Barber VS, Lean KA, Shakeshaft CE. Computers & CTGs: where are we at? *Br J Midwifery* 2010;**18**:644–9

Barber V, Linsell L, Locock L, Powell L, Shakeshaft C, Lean K, *et al.* Electronic fetal monitoring during labour and anxiety levels in women taking part in a RCT. *Br J Midwifery* 2013;**21**:394–403.

The INFANT Collaborative Group. Computerised interpretation of the fetal heart rate during labour (INFANT): a randomised controlled trial. *Lancet* 2017;**389**:1719–29.

Data sharing statement

Data can be obtained from the corresponding author.

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Appendix 1 Information for women during the antenatal period

Who can take part in the study?

All women who are having their baby's heart rate monitored in labour by continuous electronic monitoring (EFM).

The presence of the INFANT study in this hospital does not mean that midwives and doctors will be more or less likely to propose continuous electronic monitoring. The decision about whether to recommend continuous electronic monitoring in labour will be based on the same clinical criteria as is usual in this hospital.

What happens now?

You do not need to do anything now. If you and your midwife or doctor decide that continuous electronic monitoring (EFM) in labour may be necessary, you will be asked to consider taking part in the INFANT study. Your midwife or doctor will discuss the study with you at that time.

How do I get more information about the study?

More information about the INFANT study is included in a participant information leaflet. If you would like to see this leaflet, please ask your midwife at an antenatal appointment or you can see it at the website, www.ucl.ac.uk/ctu/infant

[redacted]

INFANT STUDY

Antenatal Information for Women

A study of monitoring babies during labour – the INFANT study

Northern & Yorkshire Research Ethics Committee Reference: 09/H0903/31

Version 6 September 2012

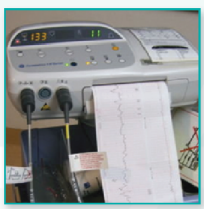
This hospital is one of many hospitals in the UK and Ireland taking part in the INFANT study.

INFANT STUDY

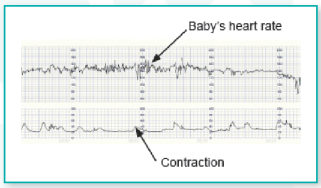
The INFANT study aims to try and improve the way that we monitor babies during labour.

Many women do not require continuous monitoring of their baby's heart rate during labour. For these women, regular but intermittent listening to the baby's heart rate is all that is required (or babies heart rates if you are expecting twins).

However, for some women it may be recommended that the baby's heart rate is recorded continuously using a monitor such as the one below.



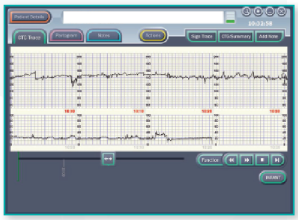
This technique is called continuous electronic fetal monitoring, sometimes referred to as EFM or CTG, after the name of the piece of equipment that is used – the cardiotocogram. It produces a continuous recording of the changes that occur in a baby's heart rate during labour and in the activity of the uterus (contractions). This is an example of the recordings produced.



Midwives and doctors caring for women in labour use continuous electronic fetal monitoring to identify changes in the baby's heart rate that suggest that the baby may not be coping well with the labour. If this happens they may recommend other tests to check how well the baby is, such as taking a small sample of the baby's blood from the scalp, or they may recommend that the baby is delivered as soon as possible.

Looking at a recording of the baby's heart rate and interpreting it is complicated and we are constantly looking for ways to make this more accurate.

One way that may be able to improve this accuracy is to use a computer to help the midwives and doctors to recognise when changes are occurring. A computer system (a picture of its screen is shown below) has been developed to provide additional information which may help the midwives and doctors to decide whether any changes occurring in the baby's heart rate are important or not.

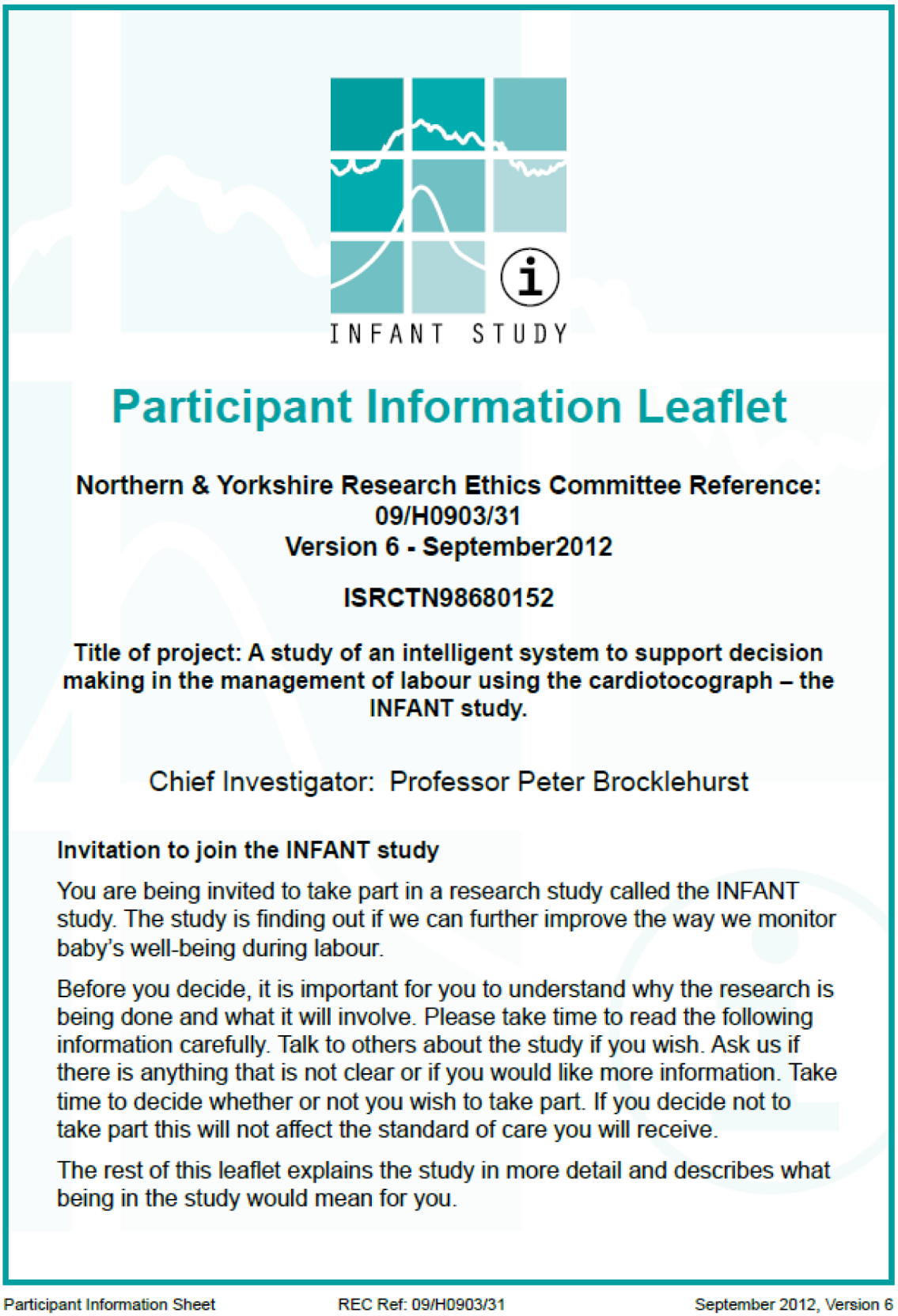


Although many women who have their labour care at this hospital will not have continuous electronic fetal monitoring in labour, we want to let everyone know about this important study.

What is the INFANT study looking at?

The INFANT study will look at whether a new computer system can help interpret the baby's heart rate in labour, specifically whether it is effective or not at improving the health and wellbeing of babies and mothers who have continuous electronic fetal heart rate monitoring (EFM) in labour.

Appendix 2 Participant information leaflet



INFANT STUDY

Participant Information Leaflet

Northern & Yorkshire Research Ethics Committee Reference: 09/H0903/31
Version 6 - September2012

ISRCTN98680152

Title of project: A study of an intelligent system to support decision making in the management of labour using the cardiotocograph – the INFANT study.

Chief Investigator: Professor Peter Brocklehurst

Invitation to join the INFANT study

You are being invited to take part in a research study called the INFANT study. The study is finding out if we can further improve the way we monitor baby's well-being during labour.

Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully. Talk to others about the study if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part. If you decide not to take part this will not affect the standard of care you will receive.

The rest of this leaflet explains the study in more detail and describes what being in the study would mean for you.

Participant Information Sheet REC Ref: 09/H0903/31 September 2012, Version 6

Title of project: A study of an intelligent system to support decision making in the management of labour using the cardiotocograph – the INFANT study.

What is the purpose of the study?

Midwives or doctors caring for women in labour often use electronic fetal monitoring – more specifically this is called a cardiotocograph or CTG. This gives information about the baby's heart rate and also on the activity of the uterus (contractions). Doctors and midwives currently have to interpret these by eye alone. Looking at a recording of the baby's heart rate and interpreting it is complicated and we are constantly looking for ways to make this more accurate. We therefore want to see if a computer system, that is a system that can analyse information electronically, can help the doctors and midwives looking at this information, and whether this will be more beneficial to you and your baby (or babies if you are having twins).

Why am I being asked to consider the study?

You are being asked to consider taking part in this study as at some point during your antenatal care or labour, a decision may be made to recommend that your baby's heart rate is monitored continuously during labour. This is a common procedure which many tens of thousands of women have each year. We know that many women do not require continuous monitoring of their baby's heart rate. However, sometimes this may become necessary during labour, so we want to let all women know about the study so they can think about whether they would like to take part or not. Agreeing to take part in the study will not determine whether or not you receive monitoring - this decision is made by you and your health professionals.

We hope that 46,000 women across the UK and Ireland will agree to participate in this study, of whom 23,000 will receive standard care and 23,000 will have standard care as well as use the 'intelligent' computer system.

Do I have to take part?

No. It is up to you to decide whether or not to take part. If you do decide to take part, you will be given this information leaflet to keep and be asked to sign a consent form. You are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

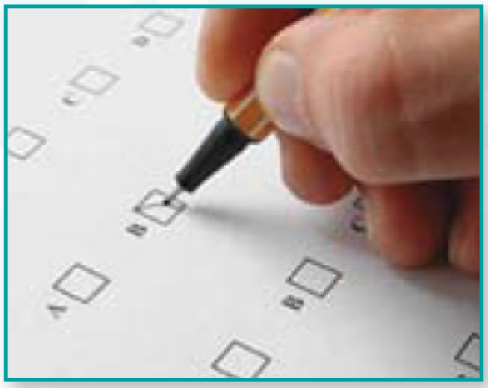
What would happen to me if I take part?

If you are happy to take part in the study, you will be asked to sign a consent form. If then continuous electronic fetal monitoring is started, your electronic monitoring would then be either (i) standard care, with your health care team looking at your readings from the monitor, or (ii) your monitoring will be looked at by the 'intelligent'

computer system as well as your health care team. The decision about which group you would be in would be made by chance, rather like the toss of a coin. This is important because it ensures that the 'intelligent' computer will be tested fairly.

What would being in the study involve?

Information will be collected during your labour on a monitoring machine. This information will be kept strictly confidential. We will also record details of when you and your baby are discharged from the hospital, and details of any treatments you and your baby receive whilst in hospital. For the majority of women this is all the information and contact that you would have with the INFANT study – and we would be pleased to include you and your baby. We would also like to register your baby's inclusion in the INFANT study with the NHS Information Centre (IC) to provide ongoing information on your baby's health status to the study team until the end of the study – this would not involve any direct contact from the study or the NHS IC.



However, we would also like to find out a bit more about 7,000 of the 46,000 babies that enter the INFANT study. This would involve asking for an extra consent and signature from you that would allow the study team to contact you with some questionnaires at 1 and 2 years after the birth of your baby. These questionnaires would ask how your baby is and about their and your general health and in some cases there would be a questionnaire asking about how often you have used the NHS since giving birth. The women and babies followed up would be chosen by chance from those that agree to the further follow-up.

There are no further tests or hospital visits or any payments available for taking part in this study.

What are the possible benefits of taking part?

We cannot promise the study will help you but the information we get from this study may help improve the care provided to women in labour in the future.

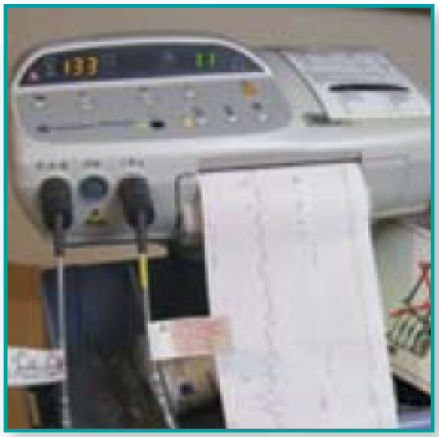
Will my taking part in the study be kept confidential?

Yes. All information we collect about you will be handled in confidence. This completes the introduction to the study. If, after reading this, the study sounds like something you may be interested in and you are considering taking part, please read the following additional information before making any decision.

Additional Information about the INFANT study

More about continuous monitoring

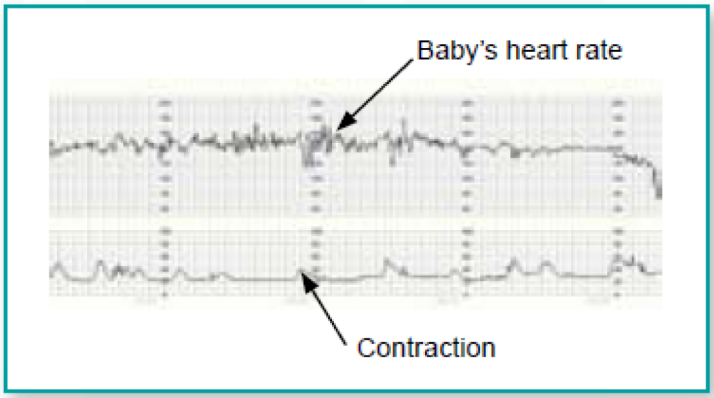
Most babies have no problems coping with labour, but there are a few who don't cope so well. During contractions blood can't get through the placenta so easily. This is normal and most babies cope without any problems. If a baby is not coping well, this may be reflected in the pattern of their heart rate. About 60% of women in the UK have continuous monitoring of their baby's heart rate during labour, with a machine called a cardiotocograph or CTG . This machine allows doctors and midwives to monitor your baby's heart rate and your contractions and record them.



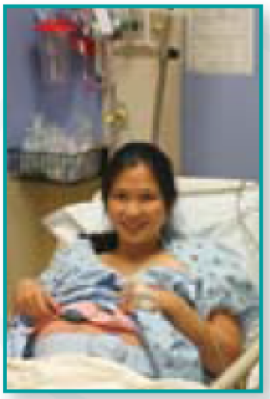
A CTG machine

The computer that displays the traces

This recording is obtained by placing two plastic pads onto your abdomen: one records the heart rate; one records the contractions, and it sends the outputs from them to a computer that is next to the bed in every labour room.



