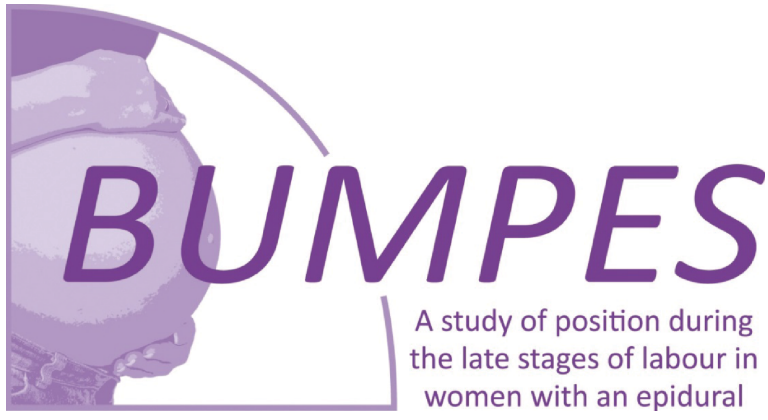

The BUMPES study

HTA project number: 08/22/02

MREC number: 09/H0605/114

ISRCTN35706297

Statistical Analysis Plan

Version 1, May 2015

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Background: As the most effective form of pain relief in labour, epidural analgesia is chosen by up to 30% of women. Previous randomised controlled trials have shown that epidural analgesia is associated with an increased risk of instrumental delivery (IVD), prolonged labour and oxytocic augmentation. These effects have been attributed to dense epidural motor block. "Low dose epidurals" which use low-dose local anaesthetic in combination with opioids (fentanyl) are now routine practice and have been shown to result in a lower risk of IVD. However, the risk of IVD is still higher compared with women with no epidural. Although low dose epidurals preserve motor function, allowing greater mobility throughout labour and can enable women to adopt upright positions, there is controversy about whether an upright posture in second stage increases the spontaneous vaginal delivery (SVD) rate. This pragmatic randomised controlled trial will test the hypothesis that amongst women in first time labour with a low-dose epidural who enter second stage, a policy of enabling upright position increases the incidence of SVD compared to a policy of lying down.

INTRODUCTION

This document details the proposed presentation and analysis for the main paper(s) reporting results from the NIHR HTA-funded multicentre randomised controlled trial investigating position during late stages of labour in women with an epidural (BUMPES).

The results reported in these papers will follow the strategy set out here. Subsequent analyses of a more exploratory nature will not be bound by this strategy, though they are expected to follow the broad principles laid down here. The principles are not intended to curtail exploratory analysis (for example, to decide cut-points for categorisation of continuous variables), nor to prohibit accepted practices (for example, data transformation prior to analysis), but they are intended to establish the rules that will be followed, as closely as possible, when analysing and reporting the trial.

The analysis plan will be available on request when the principal papers are submitted for publication in a journal. Suggestions for subsequent analyses by journal editors or referees, will be considered carefully, and carried out as far as possible in line with the principles of this analysis plan; if reported, the source of the suggestion will be acknowledged.

Any deviations from the statistical analysis plan will be described and justified in the final report of the trial. The analysis should be carried out by an identified, appropriately qualified and experienced statistician/analyst, who should ensure the integrity of the data during their processing. Examples of such procedures include quality control and evaluation procedures. This document and the interim and final analyses have been and will be produced in line with NPEU Standard Operating Procedures ST 105 Statistical Analysis Plan; ST 104 Interim Statistical Analysis; and ST 106 Final Statistical Analysis and Reporting.

BACKGROUND INFORMATION

Objectives of the Trial

The primary objective

The main objective of the trial is to evaluate whether, in nulliparous women who choose low dose epidural analgesia, a policy of adopting an “upright position” throughout the second stage of labour is associated with an increase in the incidence of spontaneous vaginal delivery compared with a policy of adopting a “lying down” position.

Secondary objectives

Secondary objectives are:

- to evaluate whether there are differences between the two policies in important clinical outcomes for women and babies around the time of birth and 12 months postpartum;
- to evaluate cost-effectiveness of the two policies for position during second stage from an NHS perspective;
- to measure women's satisfaction with and experience of labour and delivery.

Trial Design

The BUMPES study is a pragmatic, multicentre, individually randomised controlled trial that had a target recruitment of 3,000 nulliparous women who had a low dose epidural in situ. It is a two-arm parallel group trial with one arm allocated to adopting an “upright” position during the second stage of labour and one arm allocated to adopting a “lying down” position during the second stage of labour.

Date of start of recruitment:	October 2010
End date of recruitment:	January 2014
Target number of participants:	3,000 (1,500 per arm)
Target number of centres:	30
Follow up:	12 months

Eligibility

Women who were admitted to a participating labour ward who fulfilled all of the following criteria were eligible to be randomised in the trial:

- 16 years of age or older
- ≥37 weeks' gestation
- nulliparous (no previous delivery greater than or equal to 24 + 0 weeks' gestation)
- singleton cephalic presentation
- intended spontaneous vaginal birth
- in second stage of labour
- with a low dose epidural in situ during the first stage of labour, providing effective pain relief
- able to understand printed documentation produced in English
- able to give written answers in English

Planned Interventions

Intervention group

Women were allocated to a policy of **upright maternal position which would maintain the pelvis in as vertical a plane as possible** during second stage of labour with the intention of continuing this until the birth. Women allocated to the "upright" group were encouraged by their midwife to adopt positions which were as upright a posture as possible (this would include walking, standing, sitting out of bed, supported kneeling or bolt upright in an obstetric bed) for as much of the second stage as possible.

Control group

Women were allocated to a policy of **lying down maternal position which would maintain the pelvis in as horizontal a plane as possible** during second stage of labour with the intention of continuing this until the birth. Women allocated to the "lying down" group were encouraged to adopt a lying down position which would mean lateral positions or lying down in bed for as much of second stage as possible. The bed could be tilted at up to a maximum of 30 degrees from the horizontal.

Note: a truly supine position (i.e. flat on the back) should not be used during labour because of aorto-caval compression from the gravid uterus.

Principal Comparisons of Interest

The objective of the trial is to determine whether there are any differences in mode of delivery, post study entry interventions during second stage of labour, duration of labour, genital tract trauma, infant clinical outcomes, women's satisfaction of their birth experience, cost effectiveness, and longer term woman and infant outcomes between the group allocated to "upright" position and the group allocated to "lying down" position.

Definition of Primary and Secondary Outcomes

Primary outcome

Incidence of spontaneous vaginal delivery (SVD).

Secondary outcomes

Mode of delivery

- Instrumental delivery (forceps and ventouse)
  - and primary indication
- Caesarean section
  - and primary indication

Outcomes from randomisation until delivery

- Augmentation
- Major interventions to maintain blood pressure (eg Vasopressors)
- Hypotension (systolic BP < 100 mmHg prior to delivery)
- Application of fetal scalp clip
- Fetal blood sampling
- Total doses of epidural local anaesthetic and opioids administered after randomisation
- Duration of active second stage
- Duration of second stage of labour
- Additional anaesthesia used for operative delivery

Immediate post delivery outcomes

- Active management of the third stage
- Episiotomy
- Pain during delivery
- Genital tract trauma (location and severity)
- Manual removal of the placenta
- Primary PPH requiring blood transfusion

Postnatal period – Woman

- Duration of in-patient stay after delivery
- Satisfaction with experience of birth

Postnatal period - Infant

- Cord-artery pH <7.05 in second stage (this is 2 standard deviations below the mean) with base deficit ≥ 12 mmol/l