An example of a trace from the CTG



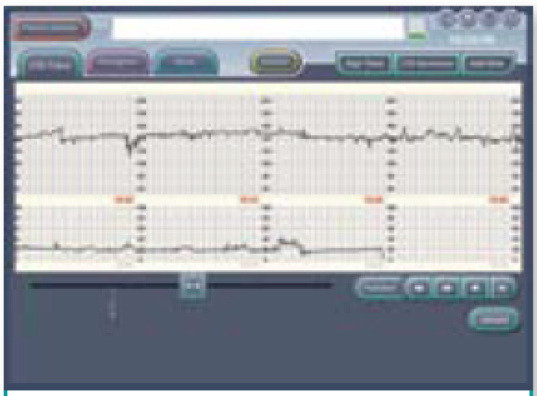
A woman with the CTG pads attached

Participant Information Sheet REC Ref: 09/H0903/31 September 2012, Version 6

Continuous monitoring keeps track of your baby's heart rate for the whole of your labour and allows doctors and midwives to check on the health of your baby.

Being attached to the monitor can limit your ability to move around. You should still be able to stand or sit up, although it may not be possible to have a bath or walk around. Ask your midwife to help you get as comfortable as possible. In some cases, you may be asked for permission to apply a small clip called a Fetal Scalp Electrode (FSE) to the skin on the baby's head. This is then connected to the CTG machine to obtain a more accurate recording.

Currently in the UK, doctors and midwives regularly look at the traces produced by the CTG machine to decide how best to look after you and your baby. In this study, half of the women that agree to take part and go onto receive continuous electronic fetal monitoring, would also have a computer system also looking at the traces. The computer system will tell the doctors and midwives if there are any changes to the baby's heart rate that the doctors and midwives need to be aware of. The computer system will do this by changing the colour of the bar at the top of the computer screen that is showing the CTG. At times the monitor may also give out a sound when the computer screen has changed colour.



An example of what the screen looks like if your labour is looked at by the computer system as well as the doctors and midwives

However, for all women, the final decisions made about you and your baby's care is by the doctors and midwives, the 'intelligent' computer is just giving them more information.

You mention sending a questionnaire later. What will the questionnaire contain?

The questionnaire is in two parts. One section will ask about how your child is, and the second section about how you are. A small number of the families that agree to be followed up will also be invited to complete an additional questionnaire about how often they have visited their GP and hospital over the 2 years after giving birth. The questionnaire will be posted out from the co-ordinating office at University College London. Once completed, it can be returned in a freepost envelope (no stamp required), which is supplied. The first questionnaire will be sent twelve months after giving birth, and the second one will be sent twelve months after the first.

Will my taking part in this study be kept confidential?

All information that is collected about you during the course of the research will be kept strictly confidential. In order to be able to contact you about your own and your baby's health in the future, your name and contact details will be made available to the researchers running this study and held at the co-ordinating centre in London, and not just your local study doctor. These details will be kept securely, with access restricted. You will not be named or otherwise identified in any study publication.

Who is organising and funding the research?

Researchers at the Clinical Trials Unit (CTU) at University College London are organising this research and work with the doctors and midwives in hospitals around the UK and Ireland.

The National Coordinating Centre for Health Technology Assessment (part of the Department of Health/UK Government) is funding the research.

Who has approved the study?

This study has been reviewed and given a favourable opinion by a NHS Research and Ethics Committee (REC). The REC looks after the rights, well being and dignity of patients. The REC reference number is given on the front page of this document. This study was also reviewed by the National Coordinating Centre for Health Technology Assessment before it was awarded funding to ensure it met the necessary scientific standards.

Is there a contact point where I can seek independent advice about participating in the study?

If you would like more information about the study itself you can ask to speak to the lead doctor or midwife for the INFANT study at this hospital. These details are on the back page of this leaflet.

The hospital's PALS Office (Patient Advice and Liaison Service) can also be contacted. They will give you advice about how to contact someone for independent advice. Ask one of the doctors or midwives for their office details.

Are there any risks?

This study is evaluating if the addition of a computer system is of help to doctors and midwives. You will still receive the same level of monitoring from the doctors and midwife whether you participate in the study or not.

What if there is a problem?

If you have a concern about any aspect of this study, you should first speak to the lead INFANT study Doctor or the INFANT study Research Midwife. If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. Details can be obtained from the hospital.

Compensation for harm arising from an accidental injury and occurring as a consequence of your participation in the study will be covered by University College London. If you are harmed and this is due to someone's negligence then you may have grounds for legal action for compensation against University College London (in respect of any harm arising out of participation in the study) or the NHS (in respect of any harm which has resulted from the clinical procedure being undertaken).

Where can I find the results of the study?

The results of the study will be published in a medical journal and on the study website when the study has finished (www.ucl.ac.uk/ctu/infant). We will send out a summary of the study findings to all participants when the study is published. You will not be identified in any report or publication.

Thank you for taking time to read this information.

Local contacts

{_LEAD_}

{_MIDWIVES_}

INFANT Study Co-ordinating Team

[redacted]

[redacted]

This study is being organised by the Clinical Trials Unit at University College London. One of the aims of the Unit is to improve the care provided to women and their families during pregnancy, childbirth and the period after birth, as well as the care provided to the newborn.
www.ucl.ac.uk/ctu/infant

[redacted]

Appendix 3 Consent form

INFANT STUDY

Consent Form

Northern & Yorkshire REC Reference: 09/H0903/31
Version 8 – September 2012
ISRCTN98680152

Please complete in **black** ballpoint pen

Title of project: A study of an intelligent system to support decision making in the management of labour using the cardiotocograph – the INFANT study.

Chief Investigator: Professor Peter Brocklehurst

		Please initial box
1.	I can confirm that I have read and understand the information sheet (Version 6, dated September 2012) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	1
2.	I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my/my baby's medical care or legal rights being affected.	2
3.	I give permission that sections of my/my baby's medical record can be looked at by responsible individuals involved with the study and transcribed onto the study forms.	3
4.	I understand that relevant sections of my/my baby's medical notes and data collected during the study may be looked at by individuals from the Sponsor or Funder, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my/my baby's records.	4
5.	I understand that information held by the NHS and records maintained by the NHS Information Centre and the NHS Central Register or national equivalent may be used to provide information about my/my baby's health status.	5
6.	I agree to take part in the above study. _____	6

Name of woman (please PRINT)	Name of person taking consent (please PRINT)
Signature	Signature
D D / M M / Y Y	D D / M M / Y Y

Follow-Up Assessment

In 1 and 2 years time, we would like to find out how some of the babies born to women in this study are getting on. This is part of the same study but you can be in INFANT without being involved in the follow-up. We are hoping to send questionnaires to parents of about 7,000 infants. Please complete this section so we know if you are happy to be sent questionnaires or not.

I would be prepared to be contacted for follow-up questionnaires and understand that information held by the NHS and records maintained by The NHS Information Centre and the NHS Central Register or national equivalent may be used to help contact me and provide information about my health status.

Yes ☐ No ☐ D D / M M / Y Y

Signature

Allocation:

Study number:

[redacted]

WHITE copy to LCM's tray; PINK copy to LCM's tray; YELLOW copy to the woman; BLUE copy to woman's notes.

Consent Form REC REF: 09/H0903/31 Version 8 September 2012 Page 1 of 1

Appendix 4 Training summary

A multicentre randomised controlled trial of an intelligent system to support decision making in the management of labour using the cardiotocogram

Training Booklet

for Midwives and Doctors

Version 6 May 2012

Contents

1. Introduction to the INFANT study

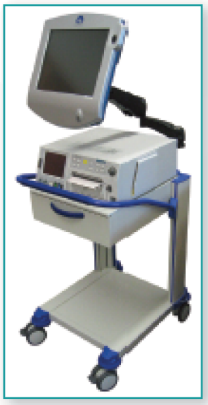
The INFANT (INtelligent Fetal AssessmeNT Monitoring) study commenced recruitment in January 2010. It is a multicentre randomised controlled trial which is taking place throughout the United Kingdom and Ireland. The study is being co-ordinated by a team at the UCL Clinical Trials Unit, based in London and local hospital based obstetricians and midwives. The study is funded by the UK Department of Health through the National Institute for Health Research, Health Technology Assessment Programme (NIHR HTA).

The aim of the study is to determine if the addition of an "intelligent" (decision-support) software giving real time analysis of cardiotocographs (CTG) to midwives and obstetricians reduces the incidence of intrapartum neonatal mortality and morbidity. The "intelligent" computer system is a piece of software that runs on the Guardian® labour system. In real time it looks for baseline rate, fetal heart rate variability, accelerations, type and timing of decelerations, short term variability rate, the quality of the signal and the contraction pattern. If the software detects an abnormal fetal heart rate (FHR) or contraction pattern, these should be highlighted on the screen.

The software has been designed by K2 Medical Systems and currently only runs on the Guardian® labour system, which is currently in use within this hospital.

The objectives of the INFANT study are to determine if the decision-support software compared to current practice will:

- Result in fewer "poor neonatal outcomes"
- Identify more clinically significant heart rate abnormalities
- Result in more prompt and timely action on clinically significant heart rate abnormalities
- Change the incidence of operative interventions



The study aims to recruit at least 46,000 women over 36 months across 10-12 sites in the UK and Ireland. Women will be split into 2 groups of 23,000. One group will receive the "intelligent" software program also known as decision-support (intervention arm) whilst the other group will be monitored conventionally and not have the decision-support software program (control arm). As this study is a randomised controlled trial, the woman, midwife or obstetrician will not have any control over what group/arm a woman gets entered into - it is a random allocation made by a computer server.

2. How will women know about the INFANT study?

There are three leaflets about research and the INFANT study that we are asking maternity sonographers and community/hospital based midwives to give to women at booking appointments, 20 week scans, 34 week midwife appointments and also when admitted in early/established labour.

Leaflet 1 – "Clinical Trials & Research in Pregnancy" (A4 – Trifold leaflet) – should be given out at the booking visit.

Leaflet 2 – "INFANT Study - Antenatal Information for Women" (A4 – Trifold leaflet) – should be given out at the 20 week anomaly scan.

Leaflet 3 – "INFANT Study – Participant Information Leaflet" (A5 booklet) – should be given out at the 34 week midwife visit, and when admitted for induction or in labour. However it can be given out at anytime during pregnancy.

Women who meet the inclusion criteria (listed below) should always be asked upon admission to delivery suite whether they have received any information about the study. If they have not, they should be given leaflet 3. (The National Childbirth Trust and other recognised antenatal tutors are also asked to help inform women about the INFANT study).

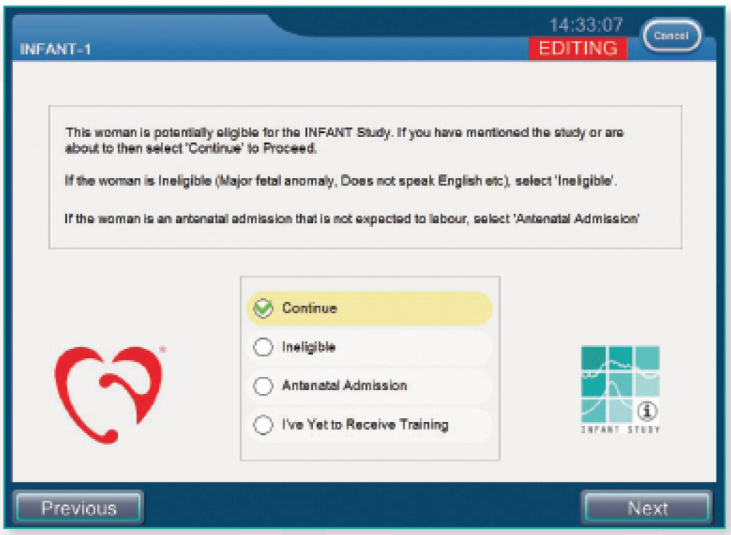
3. Who is included in the INFANT study?

All women admitted in labour who fit the following criteria:

- Singleton or twins
- ≥ 35+0 weeks gestation
- ≥ 16 years old
- No major fetal antenatal anomalies including cardiac arrhythmias such as heart block
- Able to give consent to participate in the study

All women who fit the above criteria should be approached for their consent to take part in the study whether they require continuous electronic fetal monitoring (EFM) or not. Whenever the Guardian® labour monitor is switched on and the usual admission screens entered (woman's ID, parity etc), the system will identify whether a woman is eligible for the INFANT study and prompt you to ask the woman about the study.

Example of "prompt screen"



4. How will women be entered into the INFANT study?

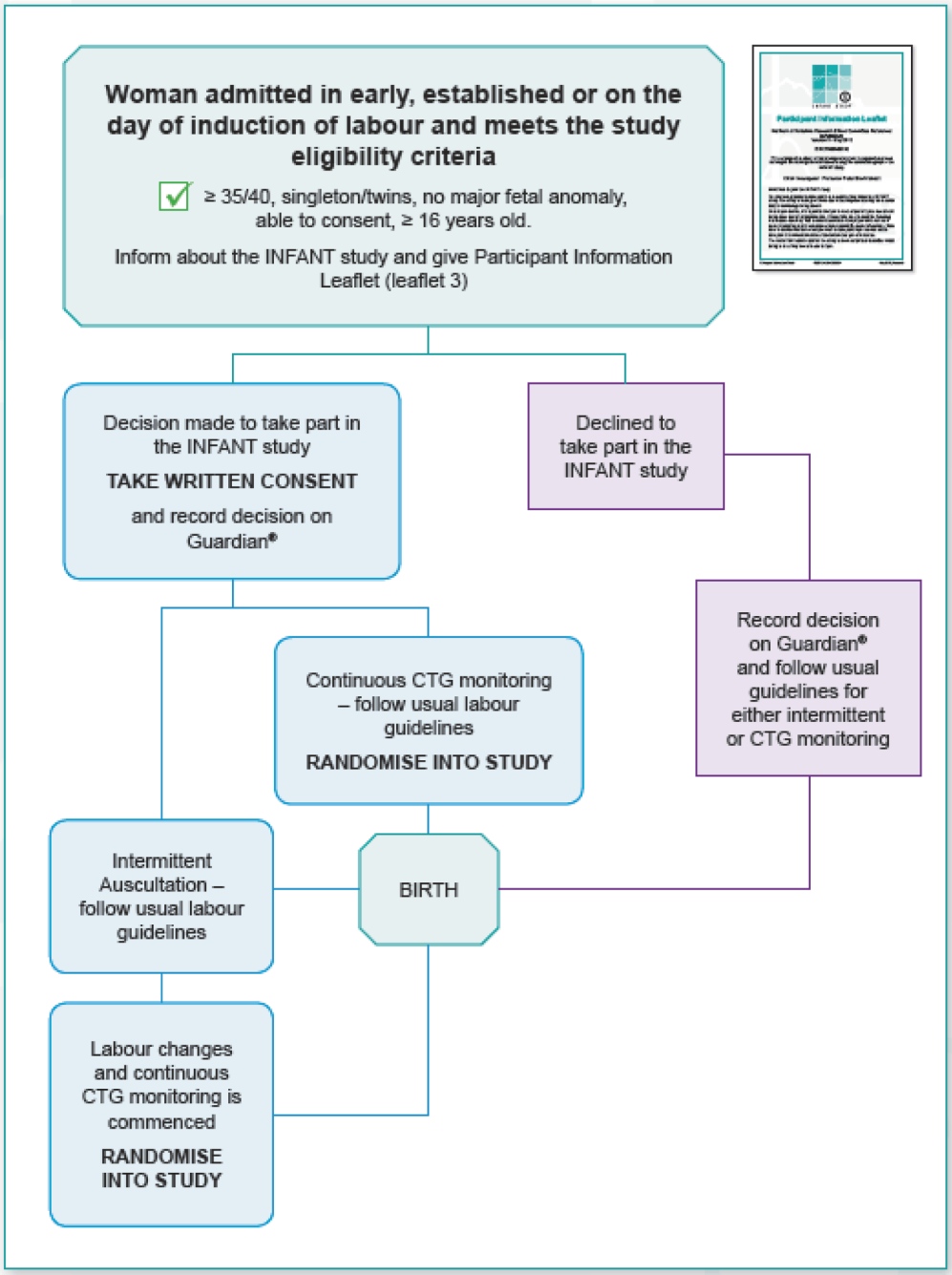
It is important that women are asked about participation in the study **as soon as they are admitted** in early or established labour, or on the day of induction of labour. This gives them the opportunity to read the "Participant Information Leaflet" and decide whether or not they wish to take part in the study. A simple explanation of what the study involves should be given by the primary midwife carer alongside the leaflet and any questions the woman has should be answered. Important points to note:-

a) If a woman does not wish to take part in the study, their care will not be altered in any way and the midwife should follow local guidelines for labour monitoring and no consent paperwork needs to be completed. However it is important that "No" to participating in the study is ticked on the admission screens so that the woman's decision is recorded on Guardian®.

b) If a woman agrees to take part in the study then the midwife/doctor must ask them to sign a study consent form (see pages 3-5 for consent guidance) and record this decision on Guardian®.

c) **It is important that all women who consent to take part in the study sign a consent form, even if they are going to be monitored intermittently. This means that the consent is already gained, and if later on in labour they are judged to require and accept continuous CTG monitoring they can be automatically entered into the study.**

Figure 1: Approach and randomisation for the INFANT Study



5. Taking informed consent for research

What is informed consent?

Informed consent is the process by which a woman voluntarily confirms her willingness to participate/allow their inclusion in something that is asked of them. Women must be informed of the benefits and risks of taking part in any study or procedure that they consent to, and they MUST be given the opportunity to ask questions about the topic concerned.

When and where should consent be taken?

When admitting a woman to delivery suite, the INFANT Participant Information Leaflet (leaflet 3) should be given to all eligible women along with a brief introduction to the study. (It is hoped that for the majority of women this will not be the first time that the INFANT study is mentioned).

Who should take consent in the INFANT study?

Consent can be taken by any health care professional who has received training from an INFANT local co-ordinating midwife (LCM) in taking consent for the INFANT study and has signed the study delegation log. If you are unsure whether you are able to take consent, you should contact your INFANT LCM.

When taking consent you should use language which is easy to understand and which is free from jargon. It is important to ensure that open and approachable body language is used. There should not be a time pressure put on the woman to make a choice as she needs to make an informed decision. Finally, the woman should understand that by not giving consent it will **not** affect the standard of care that she or her baby/babies receive.

NOTE WOMEN ARE ONLY RANDOMISED INTO THE INFANT STUDY WHEN IT HAS BEEN DECIDED TO UNDERTAKE CONTINUOUS CTG MONITORING – THEREFORE THERE WILL BE A LARGE PROPORTION OF WOMEN WHO GIVE SIGNED CONSENT THAT NEVER BECOME FULLY ELIGIBLE FOR THE STUDY.

Eight point consent checklist for taking informed consent

1. Have you given the woman an opportunity to read the INFANT Participant Information Leaflet?
2. Have you explained, and has the woman understood, the aim of the INFANT study?

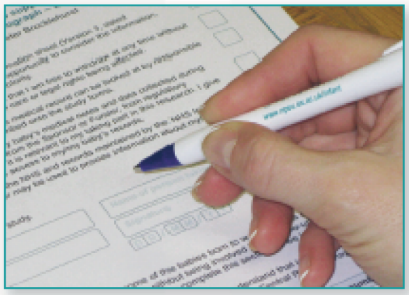
   To see if the addition of a software program can increase the number of babies born without difficulties.
3. Have you explained what the study entails – including a description of the software and that they might or might not have it. Also that all women are being approached on admission to the unit and only if continuous CTG monitoring commences will they actually be eligible – they will then be asked again verbally if they are happy to take part.

   We are always looking for ways we can improve the way we monitor babies heart rates in labour. Half of those who take part will have the computer program and half will not. We are asking all potentially eligible women in case they become eligible in the course of their labour – this would be if continuous CTG monitoring is started. However there will be a significant proportion of women who consent who never become eligible for randomisation.
4. Have you explained what a 'randomised controlled study' is?

   A study in which people are allocated at random (by chance alone) to receive one of several inteventions, in this case the decision-support software or not.
5. Have you explained the potential benefits and risks of taking part in the INFANT study?

   The benefits are that a computer will be constantly looking at the CTG as well as a midwife if the decision-support software is turned on. If the woman is allocated to no software they will still receive the same high level of care as is usual within the UK and Ireland. The potential risks of the study are minimal. It is possible that the use of decision-support software may change the number of procedures in labour, however a pilot study in Plymouth did not show any rise in caesarean section or instrumental births.
6. Have you explained that the woman is free to withdraw at any time without having to give a reason and without affecting her midwifery/obstetric care?
7. Have you explained the purpose of the 2 year follow-up?

   This is to determine if the software affects babies and their mothers in the longer term. Not all of those that agree to be followed up will be contacted, only 8,400 women and their babies will be followed up.
8. Does the woman consider they have had enough opportunity to ask questions?



If a woman agrees to take part in the study – ensure that a consent form is signed and dated by the woman and also the person taking consent *(see consent form example below)*.

Guidelines on what to do when:

A woman declines to give consent: There should be no consent form completed. On the Guardian® platform the option "No" should be ticked to the question of would the woman like to take part in the INFANT study.

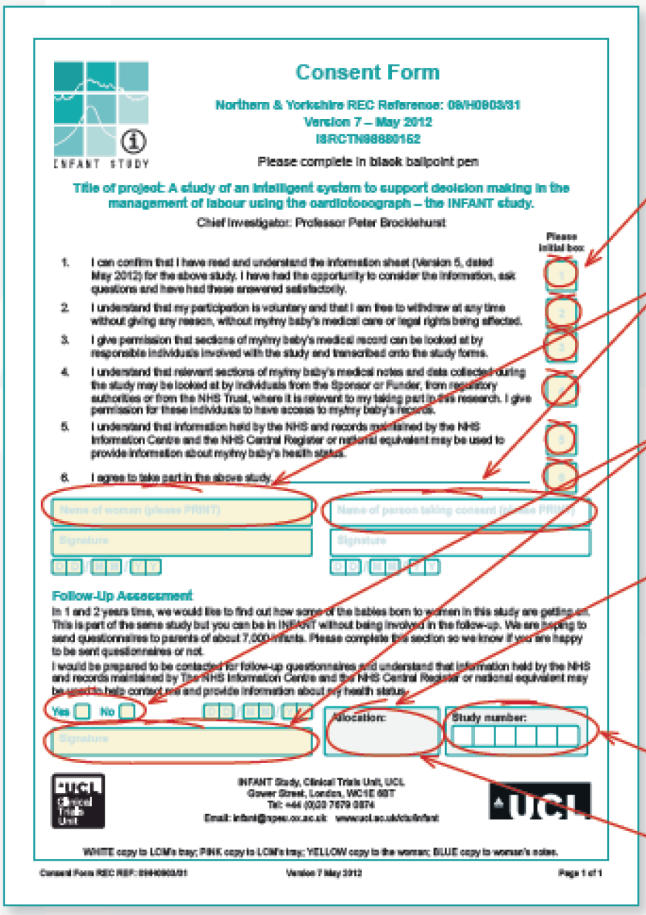
A woman consents but is not randomised: If at the end of labour a woman who consented to the study DID NOT undergo continuous CTG monitoring and thereby did not become fully eligible and was not randomised, "No CTG" should be written in the allocation box. The top and pink copy of the consent form should be put in the INFANT local co-ordinating midwife's tray; the yellow copy given to the woman and the blue copy should be filed in the notes.

A woman is randomised: Make sure the 6 digit study number for the woman and the allocation, either conventional or decision-support as stated on the Guardian® platform, is written on the consent form. The top and pink copy of the consent form should be put in the INFANT local co-ordinating midwife's tray; the yellow copy given to the woman and the blue copy should be filed in the notes.

A woman is not eligible: There should be no consent form completed.

A woman changes her mind once randomised: If this happens the midwife should write "withdrawn from the study" on the consent form, and then press the "INFANT admin" button which will give the option to withdraw the women from the study. Labour care should continue as normal.

Example of an INFANT study consent form



Consent Form

Northern & Yorkshire REC Reference: 09/H0903/31
Version 7 – May 2012
ISRCTN98880162

INFANT STUDY

Please complete in black ballpoint pen

Title of project: A study of an intelligent system to support decision making in the management of labour using the cardiotocograph – the INFANT study.

Chief Investigator: Professor Peter Brocklehurst

Please initial box

1. I can confirm that I have read and understand the information sheet (Version 5, dated May 2012) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my/my baby's medical care or legal rights being affected.
3. I give permission that sections of my/my baby's medical record can be looked at by responsible individuals involved with the study and transcribed onto the study forms.
4. I understand that relevant sections of my/my baby's medical notes and data collected during the study may be looked at by individuals from the Sponsor or Funder, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my/my baby's records.
5. I understand that information held by the NHS and records maintained by the NHS Information Centre and the NHS Central Register or national equivalent may be used to provide information about my/my baby's health status.
6. I agree to take part in the above study.

Name of woman (please PRINT) | Name of person taking consent (please PRINT)

Signature | Signature

Date | Date

Follow-Up Assessment

In 1 and 2 years time, we would like to find out how some of the babies born to women in this study are getting on. This is part of the same study but you can be in INFANT without being involved in the follow-up. We are hoping to send questionnaires to parents of about 7,000 infants. Please complete this section so we know if you are happy to be sent questionnaires or not.

I would be prepared to be contacted for follow-up questionnaires and understand that information held by the NHS and records maintained by the NHS Information Centre and the NHS Central Register or national equivalent may be used to help contact me and provide information about my health status.

Yes ☐ No ☐

Signature

Allocation:

Study number:

UCL Clinical Trials Unit

INFANT Study, Clinical Trials Unit, UCL
Gower Street, London, WC1E 6BT
Tel: +44 (0)20 7679 0874
Email: infant@ucl.ac.uk www.ucl.ac.uk/ctu/infant

UCL

WHITE copy to LOM's tray; PINK copy to LOM's tray; YELLOW copy to the woman; BLUE copy to woman's notes.

Consent Form REC REF: 09/H0903/31 Version 7 May 2012 Page 1 of 1

Filling in the consent form accurately

Ensure all 6 statements are initialled **NOT ticked** by the woman

The woman and the person taking consent must print their names, sign and date the form

The follow up assessment must be ticked yes or no, signed and dated by the woman

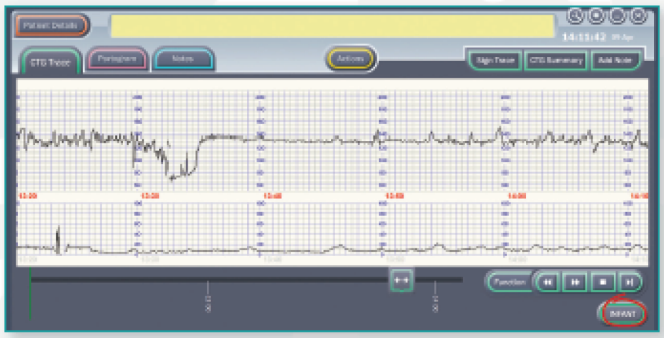
Clearly write the words decision-support OR conventional as stated on the Guardian® platform in the allocation box

The 6 digit study number will be given by Guardian® when a woman is randomised and should be written in the study number box by the midwife/ doctor. If the woman was monitored intermittently the words "NO CTG" should be written in the allocation box at the end of labour

6. How does randomisation actually take place?

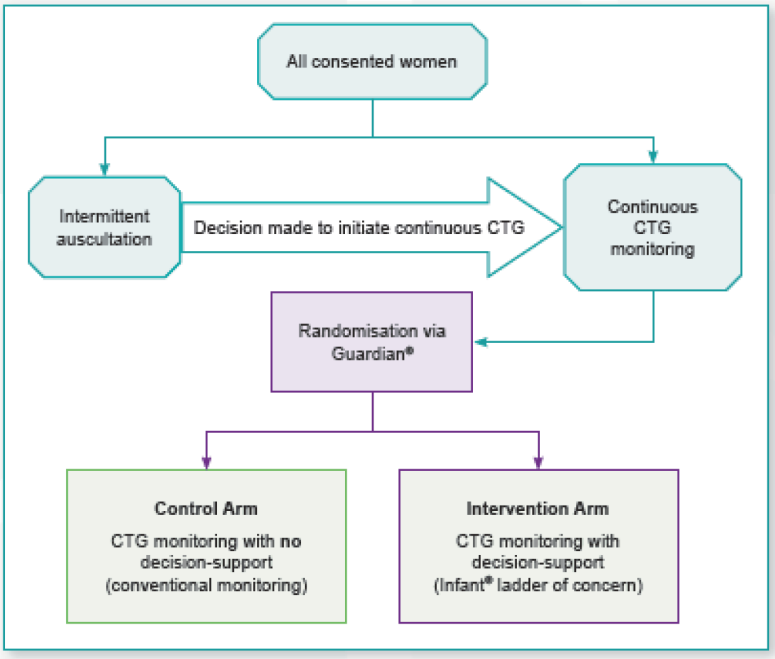
The Guardian® labour platform will prompt the midwife to record whether or not a woman has given consent to take part in the Study. Once the button of consent is pressed, there will be a series of prompts that will allow the midwife to easily randomise a woman into the INFANT study if continuous CTG monitoring is being undertaken. She/he will reach a page that will give a six digit randomisation number (generated automatically by Guardian®) and the woman's allocation. **It is very important to write this number on the bottom of the consent form in the study number box and document the woman's allocation, decision-support or conventional monitoring, in the allocation box.**

If the woman has been allocated to the control arm (conventional monitoring), the Guardian® monitor will display the CTG as usual with only the INFANT button showing in the bottom right hand of the screen. This can be pressed if a woman wishes to withdraw from the study at any point in their labour.



If a woman has been allocated to the intervention arm (where the decision-support software is active) the Infant® ladder of concern (see page 7) will appear at the right hand side of the woman's details situated at the top of the screen. The midwife should briefly inform the woman not to be anxious if she hears any "alerts or voice prompts" that the software may produce. The woman must be reassured that if a midwife is out of the room at anytime she should call via the call bell system and someone will review the rationale of the alert as soon as possible.

Figure 2: The process of randomisation into the control or intervention arms



7. How to use the Infant® Software on the Guardian® labour platform

The main identifier of the Infant® software on the Guardian® labour platform is the Infant® ladder of concern. This ladder is positioned next to the patient details and will indicate a colour coded system identifying any concern that it may have and highlight what the concern is. Below are examples of the ladder's colour codes.

GREEN (Level 4) – Indicates that the software has **no concerns** with the CTG

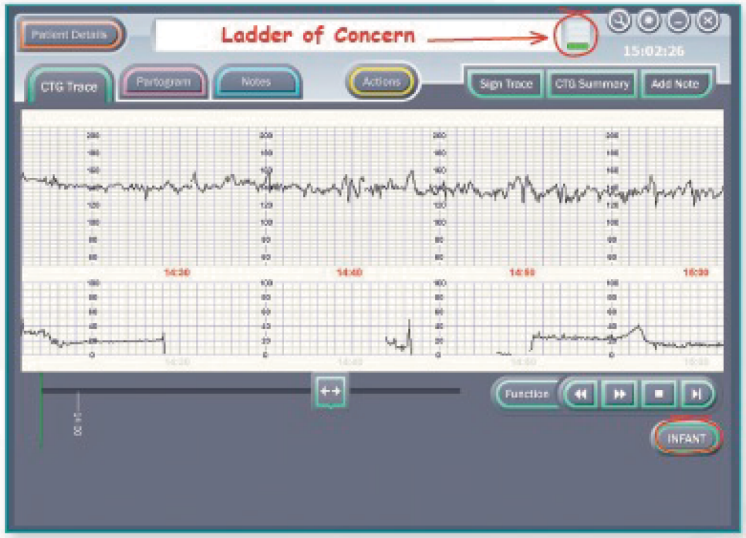
BLUE (Level 3) – Indicates that the software has **minor concerns** with the CTG

YELLOW (Level 2) – Indicates that the software has **serious concerns** with the CTG

RED (Level 1) – Indicates that the software has **urgent concerns** with the CTG

Example of Guardian® running with the Infant® software switched ON

Infant® GREEN LADDER OF CONCERN

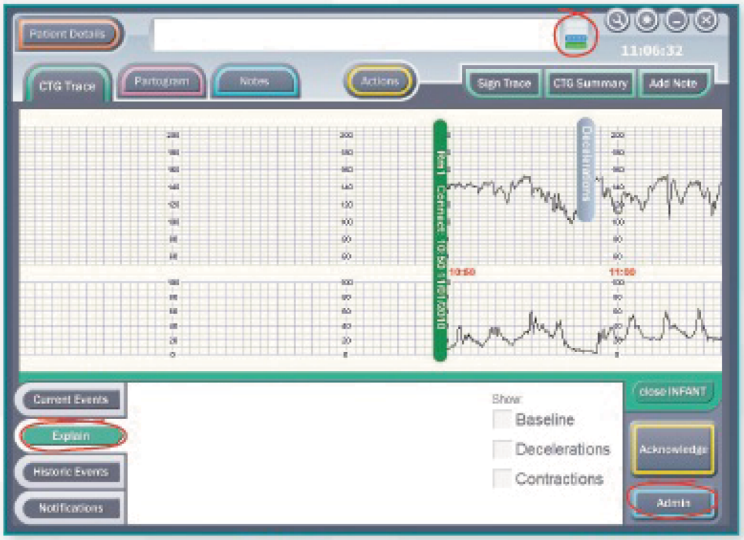


The midwife/doctor can recognise that the woman is in the intervention/decision-support arm of the study because the Infant® ladder of concern is present at the top of the screen, next to the woman's details.

In this example the level of concern showing on the ladder is GREEN indicating that the software has NO CONCERNS.

It is important to note that throughout the study all women who are monitored continuously will have the INFANT button displayed on the screen. This does NOT necessarily mean that the woman is in the study or the "intervention" arm. If the woman is not in the intervention arm or the study, this button acts as an administration button. If pressed it will allow you to enter the woman into the study if she is eligible, has given written consent, and has not been previously randomised.

Infant® BLUE LADDER OF CONCERN



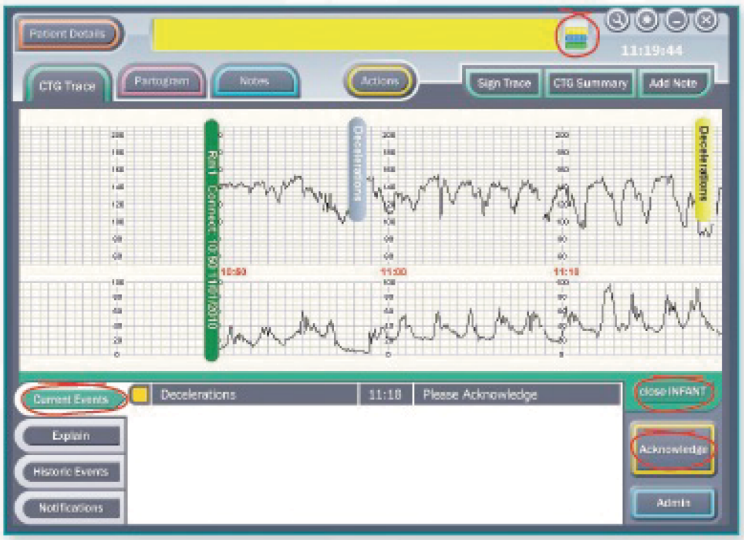
The Infant® ladder of concern is displaying **BLUE** indicating that there are now **MINOR CONCERNS**. The minor concern that it has noted is a deceleration.This is identified by a blue longitudinal marker (Infant® event marker) on the CTG.

Once a blue level of concern has occurred the software will only downgrade it to a green once the event is over and the CTG is reassuring. The midwife does not need to acknowledge any blue events on the Guardian® platform.

In this screen shot the "Explain" button has been opened. If any of the boxes entitled baseline, decelerations or contractions are ticked by the midwife/doctor, the software will show on the CTG trace where it has identified these i.e. if the baseline was ticked it would show in blue at 145 bpm (see page 10).

The "Admin" button, if pressed, will give options if the woman wishes to withdraw from the study. It is expected that this should be an extremely unusual event.

Infant® YELLOW LADDER OF CONCERN



Once the software has noted several incidents it will trigger a **YELLOW** alert, indicating **SERIOUS CONCERNS**. The ladder will now be "flashing" yellow. The bar with the woman's details will also turn yellow and the concern will be noted on the CTG by a yellow Infant® event marker. Alongside this visual display a tone will sound after **5 minutes and repeat at regular intervals** until it has been acknowledged by a midwife or doctor.

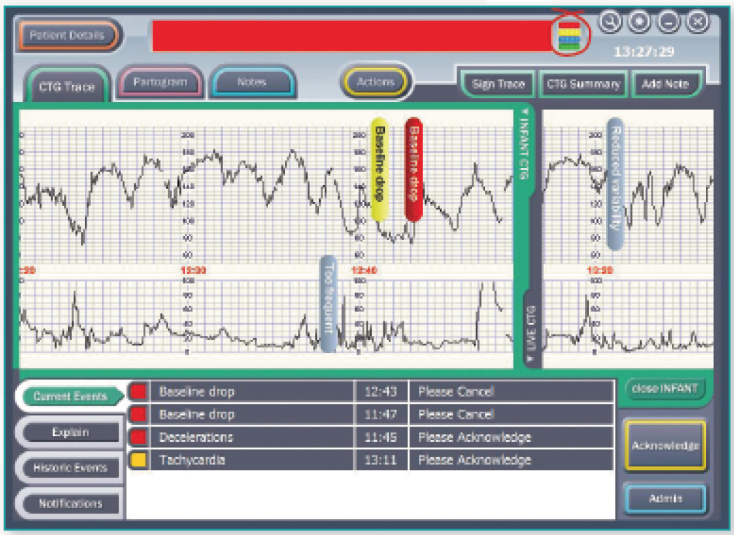
To acknowledge the alert, the acknowledge button must be pressed and the midwife/doctor must then "thumbprint" to complete the acknowledgment. Once this is done the ladder will remain a constant yellow until the software recognises that the incident is over. Only when the Infant® software recognises that the event is over will it downgrade the alert to a **BLUE**/**GREEN** status. The midwife's/doctor's name who acknowledged the alert will appear next to the description of the alert under the current events, to show that they were the person who acknowledged the alert.

NB: If this tone is not acknowledged **after 10 minutes,** a voice message stating "Warning, there are some anomalies with the trace, please acknowledge" will be sounded **at regular intervals** until it is acknowledged.

A yellow alarm automatically triggers the current events screen to open to show the detail of the concern i.e. decelerations so that the midwife/doctor can review and acknowledge the alert.

To return to the screen with no current events shown, all open current events must be acknowledged and the "close INFANT" button pressed. This will then stay closed until another level of concern is noted or until the INFANT button (shown on page 7) is pressed by the user. This does not turn the Infant® software off. If the screen displays an Infant® ladder of concern, the software is on.

Infant® RED LADDER OF CONCERN



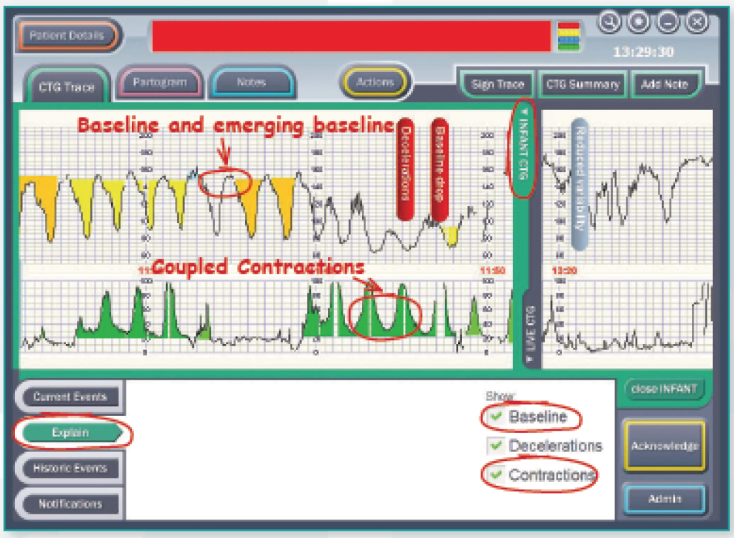
In the above screen shot the Infant® ladder of concern is **RED**. The ladder will now be "flashing" **RED** indicating **URGENT CONCERNS**. The bar with the woman's details will also be highlighted in red and the Infant® event marker on the CTG will be red.

An audible warning tone (slightly different to the yellow alert) will sound **after 2 minutes** and repeat at regular intervals to alert the midwife/doctor that the software has detected some **URGENT CONCERNS**. If the tone remains unacknowledged for a period of **2 minutes** a vocal warning stating "Warning, the trace is abnormal, senior review is urgently required" will sound at regular intervals until the midwife/doctor acknowledges the alert.

The alert is acknowledged by pressing the "acknowledge" button and using the thumbprint recognition. Once this has been acknowledged, the ladder will remain a constant **RED** until the software recognises that the incident is over and downgrades the level of concern to **YELLOW**, **BLUE** or **GREEN** if applicable.

When a RED concern is triggered, the midwife would be expected to not only acknowledge the alert with a thumbprint but to get a senior member of the labour ward team to review the CTG.

Infant® EXPLAIN ALERT FUNCTION



When an alert is noted by the colour change on the Infant® ladder of concern the midwife or doctor can question the decision-support software to observe three characteristics of the trace (baseline, decelerations, and contractions). This can be done anytime during the labour and not just when a concern state is triggered. This is done by pressing the "Explain" button and ticking the boxes of what you want to see. The decision-support software can highlight in different colours the various concerns. If you wanted to see the frequency of contractions, you would tick the contractions option and the contractions would be highlighted for you to clearly review.

The fetal heart rate/contractions are colour coded with the following colours:

Baseline: Blue

Emerging Baseline: Green

Decelerations: Shallow – Pink; Insignificant – Green; Moderate – Yellow; Severe – Orange

Contractions: Normal – Green; Coupled - Dark Green; Red – if they have pushing detected on them

In the above screen shot the left hand side of the trace is showing the Infant® review CTG. This trace will show the position of any Infant® event if selected from the current event list window or can be scrolled by the user to review the trace in its entirety.

The right hand side of the trace will show the latest 10 minutes of real time CTG data.

The dividing banner clearly defines the traces.

Please note, if a woman is randomised to the intervention arm (decision-support software turned on) this should not affect your care of the woman. You should still be manually reviewing the CTG as you would for a woman randomised to the control arm or not in the study. The decision-support software is meant to be an additional review and not a replacement.

8. Guardian® Central Station

The central station has been adapted to incorporate the Infant® study software. The above screen shot demonstrates how the CTGs will appear if they have the Infant® software running. The Infant® ladder of concern will show on the left hand side of the CTG if the woman is randomised into the decision-support arm. Rooms 1, 2 and 3 are displaying the Infant® ladder of concern whereas the trace in the bottom right hand corner from theatre 2 does not have the Infant® study software running alongside it. This woman is either in the control arm of the study or not in it at all.

At the top of the screen the delivery room boxes are highlighted to correlate with the colour coding on the Infant® ladder of concern. For example the Infant® study software in room 1 has noted that the trace is non-reassuring which has escalated the Infant® concern state to red, the room number at the top of the screen has also turned red. If the room number is flashing, this indicates that the alert has not yet been acknowledged. In the table at the bottom of the screen the end column is also displaying a red number 1 – this indicates that the Infant® software has been triggered to the highest concern state. Theatre 2 has a black box around it which indicates that the woman is in the control arm of the study. If there is not a black outline or a colour in these boxes the woman is not randomised into the study.

It is extremely important to note that a CTG can be running even if the room boxes are grey – a grey box only indicates that the Infant® study software is not running alongside the CTG. All CTGs must still be consistently reviewed by midwives and doctors.

NB: Central stations may not be available in all hospitals.

9. Articles/Journals of Interest

Altaf, S., C. Oppenheimer, et al. (2006). "Practices and views on fetal heart monitoring: a structured observation and interview study." *British Journal of Obstetrics and Gynaecology* 113(4): 409-18.

Amer-Wahlin, I., C. Hellsten, et al. (2001). "Cardiotocography only versus cardiotocography plus ST analysis of fetal electrocardiogram for intrapartum fetal monitoring: a Swedish randomised controlled trial." *Lancet* 358(9281): 534-8.

Ayres-de-Campos D., et., A randomised clinical trial of intrapartum fetal monitoring with computer analysis and alerts versus previously available monitoring. BMC Pregnancy Childbirth, 2010: 10:71

Ayres-de-Campos D., et al., Knowledge of adverse neonatal outcome alters clinicians' interpretation of the intrapartum cardiotocograph. BJOG, 2011: 118(8): 978-84.

Barber V.S., et al Computers and CTG: where are we at?. British Journal of Midwifery, 2010: 18(10): p. 644-649.

Chester, B. (1998). "Electronic Fetal Monitoring: A brief summary of its development, problems and prospects." *European Journal of Obstetrics and Gynaecology* 78: 133-40.

Costa A., et al., Access to computerised analysis of intrapartum cardiotocographs improves clinicians' prediction of newborn umbilical artery blood pH. BJOG, 2010; 117(10): 1288-93

Devoe, L. D. (2009). "The future of intrapartum care: navigating the perfect storm--an obstetrician's odyssey." *American Journal of Obstetrics and Gynecology* 201(1): 100-4.

Georgieva, A., S. J. Payne, et al. (2009). "Computerised electronic foetal heart rate monitoring in labour: automated contraction identification." *Medical Biological Engineering and Computing* 46(12): 1315-20.

Hindley, C. and A. M. Thomson (2005). "The rhetoric of informed choice: perspectives from midwives on intrapartum fetal heart rate monitoring." *Health Expectations* 8(4): 306-14.

Medicines and Healthcare products Regulatory Agency, Medical Device Alert (Action Update).Ref: MDA/2010/054.

Sameshima, H., T. Ikenoue, et al. (2004). "Unselected low-risk pregnancies and the effect of continuous intrapartum fetal heart rate monitoring on umbilical blood gases and cerebral palsy." *American Journal of Obstetrics and Gynecology* 190(1): 118-23.

Sinclair, M. (2001). "Midwives' attitudes to the use of the cardiotocograph machine." *Journal of Advanced Nursing* 35(4): 599-606.

Stout, M, et al., Electron Fetal Monitoring: Past, Present, and Future. Clin Perinatol, 2011: 38; 127-142.

Please note: The full text of the above journal papers can be located in the INFANT study resource file in Delivery suite, Community Office, Ultrasound Scan Department and the Antenatal Clinic.

A copy of the full INFANT study protocol can also be found in the resource files or ask your INFANT LCM for a copy. The protocol can also be found at www.npeu.ox.ac.uk/infant

Appendix 5 Data collection form for a baby admitted to a neonatal unit

INFANT STUDY

Post Birth Data Collection Form B (Baby)

INFANT Study number: | | | | | | |

Please tick which baby this form refers to:
Baby 1 ☐ Baby 2 ☐

This form should only be completed if a baby delivered to a woman randomised in the INFANT study received a higher level of care (e.g. NICU/SCBU) for any period of time **OR** *had surgery following its birth.*

Please complete this form for care received by this baby in this hospital:

Baby's first name: _____ **Baby's surname:** _____

Category of Neonatal Care

1. **What type of higher care did this baby receive?** *(please tick all that apply)*
   - A. **Normal Care:** Care given by the mother or mother substitute with medical and neonatal nursing advice if needed. (*If this is the only care given please go to question 2*) . . . . . ☐
   - B. **Special Care:** A nurse should not be responsible for care of more than four babies receiving Special or Normal Care
     Special care is provided for all other babies who could not reasonably be expected to be looked after at home by their mother. . . . . ☐
   - C. **High Dependency Care:** A nurse should not be responsible for the care of more than two babies in this category -
     1) receiving NCPAP for any part of the day and not fulfilling any of the criteria for intensive care
     2) below 1000g current weight and not fulfilling any of the criteria for intensive care
     3) receiving parenteral nutrition
     4) receiving oxygen therapy and below 1500g current weight
     5) requiring treatment for neonatal abstinence syndrome
     6) requiring specific procedures that do not fulfil any criteria for intensive care:
        Care of an intra-arterial catheter or chest drain
        Partial exchange transfusion
        Tracheostomy care until supervised by a parent
     7) requiring frequent stimulation for severe apnoea.. . . . . ☐
   - D. **Intensive Care:** These babies have the most complex problems. They need 1:1 care by a nurse with a neonatal qualification. The possibility of acute deterioration is such that there should be the constant availability of a competent doctor
     1) receiving any respiratory support via a tracheal tube and in the first 24 hours after its withdrawal
     2) receiving NCPAP for any part of the day and less than five days old
     3) below 1000g current weight and receiving NCPAP for any part of the day and for 24 hours after withdrawal
     4) less than 29 weeks gestational age and less than 48 hours old
     5) requiring major emergency surgery, for the pre-operative period and post-operatively for 24 hours
     6) requiring complex clinical procedures:
        Full exchange transfusion

Post Birth Data Collection Form (B) Version 3 May 2012

STUDY OFFICE USE ONLY:
First Entry: ☐ Second Entry: ☐

INFANT Study number: ☐☐☐☐☐☐

Peritoneal dialysis
Infusion of an inotrope, pulmonary vasodilator or prostaglandin and for 24 hours afterwards

7) any other very unstable baby considered by the nurse-in-charge to need 1:1 nursing: for audit, a register should be kept of the clinical details of babies recorded in this category

8) a baby on the day of death . . . . ☐

Please give details of length of stay and reasons for admission to higher level of care:

Level of Unit *(Please give the level of unit as per the bold headings above using the appropriate letter)*	Date & time of admission	Date & time of discharge	Main reason for admission *(e.g. infection, respiratory problems)*	Treatment(s) received *(e.g. cooling, parenteral nutrition etc)*
	DD/MM/YY hh:mm 24hr	DD/MM/YY hh:mm 24hr		
	DD/MM/YY hh:mm 24hr	DD/MM/YY hh:mm 24hr		
	DD/MM/YY hh:mm 24hr	DD/MM/YY hh:mm 24hr		
	DD/MM/YY hh:mm 24hr	DD/MM/YY hh:mm 24hr		
	DD/MM/YY hh:mm 24hr	DD/MM/YY hh:mm 24hr		
	DD/MM/YY hh:mm 24hr	DD/MM/YY hh:mm 24hr		

2. **Was this baby admitted to Neonatal care/Neonatal Unit (whatever level) within 48 hours of birth for a period of ≥ 48 hours?** Yes ☐ No ☐

Surgery or Referral to a Surgeon

3. **Did this baby undergo any surgery or surgery referrals following its birth (including paracentesis) before its discharge from hospital?** Yes ☐ No ☐

If Yes, please give details below:

Date of surgery/ surgical review	Type of surgery/ Nature of surgical review (state if review or if surgery conducted)	Hospital of surgery (if not hospital of birth)
DD/MM/YY		
DD/MM/YY		
DD/MM/YY		

Post Birth Data Collection Form (B) Version 3 May 2012

STUDY OFFICE USE ONLY:
First Entry: ☐ Second Entry: ☐

INFANT Study number: ☐☐☐☐☐☐

Investigations

4. **Did this baby undergo any of the following investigations after trial entry?** *(please tick all that apply)*

- Ultrasound scans ☐
  - If ticked, how many? ☐☐
- X-rays ☐
  - If ticked, how many? ☐☐
- MRI ☐
  - If ticked, how many? ☐☐
- Stand alone ECGs ☐
  - If ticked, how many? ☐☐
- CT-scan ☐
  - If ticked, how many? ☐☐
- Septic screens ☐
  - If ticked, how many? ☐☐
- EEG ☐
  - If ticked, how many? ☐☐

Conditions/diagnoses/treatments

5. **Did this baby receive any respiratory support (ventilator or CPAP)?** Yes ☐ No ☐
   If Yes, total number of days receiving respiratory support (ventilator or CPAP) (Include any part of a day as a day) ☐☐☐ days

6. **Did this baby receive any non-mechanical supplemental oxygen (e.g. nasal specs/head box)?** Yes ☐ No ☐
   If Yes, total number of days receiving supplemental oxygen days (Include any part of a day as a day) ☐☐☐ days

7. **Did this baby have seizures whilst in this hospital?** Yes ☐ No ☐
   If Yes, were they treated? Yes ☐ No ☐

8. **Did this baby have neonatal encephalopathy (NNE)?** Yes ☐ No ☐
   If Yes, please complete a NNE chart for each day of the baby's higher level of care. Please state when this form is completed how many NNE assessments are included in this form ☐☐☐

9. **Did this baby have any feeding difficulties?** Yes ☐ No ☐
   If Yes, please indicate whether any of the following were used:
   - Tube feeding ☐
   - Parenteral feeding ☐

10. **Did the baby achieve full oral sucking feeds before discharge or transfer?** Yes ☐ No ☐
    If Yes, what date did the baby achieve full oral sucking feeds? D D / M M / Y Y

Post Birth Data Collection Form (B) Version 3 May 2012

STUDY OFFICE USE ONLY:
First Entry: ☐ Second Entry: ☐

INFANT Study number: ☐☐☐☐☐☐

OUTCOME – *Please complete either box A, B or C*

A) Discharge Home

11. **Was the baby discharged home?** Yes ☐

12. **Date of discharge home:** D D / M M / Y Y

B) Transfer

13. **Was the baby discharged to another hospital?** Yes ☐ No ☐

Date of transfer: D D / M M / Y Y

If Yes, please give details of where the baby was transferred to: _____

_____

_____

Please describe how the baby was transferred:

Ambulance ☐

Helicopter ☐

Other (*please specify*): _____

C) Death

14. **Did the baby die?** Yes ☐ No ☐

Date of death: D D / M M / Y Y

If Yes, has a cause of death been identified? Yes ☐ No ☐

If Yes, please provide details on what was written on the death certificate:

_____

_____

_____

_____

_____

Has a post-mortem been performed? Yes ☐ No ☐

Form completed by *(please PRINT)* _____ **Date:** D D / M M / Y Y

[redacted] [redacted] [redacted]

Post Birth Data Collection Form (B) Version 3 May 2012

Appendix 6 Data collection form for a baby with neonatal encephalopathy

INFANT STUDY

Post Birth Data Collection Chart B (Baby)
Neonatal Encephalopathy Data

INFANT Study number: ☐☐☐☐☐☐

Please tick which baby this form refers to: Baby 1 ☐ Baby 2 ☐

*This form should **only** be completed if a baby delivered to a woman randomised in the INFANT study had neonatal encephalopathy (NNE). 1 form should be completed for every day a baby is in a higher level of care and has been classified as having NNE.*

Please complete this form for care received by this baby in this hospital:

Baby's first name: _____ **Baby's surname:** _____

Day (1)

Date of assessment _____ **Date:** D D / M M / Y Y

1. Did this baby have neonatal encephalopathy? Yes ☐

Please circle the corresponding answer to the below hypoxic ischaemic encephalopathy signs. *(Indicate most severe manifestation and please circle EVERY sign)*

Sign	0	1	2	3
Tone	Normal	Hyper	Hypo	Flaccid
LOC	Normal	Hyper- alert, stare	Lethargic	Comatose
Fits	None	Infrequent <3/day	Frequent >2/day	
Posture	Normal	Fisting, cycling	Strong distal flexion	Decerebrate
Moro	Normal	Partial	Absent	
Grasp	Normal	Poor	Absent	
Suck	Normal	Poor	Absent/bites	
Respiration	Normal	Hyperventilation	Brief apnoea	Apnoeic
Fontanelle	Normal	Full, not tense	Tense	

Did the baby undergo therapeutic hypothermia to treat encephalopathy? Yes ☐ No ☐
Was cerebral function assessed by aEEG? Yes ☐ No ☐
Was cerebral function assessed by EEG? Yes ☐ No ☐

If Yes to aEEG OR EEG, *please summarise the findings:* _____

_____

_____

_____

_____

Name: *(please PRINT)* _____ **Date:** D D / M M / Y Y

STUDY OFFICE USE ONLY: First Entry: ☐ Second Entry: ☐

Post Birth Data Collection Form (B2 NNE) Version 3 May 2012

INFANT STUDY

Post Birth Data Collection Chart B (Baby)
Neonatal Encephalopathy Data

INFANT Study number: | | | | | | |

Please tick which baby this form refers to:
Baby 1 ☐ Baby 2 ☐

*This form should **only** be completed if a baby delivered to a woman randomised in the INFANT study had neonatal encephalopathy (NNE). 1 form should be completed for every day a baby is in a higher level of care and has been classified as having NNE.*

Please complete this form for care received by this baby in this hospital:

Baby's first name: _____ **Baby's surname:** _____

Day ☐☐☐

Date of assessment _____ **Date:** D D / M M / Y Y

2. Did this baby have neonatal encephalopathy? Yes ☐

Please circle the corresponding answer to the below hypoxic ischaemic encephalopathy signs. *(Indicate most severe manifestation and please circle EVERY sign)*

Sign	0	1	2	3
Tone	Normal	Hyper	Hypo	Flaccid
LOC	Normal	Hyper- alert, stare	Lethargic	Comatose
Fits	None	Infrequent <3/day	Frequent >2/day	
Posture	Normal	Fisting, cycling	Strong distal flexion	Decerebrate
Moro	Normal	Partial	Absent	
Grasp	Normal	Poor	Absent	
Suck	Normal	Poor	Absent/bites	
Respiration	Normal	Hyperventilation	Brief apnoea	Apnoeic
Fontanelle	Normal	Full, not tense	Tense	

Did the baby undergo therapeutic hypothermia to treat encephalopathy? Yes ☐ No ☐
Was cerebral function assessed by aEEG? Yes ☐ No ☐
Was cerebral function assessed by EEG? Yes ☐ No ☐

If Yes to aEEG OR EEG, *please summarise the findings:* _____

_____

_____

_____

_____

Name: *(please PRINT)* _____ **Date:** D D / M M / Y Y

STUDY OFFICE USE ONLY: First Entry: ☐ Second Entry: ☐

Post Birth Data Collection Form (B2 NNE) Version 3 May 2012

Appendix 7 Data collection form for a neonatal death

INFANT STUDY

Death of a baby in the INFANT study

Date: {_DATE_} Site name: {_SITE_NAME_}

Dear LCM,

You have received this form as the death of a baby at your centre has been registered in the study office. Please could you check and amend this form as appropriate, and then return it to the study office.

Mother's study number: {_STUDY_NUMBER_}

Baby's details: {_BABY_DETAILS_}

Name: {_NAME_}

NHS Number: {_NHS_NUMBER_}

Date of death: {_DEATH_DATE_}

Our records show the following: *(please tick each line if correct, if not please amend)*

Cause of death identified? {_DEATH_IDENTIFIED_} ☐

Cause of death given: {_DEATH_CAUSE_} ☐

Postmortem performed? {_POSTMORTEM_} ☐

Did the baby have the presence of a congenital anomaly? Yes ☐ No ☐

If Yes, what was the congenital anomaly? _____

Did the congenital anomaly contribute to the baby's death? Yes ☐ No ☐

Any other comments regarding this death: _____

_____

_____

_____

_____

_____

_____

Form completed by : *(please PRINT name)* _____

Date completed: D D / M M / Y Y

[redacted] [redacted] [redacted]

Post Birth Data Collection Form (Death) Version 3 May 2012

Appendix 8 Data collection form for a mother admitted to a higher level of care

INFANT STUDY

Post Birth Data Collection Form M (Mother)

INFANT Study number:

Please complete firmly in **black** ballpoint pen

Please complete this form for all women who received a higher level of care (e.g. ICU/HDU care) OR who had surgery OR a procedure in theatre following their delivery.

Mother's surname: _____

Surgery/Procedure

1. **Did this woman undergo any surgery/procedure in theatre following her delivery (not including a caesarean section)?** Yes ☐ No ☐

If Yes, *please give details below*:

Date of surgery	Type of surgery	Hospital of surgery (If not hospital of delivery)
D D / M M / Y Y		
D D / M M / Y Y		
D D / M M / Y Y		
D D / M M / Y Y		

Higher Level Of Care & Investigations

2. **Did this woman receive a higher level of care following her delivery?** *(e.g. ICU/HDU care) including HDU care on the delivery suite post delivery.* Yes ☐ No ☐

If Yes, what type of higher level of care did this woman receive? *(please tick all that apply)*

High Dependency Unit or Area
(this includes if the HDU care was on the delivery suite post delivery) . . . . . ☐
Intensive Care Unit . . . . . ☐
Specialist unit e.g. dialysis unit . . . . . ☐
Type of specialist unit *(please state)*: _____

Please give details of length of stay and reasons for admission to higher level of care:

Type of Unit	Date & time of admission	Date & time of discharge	Main reason for admission	Treatment(s) received *(e.g. ventilation, dialysis etc)*
	D D / M M / Y Y h h : m m 24hr	D D / M M / Y Y h h : m m 24hr		
	D D / M M / Y Y h h : m m 24hr	D D / M M / Y Y h h : m m 24hr		
	D D / M M / Y Y h h : m m 24hr	D D / M M / Y Y h h : m m 24hr		
	D D / M M / Y Y h h : m m 24hr	D D / M M / Y Y h h : m m 24hr		

Post Birth Data Collection Form (M) Version 3 May 2012

STUDY OFFICE USE ONLY:
First Entry: ☐ Second Entry: ☐

INFANT Study number: ☐☐☐☐☐☐

3. **Did this woman undergo any of the following investigations after trial entry prior to her discharge from hospital or death?** *(please tick all that apply)*

Ultrasound	☐	If ticked, how many?	☐
MRI	☐	If ticked, how many?	☐
CT-scan	☐	If ticked, how many?	☐
X-ray	☐	If ticked, how many?	☐

OUTCOME – *Please complete **either** box A, B or C*

A. Discharge Home

4. **Was the woman discharged home?** Yes ☐ No ☐

5. **Date of discharge home:** DD/MM/YY

B. Transfer

6. **Was the woman discharged to another hospital?** Yes ☐ No ☐

Date of transfer: DD/MM/YY

If Yes, please give details of where the woman was transferred to: _____

_____

Please describe how the woman was transferred:

Ambulance ☐

Helicopter ☐

Own transport ☐

Other (*please specify*): _____

C. Death

7. **Did this woman die?** Yes ☐ No ☐

Date of death: DD/MM/YY

If Yes, has a cause of death been identified? Yes ☐ No ☐

If Yes, please provide details: _____

_____

Has a post-mortem been performed? Yes ☐ No ☐

Name: *(please PRINT)* _____ **Date:** DD/MM/YY

[redacted]

Post Birth Data Collection Form (M) Version 3 May 2012

Appendix 9 Two-year follow-up questionnaire

INFANT STUDY

Parent's Questionnaire

INFANT Study number: {_SN_}

[redacted]

Your Child's details

Surname: {_BABY-SURNAME_}

First names: {_BABY-FIRST-NAME_}

Date of Birth: {_DOB1_}

Only complete if different:

Surname: _____

First name: _____

(Please correct any of these details if they have changed)

- This questionnaire should be completed by a child's parent or main care giver. Please answer the questions as best as you can.
- The questionnaire will take you about 15 minutes to fill in. We appreciate it can be difficult to find the time but your answers are a very important part of this study and will help other mothers like you in the future.The details you give us about your child's progress will be used to find out whether computer support to monitor babies heart rates in labour is helpful.
- All the information you give will be treated in the strictest confidence and will only be seen by staff working on the study.
- Please answer the questions as completely as you can. If you have any difficulties with the questions you can phone the INFANT office to ask for help on 020 7679 0874 (UK residents) or 44 207 679 0874(Ireland residents), we would then be happy to call you back.

Is the address this form was sent to correct? Yes ☐ No ☐

If No, please give us your correct address and postcode

What is your telephone number? *(include area code)*

Who completed this form? Mother ☐ Father ☐ Other ☐

If Other, please specify _____

What was the date this form was completed? DD/MM/YY

Name of person completing this form: _____

INFANT Main 24 Questionnaire V3 09/H0903/31 Version 3, Apr 2013

INFANT Study number: { _ S N _ }

A) Your Child at Play

Below is a list of activities we would like you to fill in about your child. It is aimed for children between 18 months to 4 years of age. Some will be easy for your child, others may be difficult. Most children of your child's age will not be able to do many of the activities so please do not worry.

Please fill in every question.

	Yes	No	Don't Know
1. **Does your child copy things you do such as cuddling a teddy?** *(Try it out if not sure by cuddling the teddy and then giving it to your child. Say: Now you cuddle teddy)*	☐	☐	☐
2. **When you hide a toy in full view of your child, will he/she look for it and find it?** *(Try this out by covering a small toy with a cloth or a cup and seeing if he/she uncovers the toy)*	☐	☐	☐
3. **Can your child put a simple piece, such as a square or an animal, into the correct place in a puzzle board?**	☐	☐	☐
4. **Some toys have several holes or openings with different shapes such as a circle, triangle and star. Could your child put the shapes into the right openings?**	☐	☐	☐
5. **Can your child stack two small blocks or toys on top of each other by him/herself?**	☐	☐	☐
6. **Can your child put together, by him/herself, a puzzle or something similar where the pieces fit together?**	☐	☐	☐
6a. If Yes, can he/she do this for a puzzle with ten or more pieces?	☐	☐	☐
7. **Can your child mark on a piece of paper using the tip of a crayon, pencil or chalk?**	☐	☐	☐
8. **Can your child draw a more or less straight line on paper?**	☐	☐	☐
9. **Does your child turn, or try to turn, pages of a book one at a time?**	☐	☐	☐
10. **Does your child ever pretend that one object, such as a block is another object, such as a car or a telephone?**	☐	☐	☐
11. **Can your child stack three small blocks or toys on top of each other by him/herself?**	☐	☐	☐
12. **Does your child pretend to do things? For example, riding a horse or making a cup of tea?**	☐	☐	☐
13. **Can your child push a car along the floor with the wheels on the floor?**	☐	☐	☐
14. **Does your child look with interest at pictures in a book?**	☐	☐	☐
15. **Does your child point to pictures in a book?**	☐	☐	☐
16. **Does your child try to copy things you do, such as stirring with a spoon in a cup?**	☐	☐	☐

INFANT Study number: { _ S N _ }

	Yes	No	Don't Know
17. Can your child stack seven small blocks or toys on top of each other by him/herself?	☐	☐	☐
18. Does your child point or show where people or objects are when you ask: "Where is the light?" "Where is Daddy?" or "Where is Teddy?"	☐	☐	☐
19. Does your child ever pretend that two dolls are playing together, or are talking to each other, or one is feeding the other?	☐	☐	☐
20. Does your child play pretend games with another child, pretending to be someone else, such as a mummy, daddy, policeman or nurse?	☐	☐	☐
21. Does your child every play any game with another child that involves taking turns?	☐	☐	☐
22. Does your child ever copy some action shortly (within a few minutes) after he/she has seen it?	☐	☐	☐
23. Can your child fetch something, such as a toy, from another room by him/herself when you ask?	☐	☐	☐
24. Does your child know where some things belong, such as, that his/her toys belong in a box?	☐	☐	☐
25. Does your child ever save or put to one side a biscuit (or other snack) for later, on his/her own?	☐	☐	☐
26. Have you ever seen your child get together three or more toys before beginning to play with them?	☐	☐	☐
27. Have you ever seen your child sort things (blocks, other toys) into groups or piles that go together on his/her own?	☐	☐	☐
28. If your child wants something out of reach, does he/she go and find a chair or box to stand on?	☐	☐	☐
29. When your child uses or plays with a telephone, does he/she speak into the mouthpiece not the earpiece?	☐	☐	☐
30. When your child drinks from a cup, is he/she careful about putting it down trying it not to spill it?	☐	☐	☐
31. Does your child try to turn doorknobs, twist tops or screw lids on or off jars?	☐	☐	☐
32. Does your child recognise him/herself when looking in the mirror?	☐	☐	☐
33. Does your child ever use his/her index (first) finger to point to show an interest in something?	☐	☐	☐

INFANT Study number: { _ S N _ }

B) What Your Child Can Say

Does your child use any recognisable words *(this includes signed words)*? Yes ☐ No ☐

If Yes, approximately how many? ☐☐☐

If No, do they use any sounds that you understand? Yes ☐ No ☐

If Yes, how many? ☐☐☐

If No, *please go to the next section*

Children understand many more words than they say. We are particularly interested in the words your child SAYS. Please TICK all the words you have heard your child use. If your child uses a different pronunciation of a word – for example "tend" for "pretend" or "duce" for "juice" – tick it anyway. This is only a sample of words; your child may know many other words not on this list

Words children say *(Please tick each box that applies)*

☐ baa baa	☐ cream cracker	☐ bed	☐ carry	☐ last
☐ meow	☐ juice	☐ bedroom	☐ chase	☐ tiny
☐ ouch/ow	☐ meat	☐ settee/sofa	☐ pour	☐ wet
☐ uh-oh/oh dear	☐ milk	☐ oven/cooker	☐ finish	☐ after
☐ woof woof	☐ peas	☐ stairs	☐ fit	☐ day
☐ bear	☐ hat	☐ flag	☐ hug/cuddle	☐ tonight
☐ bird	☐ necklace	☐ rain	☐ listen	☐ our
☐ cat	☐ shoe	☐ star	☐ like	☐ them
☐ dog	☐ sock	☐ swing	☐ pretend	☐ this
☐ duck	☐ chin	☐ school	☐ rip/tear	☐ us
☐ horse	☐ ear	☐ sky	☐ shake	☐ where
☐ aeroplane	☐ hand	☐ zoo	☐ taste	☐ beside
☐ boat	☐ leg	☐ friend	☐ gentle	☐ down
☐ car	☐ pillow	☐ mummy/mum	☐ think	☐ under
☐ ball	☐ comb	☐ person	☐ wish	☐ all
☐ book	☐ lamp/torch	☐ bye/byebye	☐ all gone	☐ much
☐ game	☐ plate	☐ hi/hello	☐ cold	☐ could
☐ sandwich	☐ rubbish	☐ no	☐ fast	☐ need to
☐ fish	☐ tray	☐ shopping	☐ happy	☐ would
☐ sauce	☐ towel	☐ thank you	☐ hot	☐ if

INFANT Study number: { _ S N _ }

C) Your Child's Understanding

We would like to know how your child uses the words s/he can say. Please tick one box for each question below. **Please keep in mind that these questions are for children up to 4 years of age. Many children of your child's age will not be able to say some of the words or sentences below so please do not worry.**

Does your child show he/she understands any words or signs? Yes ☐ No ☐

If No, *please go to section D*

	Often	Sometimes	Not Yet
1. Does your child ever talk about past events or people who are not present? For example, a child who saw a carnival last week might later say 'carnival', 'clown', or 'band'.	☐	☐	☐
2. Does your child ever talk about something that is going to happen in the future? For example, saying "choo-choo" or "bus" before you leave the house on a trip, or saying "swing" when you are going to the park.	☐	☐	☐
3. Does your child talk about objects that are not present, such as asking about a missing toy not in the room, or asking about someone not present?	☐	☐	☐
4. Does your child understand if you ask for something that is not in the room? For example, would he/she go to the bedroom to get a teddy bear when you say "where's the bear?"	☐	☐	☐
5. Does your child know who things belong to? For example, a child might point to Mummy's shoes and say "Mummy".	☐	☐	☐
6. Has your child begun to put together words yet, such as "Daddy gone" or "Doggie bite"?	☐	☐	☐

If you answered "Sometimes" or "Often" to Question 6, *please answer the next few questions on this page.*

If you answered "Not Yet" to Question 6, *please finish this section here and go to Section D.*

For each pair of sentences below – A and B – please tick the one that sounds MOST like the way your child talks at the moment, even if s/he would not say that EXACT sentence. If your child is saying sentences even more complicated than the two examples provided, tick B.

6a. *(Talking about something happening right now)*
- ☐ A: I make tower
- ☐ B: I making tower

6b. *(Talking about something that already happened)*
- ☐ A: Daddy pick me up
- ☐ B: Daddy picked me up

7.
- ☐ A: That my truck
- ☐ B: That's my truck

8.
- ☐ A: Baby crying
- ☐ B: Baby is crying

9.
- ☐ A: There a doggie
- ☐ B: There's a doggie

10.
- ☐ A: Coffee hot
- ☐ B: That coffee hot

11.
- ☐ A: I no do it
- ☐ B: I can't do it

12.
- ☐ A: I like read stories
- ☐ B: I like to read stories

13.
- ☐ A: Biscuit Mummy
- ☐ B: Biscuit for Mummy

14.
- ☐ A: Don't read book
- ☐ B: Don't want you read that book

15.
- ☐ A: Baby want eat
- ☐ B: Baby want to eat

16.
- ☐ A: Look at me
- ☐ B: Look at me dancing

INFANT Study number: { _ S N _ }

D) Your Child's Physical Ability

The questions below are intended to look at your child's physical capabilities.

Please tick the choice below which best describes your child's ability: *(tick one box for each section)*

Walking
- ☐ Walks well without help
- ☐ Has an unsteady walk but doesn't need help
- ☐ Unable to walk without help
- ☐ Unable to walk even with help

Sitting
- ☐ Sits alone for long periods
- ☐ Sits unsupported but unstable (may fall over when sitting alone)
- ☐ Sits only with support
- ☐ Unable to sit

Left hand
- ☐ Uses thumb and tip of index finger
- ☐ Picks up by other means
- ☐ Unable to pick up object

Right hand
- ☐ Uses thumb and tip of index finger
- ☐ Picks up by other means
- ☐ Unable to pick up object

Hands
- ☐ Uses both hands well
- ☐ Has difficulty using one hand
- ☐ Unable to use both hands

Control
- ☐ Controls head movements well
- ☐ Poor control but does not need support
- ☐ Can control head only with support

E) Your Child's Vision

1. **Does your child wear glasses?** Yes ☐ No ☐

   If you answered 'Yes', please tick the box below which best describes your child's ability to see with glasses: *(tick one box only)*

   - Sees well ☐
   - Has some difficulty but sees well enough for everyday activities ☐
   - Has considerable difficulty but can see objects if near ☐
   - Is able to see light only or has no vision ☐

F) Your Child's Hearing

1. **Please tick the box which best describes your child's ability to hear:** *(tick one box only)*

   - Hears well (**if your child hears well,** *please go to section G*) ☐
   - Has some hearing problems but does **NOT** need a hearing aid ☐
   - Hears well or with only a little difficultly **WITH** a hearing aid ☐
   - Has severe hearing difficulty even with a hearing aid or hearing ☐
   - Is not helped with an aid ☐

2. **Is the hearing problem due to recurrent ear infections or 'glue' ear?**

   Yes ☐ No ☐ Don't know ☐

3. **Please describe the reason for your child's hearing problems if you know:**

INFANT Study number: { _ S N _ }

G) Your Child's General Health

1. **What is your child's height?** ☐☐.☐ cm OR ☐.☐☐ m
2. **What is your child's weight?** ☐☐.☐☐ kg OR ☐ st and ☐☐ lbs
3. **Has your child had any fits, seizures or convulsions?** Yes ☐ No ☐
   - **If Yes**, did it (they) happen only when your child had a fever? Yes ☐ No ☐
   - Please tick the choice below which best describes any treatment for your child's seizures *(tick one box only)*
     - No treatment required now ☐
     - On treatment now and has no seizures ☐
     - Has up to 1 seizure every month on treatment ☐
     - Has more than 1 seizure every month on treatment ☐
4. **Please tick the choice below which best describes your child's feeding:** *(tick one box only)*
   - Has no serious feeding difficulty ☐
   - Is fed with a tube passed from nose to stomach ☐
   - Is fed with a tube passed directly into the stomach (gastrostomy) ☐
   - Other ☐
     - **If Other**, please describe: _____
5. **Does your child suffer from coughing?** Yes ☐ No ☐
   - **If No**, *please go to question 7*
   - Does the coughing start with exercise? Yes ☐ No ☐
   - Does the cough start with an infection? Yes ☐ No ☐
     - **If Yes**, to any of the above, please indicate how often: *(tick one box only)*
       - More than once a week ☐
       - Once a week or less but more than once a month ☐
       - Once a month or less ☐
6. **Does your child suffer from wheezing?** Yes ☐ No ☐
   - **If No**, *please go to 8*
   - **If Yes**, please indicate how often: *(tick one box only)*
     - More than once a week ☐
     - Once a week or less but more than once a month ☐
     - Once a month or less ☐
7. **Is your child currently on any medicines for chest symptoms?** Yes ☐ No ☐
   - **If No**, *please go to 9*
   - **If Yes**, please indicate which of the following he/she needs:

Relievers (e.g. ventolin or bricanyl)	Every day ☐	When needed ☐
Preventers (e.g. pulmicort, becotide, flixotide)	Every day ☐	When needed ☐
Steroids (e.g. prednisolone)	Every day ☐	When needed ☐
Antibiotics	Every day ☐	When needed ☐
Other	Every day ☐	When needed ☐

INFANT Study number: { _ S N _ }

8. **Has your doctor told you your child has asthma?** Yes ☐ No ☐

9. **Has your doctor told you your child has cerebral palsy?** Yes ☐ No ☐

If No, *please go to 11*

If Yes, does your child have difficulty using: *(tick one box only)*

- Both legs only? ☐
- Both arms and both legs? ☐
- Right arm and leg only? ☐
- Left arm and leg only? ☐
- Three limbs? (both legs and one arm or both arms and one leg) ☐
- Other ☐

If Other, please describe: _____

10. **Does your child have small jerky or writhing movements of limbs?** Yes ☐ No ☐

11. **Has your doctor told you your child has hydrocephalus?** Yes ☐ No ☐

12. **Does your child have any long-term problems for which he/she is under the care of the doctor?** Yes ☐ No ☐

If Yes, please tell us about these problems and the diagnosis if you know:

_____

_____

Which statement best describes how these problems affect your child's everyday activities?

- No limitation ☐
- Some limitation but able to function independently ☐
- Needs assistance or aids for some activities ☐
- Is completely dependent on you ☐

Is there anything else you would like to tell us about your child?

If you would like a summary of the results of the study when it is complete, please tick this box ☐ and make sure that we have your correct address on this form.

Please check that you have answered every question. If there are any questions you have not answered, because you are unsure how to answer them, please phone the INFANT Co-ordinating Centre on 0207 6790874 (UK residents) or 44207 679 0874 (Ireland residents) and we will try to help.

Please return the completed questionnaire to us in the FREEPOST envelope enclosed.

THANK YOU FOR COMPLETING THIS QUESTIONNAIRE

[redacted]

INFANT Main 24 Questionnaire V3 09/H0903/31 Version 3, Apr 2013

Appendix 10 Economic evaluation analysis plan

INFANT economic evaluation analyses plan

Liz Schroeder

February 2014

Glossary

CEA cost-effectiveness analysis

CUA cost–utility analysis

ICER incremental cost-effectiveness ratio

QALY quality-adjusted life-year

Aims of the INFANT Health Economic Evaluation

As shown above, determining whether or not the use of the decision support software is cost-effective for the management of labour and birth is an objective of the trial. This objective will be met through component studies that address specific research questions (aims).

Firstly to consider the incremental cost of an adverse perinatal outcome prevented at hospital discharge.

However, this outcome is likely to have longer-term consequences in terms of health status and health service utilisation over the infant's lifetime. Two longer-term evaluations are therefore planned.

In the first instance to estimate the cost-effectiveness of the decision support when surviving children reach age 2 years (aim 2), estimated as the incremental cost per disability free life-years gained at 2 years. These estimates will be informed with individual patient level data collected from parents participating in the INFANT trial.

Secondly, to extrapolate long-term outcomes and costs over a lifetime expressed as an incremental cost per quality-adjusted life-year (QALY) gained using decision–analytic modelling techniques (aim 3).

Finally, to explore the potential effect of the intervention on litigation claims for obstetrics (aim 4) in a 'stand-alone' study.

These aims are shown in the following table (*Table 45*).

Methods

Data collection

A prospective economic evaluation is being conducted alongside the trial, with the aim of estimating the cost-effectiveness of the intelligent decision support software. Information on resource utilisation will be collected through the Guardian data collection system, hospital-patient administration and maternity information systems. Observational research methods will be used to collect additional costs in intrapartum, postpartum or neonatal care for the first analysis (study aim 1).

TABLE 45 Aims of the INFANT economic evaluation

	Aim			
	1	2	3	4
Outcome measure	Poor perinatal outcome averted	Disability-free life-years	'derived' QALYs (using clinical diagnosis of mild, moderate or severe outcomes at 2 years)	Predicted changes in obstetric claims (modelled scenarios)
Timeframe	Initial hospital discharge	2 years	Long term (e.g. lifetime/18-year time horizon)	Long term (e.g. lifetime/18-year time horizon)
Data	47,112 women	5–7000 + all primary outcome cases (for which we have 2-year outcome data) 1500 for resource use data	As in (1) & (2) + secondary information derived from literature reviews – mapping economic data between health states obtained from literature	Use of INFANT data for possible changes to baby outcomes, modelled scenarios using litigation information from the NHS LA
Data collection	Guardian system, hospital information system + observational data	As in (1) + parent questionnaires at 1 and 2 years	As in (1&2) + literature reviews	As in 3, + NHS LA 10-year litigation data
Analysis	Intention-to-treat analysis, ICERs and net benefit statistics presented using non-parametric statistical methods with 95% confidence ellipses	As in (1) PARCA-R defined predictors of mild, moderate and severe disability mapped to disability-adjusted life-years	Extrapolation model for long-term outcomes (+ decision-analytic modelling + sensitivity analysis)	Modelled scenarios of changes to clinical practice; baby outcomes; modelled longer-term outcomes and litigation payouts

Postal questionnaires sent to parents at 1 year and 2 years post discharge collect resource use data for the health service over that period (study aim 2).

Decision-analytic modelling methods (or Markov methods if required) synthesising primary INFANT and secondary cost and epidemiological data will be used to estimate the cost-effectiveness of longer-term outcomes (study aim 3).

A stand-alone study exploring litigation for obstetrics in the NHS and the potential effect that this intervention may have, using current primary data sources provided by the NHS LA and outcomes from the trial will also be undertaken (study aim 4).

The recruitment of study participants and data collection for the health economics can be viewed in the following flow chart (*Figure 42*).

Brief overview of cost-effectiveness analysis and cost–utility analysis

Cost-effectiveness analysis (CEA) is a form of economic evaluation that compares the relative costs and outcomes (effects) of two or more courses of action, using a common outcome measure. In cost-effectiveness analyses, the costs are expressed in monetary units, while benefits are expressed in natural or physical units, such as survival, physical abilities and health-related quality of life. CEA involves calculating the difference in costs and difference in outcomes between the health-care interventions being compared, and then expressing these as a ratio. Typically the ratio is measured as a value where the denominator is a gain in health from a measure (years of life, premature births averted) and the numerator is the cost associated with the health gain. The ICER represents the additional cost of one unit of outcome gained by a healthcare intervention or strategy, when compared with the next best alternative, mutually

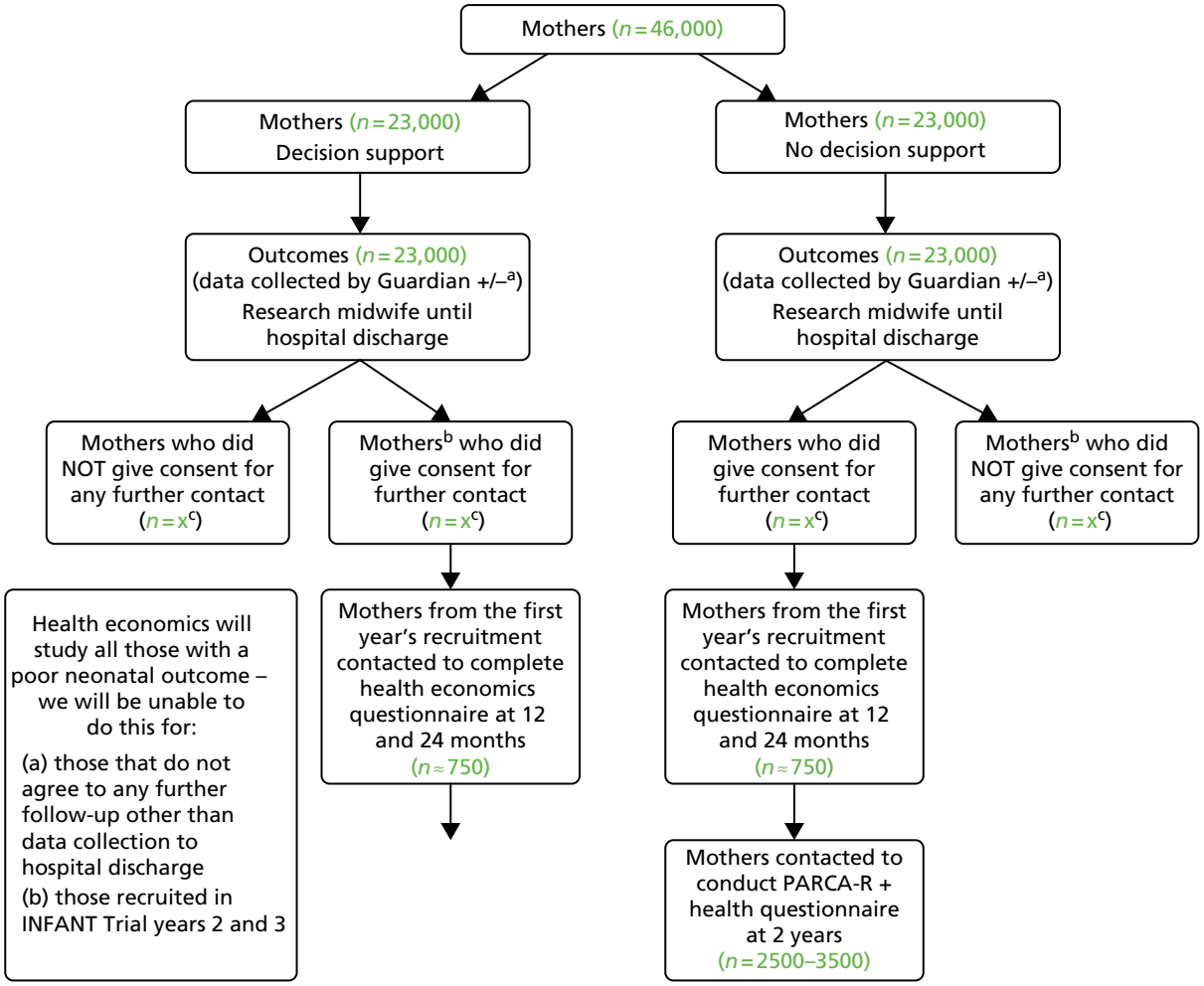


FIGURE 42 Flow chart depicting recruitment and data collection for INFANT health. a, +/– represents with or without additional data collected by the midwife as necessary. b, Only mothers recruited during the first year of the trial so that follow-up of this group can be completed around the time that the trial stops recruiting. c, x represents the actual numbers that would be collected.

exclusive intervention or strategy. Three incremental cost-effectiveness ratios, or ICERs, will represent the additional cost of one unit of outcome gained by the incorporation of the intelligent decision support system for the management of women who are judged to require continuous electronic fetal monitoring (EFM) compared with current clinical practice. These are the incremental cost of poor perinatal outcome prevented at hospital discharge, the incremental cost per disability free life-years gained at 2 years and the incremental cost per quality-adjusted life-year (QALY) gained at 18 years. A threshold value is often set by policy makers, who may decide that only interventions with an ICER below the threshold are cost-effective (and therefore should be funded). Various thresholds around £20,000/QALY and £40,000/QALY gained will be explored in the analysis.

Economic evaluation design issues for INFANT study aims 1 and 2 (within-trial economic evaluation)

Trial design

INFANT is a multicentre individually randomised controlled trial of 47,112 women who are judged to require continuous electronic fetal monitoring in labour. It is a two-arm parallel trial with one arm allocated to CTG monitoring with decision support and one arm allocated to CTG monitoring only. At 2 years after trial entry, a random sample of 5000–7000 children (2500–3500 in each group) are followed up at

2 years. This sample is taken from within the sample recruited during the second year of the trial so that follow-up of this group can be completed around the time that the trial stops recruiting.

For the economic evaluation, a subsample of approximately 750 infants from each trial arm randomly selected within the second year, as well as all babies with the primary outcome who survive to hospital discharge, are followed up at 1 and 2 years for resource use data in order to estimate the incremental cost per disability free life-years gained at 2 years. Decision-analytic modelling techniques will be used to extrapolate cost-effectiveness over a lifetime.

Time horizon and perspective of the INFANT economic evaluation

The economic evaluation will be conducted from a health service perspective and therefore only direct costs to NHS hospital providers will be included. Societal costs, such as travel time and lost productivity to families will not be captured. (Estimates of the longer-term costs of care including litigation costs are discussed in *Economic evaluation design issues for INFANT study aim 3 (modelling longer-term outcomes)* and *Economic evaluation design issues for INFANT study aim 4 (modelling clinical scenarios that will impact on obstetric litigation claims)*.

Sample size and power

The sample size of the INFANT economic evaluation is based on the primary clinical outcomes of the INFANT trial, which is currently a pragmatic approach to the determination of sample size and power calculation. Different techniques have been proposed for the estimation of statistical power and sample size for economic evaluation in randomised trials, but current practice tends to prefer power calculations based on primary clinical outcomes. This is partly because of the complexity of trying to predict the main outcome of interest to economists, which is the joint distribution of the difference in costs and benefits between treatment arms.[6]

Study end points

In the baseline study (study aim 1), we are using an intermediate outcome (poor perinatal outcome prevented at hospital discharge) and hence additional resource use and unit cost data are needed to capture longer-term costs and outcomes. This is the purpose of the study at 2 years where the outcome measure is quantified in terms of disability free life-years gained (study aim 2) and for the extrapolation of longer-term outcomes expressed as QALYs over a lifetime or to 18 years (study aim 3).

Database design and management

Collection and management of the economic data are fully integrated with the management of the clinical data and, as such, there will be no distinction between the data sets for study aim 1. Ongoing data quality monitoring occurs timeously to address missing and poor-quality data issues. Data queries are consistently managed to maximise data completeness and quality. The data formatting procedures needed for the economic analysis were prespecified such that the transfer of all necessary data for the economics study is timely, and the design and piloting of the data capture system is complete. Double data entry for the 12- and 24-month parental questionnaires is in process.

Collection and measurement of trial costs

Trial costs/resource use

The economic evaluation focuses on main cost drivers (such as days spent in intensive care) as well as resources that are expected to differ between the trial arms. All resource use including intervention related resources will be included in the cost analysis. *Table 46* documents the resource use data identified for the health economics component.

For each resource, the level of aggregation will be prospectively determined. As an example, inpatient hospitalizations might be considered in disaggregated units, such as staff time, or in highly aggregated

TABLE 46 Resource use identified in the INFANT economic evaluation

	Trial arm, Mean resource use (SE)		
Resource use variable	Intervention group	Standard care group	Unit cost (£)
Inpatient stay			
Intensive care (level 1)			
High-dependency care (level 2)			
Special care (level 3)			
Ordinary care (level 4)			
Cooling (additional to IC care)			
Readmission after initial discharge			
Associated with transfer (number of transfers)			
Transfer			
Community resource use in first year (visits)			
General practitioner			
Health visitor			
Practice nurse			
Community nurse			
Community paediatrician			
Physiotherapist			
Community resource use in second year (visits)			
General practitioner			
Health visitor			
Practice nurse			
Community nurse			
Community paediatrician			
Physiotherapist			
Resource use of mother			
Inpatient stay			
Inpatient stay ward			
Inpatient stay IC			
Additional investigations			
Radiography			
Ultrasound scans			
Surgery			
Other procedures (number of)			
Associated with transfer (number of transfers)			
Transfer			

units, such as numbers of hospitalizations or days in the hospital. A mixed case approach to costing will be used, dependent on resource use patterns expected, and availability of national standardised cost data (from Department of Health reference costs, typically used in economic evaluations). Items will be captured in disaggregated units where relevant, and such costing is typically labelled 'bottom up'. This will be achieved by asking midwives/clinicians to document relevant staffing, medications and equipment. They will then be sent a micro-costing sheet to correct with their own resource components (*Table 47*) which will be very detailed, capturing all resource components that might be used. Further information will also be captured during formal interviews to include cost of the intervention itself, including the potential impact on staff working patterns.

Total cost will be measured by multiplying unit costs to resource use data. Unit costs are the cost per standard unit. Unit costs will be consistent with measured resource use, the study's perspective, and its time horizon (for instance valued at 2012 prices). In some cases, unit costs will be estimated from trial data collection sites, but more commonly they will be derived from national data sources (Department of Health reference costs).

Statistical tests

The purpose of clinical trial cost analysis is to estimate costs, cost differences associated with treatment, the variability of differences, and whether or not the differences occurred by chance.

Once resources have been identified and valued, differences between groups must be summarised. Arithmetic mean cost differences are generally considered the most appropriate and robust measure, however, cost data often do not conform to the assumptions for standard statistical tests for comparing differences in arithmetic means. Nonparametric methods of estimating incremental net benefit will be used to compute the cost-effectiveness acceptability curves and the confidence ellipses.

Missing data

Missing data are inevitable in economic analyses conducted alongside trials. Eliminating cases with missing data is not recommended because it may introduce bias or severely reduce power to test hypotheses. Nevertheless, ignoring small amounts of missing data is acceptable if a reasonable case can be made that doing so is unlikely to bias treatment group comparisons. Imputation refers to replacing missing fields with estimates. A strict quality control is currently in place for the INFANT data collection to minimise missing data. However, it is expected that some missing data will occur and we will be using appropriate methods such as multiple imputation if necessary to impute missing resource use and health-related quality of life data.

Uncertainty

Results of economic assessments in trials are subject to a number of sources of uncertainty, including sampling uncertainty and uncertainty in parameters such as unit costs. The revised point estimate and revised 95% CIs that result from the sensitivity analysis will be reported.

Reporting the methods and results

Cost-effectiveness acceptability curves and incremental net benefit statistics with 95% CIs will be presented. The differences in resource use and costs tested using *t* tests and differences in effects will be presented using relative risks. Net benefits are defined as $Rc.\Delta E - \Delta C$, (where *Rc* is the threshold cost ratio, ΔE is the change in effects between the trial arms, and ΔC the change in costs for the trial arms). These will be estimated for alternative values of *Rc*, together with their 95% confidence ellipses.

A series of sensitivity analyses will be undertaken to explore the implications of uncertainty on the base-case incremental cost-effectiveness ratios. This will include varying variables found to be the key cost-drivers in early analyses for cost.

TABLE 47 Example of bottom up cost data collection extraction form

Staffing			Medications					Equipment			Total Cost
Staff title and grade	Length of contact time/procedure	Staffing cost (£)	Drug	Dose	Mode of administration	No of treatments per day	Cost (£)	Piece	Llifespan	Annuitised cost (£)	∑ of costs

The health economist will receive a 'cleaned' database of resource use and effectiveness data from the main INFANT statistical team conducting the primary analysis. All analyses will be performed with a microcomputer using Stata version 13, and Microsoft Excel® 2010 (Microsoft Corporation, Redmond, WA, USA) software.

Economic evaluation design issues for INFANT study aim 3 (modelling longer-term outcomes)

Long-term cost-effectiveness of intelligent system to support decision-making in the management of labour using cardiotocogram

An analysis of the cost-effectiveness of the intelligent decision support software during labour will take into account the potential long-term outcomes to mother and child. Cost-effectiveness will be calculated in terms of the incremental cost per QALY gained. The analysis will be intended to account for the expected lifetime of the children, but depending on data availability we will consider shorter life horizons that can be populated with good evidenced data such as 18 years. *Tables 48* and *49* show the primary data inputs that will be derived from the INFANT trial to populate the model.

TABLE 48 Estimated model parameter inputs (baseline model) using primary data collected from INFANT

	Trial arm, mean (95% CI)	
Parameter	Intervention group	Standard care group
First 12 months: outcomes, and costs		
Survival with NNE		
Death of child		
Composite: poor neonatal outcomes		
EQ-5D of mother		
Cost of ECG decision software		
Hospital costs to discharge for surviving children		
Hospital costs to discharge for women		
Hospital costs for non-surviving children		
Inpatient costs of children post discharge		
Community care costs of children post discharge		
12 to 24 months: outcomes and costs		
Age assessed for DQ		
Survival without neurological abnormality (using Development Quotient)		
Survival with neurological abnormality (using Development Quotient)		
EQ-5D child (from mapping study)		
EQ-5D of mother		
Death of child		
Inpatient costs, children without neurological abnormality		
Inpatient costs, children with neurological abnormality		
Community care costs, children without neurological abnormality		
Community care costs, children with neurological abnormality		

TABLE 49 Cost-effectiveness results and sensitivity analyses

Parameter	Trial arm, mean (95% CI)		Mean difference† (95% CI)
	Intervention group	Standard care group	
Analysis 1 (incremental cost per poor neonatal event averted)			
Cost			
Effectiveness			
ICER			
$\lambda = 20{,}000$			
$\lambda = 30{,}000$			
Analysis 2 (incremental cost per disability free life-year gained; using the DQ obtained at 2 years)			
Cost			
Effectiveness			
ICER			
$\lambda = 20{,}000$			
$\lambda = 30{,}000$			
Analysis 3 (incremental cost per quality-adjusted life-year gained; long-term analysis)			
Cost			
Effectiveness			
ICER			
$\lambda = 20{,}000$			
$\lambda = 30{,}000$			
Sensitivity Analysis 1 (incremental cost per quality-adjusted life-year gained including medical legal claims)			
Cost			
Effectiveness			
ICER			
$\lambda = 20{,}000$			
$\lambda = 30{,}000$			
Sensitivity Analyses 2 to 4 will vary the inputs to each of the main analysis			
Cost			
Effectiveness			
ICER			
$\lambda = 20{,}000$			
$\lambda = 30{,}000$			

ICER = incremental cost-effectiveness ratio; λ = willingness to pay threshold held by decision-makers for an additional quality of life gain. † The mean of the standard care group is subtracted from the mean of the intervention group. The probability of cost-effectiveness at $\lambda = £20{,}000$ and $\lambda = £30{,}000$ was reported unless there was a 95% probability of cost-effectiveness at a $\lambda \leq £20{,}000$. All costs are reported in 20xx-20xx £Sterling.

The long-term economic evaluation will require extrapolating and identifying future health-care costs and the health status of mothers and infants from literature as well as the application of decision-analytic methods to synthesise information from different sources.

A brief review of the NIHR HTA website (www.hta.ac.uk/project/htapubs.asp), the NHS Economic Evaluation Database (NHS-EED, www.crd.york.ac.uk/) and PubMed (www.pubmed.gov) reveals only one previous study of the long-term cost-effectiveness of cardiotocography methods in fetal monitoring during labour.[7] We will build on the results of this literature, but we will develop a de novo cost-effectiveness model that will be populated based on available evidence, including the data collected during the trial. At this stage, the proposed design is to use a Markov model described and simplified in *Figure 43*. A structured review of the published literature available for cost-effectiveness and cost-utility modelled from patient level data is currently in progress. The data, including an inventory of health state utility weights is being searched through the Paediatric Economic Database Evaluation (PEDE) made available by the Research Institute at The Hospital for Sick Children, Toronto.

Decisions about the model structure might be revised after systematic searches of the literature are undertaken and expert clinical input is considered. Following decisions about model structure, a list of parameter estimates required for the model will be developed. These are likely to include the series of parameters reported in *Table 50*. Data collected in this trial will provide information to populate the model which will be supplemented with available evidence in the literature following systematic searches. Parameters may require additional modelling to capture the long-term and time-dependent nature of the estimate values.

We will undertake deterministic and probabilistic sensitivity analysis. For the latter input parameters will be assigned probability distributions to reflect their imprecision and Monte Carlo techniques will be used to reflect this uncertainty in the results. We will construct cost-effectiveness acceptability curves and cost-effectiveness confidence ellipses.

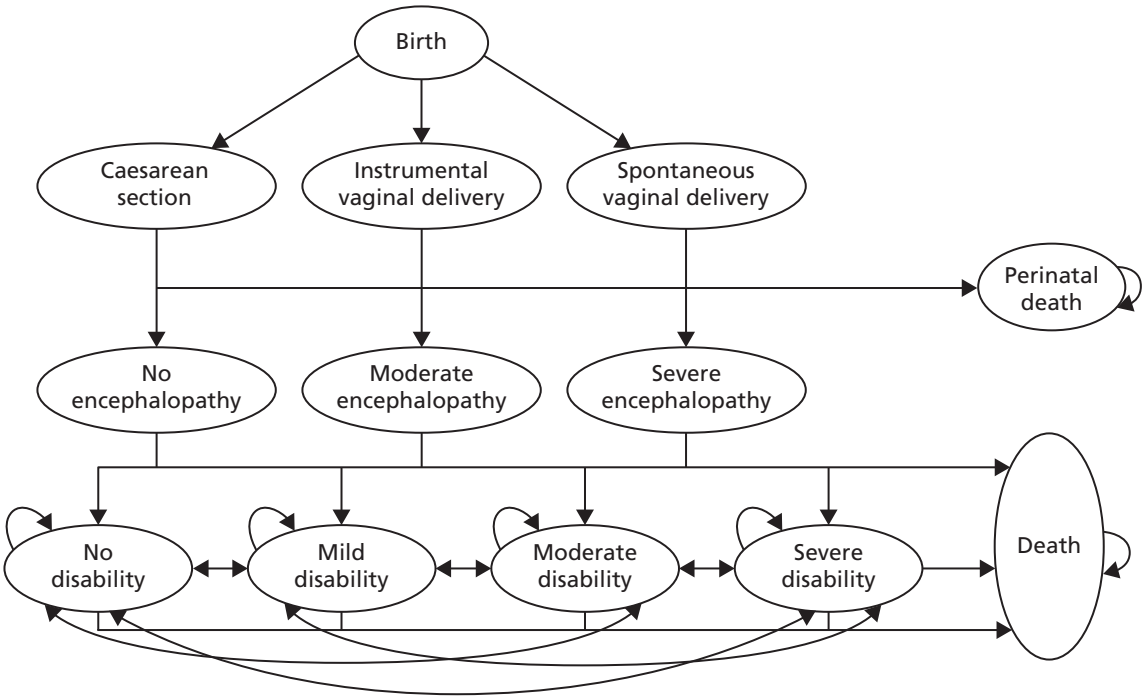


FIGURE 43 Markov model for long-term cost-effectiveness model.

TABLE 50 Parameters to populate long-term cost-effectiveness model

Transition probability parameters	
Caesarean delivery	Mortality first 2 years after moderate encephalopathy
Instrumental vaginal delivery	Mortality first 2 years after severe encephalopathy
Spontaneous vaginal delivery	Remain without disability
No encephalopathy after caesarean section	From no disability to mild disability
No encephalopathy after instrumental delivery	From no disability to moderate disability
No encephalopathy after spontaneous delivery	From no disability to severe disability
Moderate encephalopathy after caesarean section	From no disability to death
Moderate encephalopathy after instrumental delivery	Remain with mild disability
Moderate encephalopathy after spontaneous delivery	From mild disability to no disability
Severe encephalopathy after caesarean section	From mild disability to moderate disability
Severe encephalopathy after instrumental delivery	From mild disability to severe disability
Severe encephalopathy after spontaneous delivery	From mild disability to death
Perinatal death after caesarean section	Remain with moderate disability
Perinatal death after instrumental delivery	From moderate disability to no disability
Perinatal death after spontaneous delivery	From moderate disability to mild disability
No disability after no encephalopathy	From moderate disability to severe disability
No disability after moderate encephalopathy	From moderate disability to death
No disability after severe encephalopathy	Remain with severe disability
Mild disability after no encephalopathy	From severe disability to no disability
Mild disability after moderate encephalopathy	From severe disability to mild disability
Mild disability after severe encephalopathy	From severe disability to moderate disability
Moderate disability after no encephalopathy	From severe disability to death
Moderate disability after moderate encephalopathy	Litigation if mild disability
Moderate disability after severe encephalopathy	Litigation if moderate disability
Severe disability after no encephalopathy	Litigation if severe disability
Severe disability after moderate encephalopathy	Litigation if perinatal death
Severe disability after severe encephalopathy	Litigation if death within first 2 years
Mortality first 2 years after no encephalopathy	Litigation if death after first 2 years
Resource cost	
Cost of caesarean section in CG	Cost moderate encephalopathy in first 2 years
Cost of caesarean section in IG	Cost severe encephalopathy in first 2 years
Cost of instrumental delivery in CG	Costs no disability
Cost of instrumental delivery in TG	Costs mild disability
Cost of spontaneous delivery in CG	Cost moderate disability
Cost of spontaneous delivery in TG	Cost severe disability
Cost of decision support software	Cost of litigation if mild disability
Cost no encephalopathy until discharge	Cost of litigation if moderate disability

continued

TABLE 50 Parameters to populate long-term cost-effectiveness model (*continued*)

Cost moderate encephalopathy until discharged	Cost of litigation if severe disability
Cost severe encephalopathy until discharged	Cost of litigation if perinatal death
Cost of perinatal death	Cost of litigation if death within first 2 years
Cost no encephalopathy in first 2 years	Cost of litigation if death after first 2 years
Outcomes	
Utility no encephalopathy – child	Utility no encephalopathy – parent
Utility moderate encephalopathy – child	Utility moderate encephalopathy – parent
Utility severe encephalopathy – child	Utility severe encephalopathy – parent
Utility no disability – child	Utility no disability – parent
Utility mild disability – child	Utility mild disability – parent
Utility moderate disability – child	Utility moderate disability – parent
Utility severe disability – child	Utility severe disability – parent

CG = control group; IT = intervention group

In addition to this analysis, we will also consider the effect on potential medico-legal claims that result from adverse events during the intrapartum and neonatal periods. We will model the probability of these claims and estimate the litigation costs related to them. We will explore different scenarios in our analyses as can be seen in *Economic evaluation design issues for INFANT study aims 4 (Modelling clinical scenarios that will impact on obstetric litigation claims)*.

Economic evaluation design issues for INFANT study aim 4 (modelling clinical scenarios that will impact on obstetric litigation claims)

The prevention of a modest proportion of perinatal asphyxia will improve the health and well-being of thousands of children and their families throughout the world each year. A reduction in the number of babies born with perinatal asphyxia will reduce the associated mortality and, among survivors, the burden of ill health and incapacity over their lifetime. The implications of this cost burden to society is that maternity services are associated with far higher litigation costs than other services and a single 'successful' litigation case may result in a settlement worth millions of pounds.

Medical negligence data is one method of estimating the longer-term costs of perinatal asphyxia because the financial projections should be indicative of the cost implications for the value of life for the rest of life. However, evaluations for litigation purposes are often not reached until 5–6 years after the birth event, when neuro-paediatricians can identify patterns of brain damage reflecting birth asphyxia and when the baby is likely to have cerebral palsy. It is possible that some claims are processed in 2–3 years and others over 10–15 years.

The prevention of a modest proportion of perinatal asphyxia could thus result in substantial savings in litigation costs in the UK. However, litigation claims and pay outs are only slightly associated with negligence. All cases of litigation which are paid are likely to be associated with negligence. For various reasons outcomes as a result of negligence may not lead to litigation, and other cases [which incur economic (lawyers) costs] are brought where no settlement is made because there was no negligence.

Given that the NHSLA is the recipient of the Clinical Negligence Scheme for Trusts risk pooling schemes and has a unique database of all claims for births, we have proposed a stand-alone study with the NHSLA

to understand the proportion of cases of perinatal asphyxia that have resulted in both successful and unsuccessful litigation (to generate baseline estimates of all successful litigation cases), the consequent pay-outs in the cases of successful claims and how these estimates have been derived over the past 10 years.

This would use a database of time series data that shows the costs involved in settled claims, including the initial capital compensation and then the 'periodicals' (annual payment for life), or any payments processed for deaths would satisfy this evidence gap. We will then develop a model estimating the longer-term cost of perinatal asphyxia. We understand that financial projections should be indicative of the cost implications for the value of life for the rest of life. Furthermore, it may encompass health-care and family costs, though may not include other therapies and state funded or local authority costs, so we would estimate these separately.

Together, these estimates will also assist us to identify potential savings in litigation costs in the UK from the decision support.

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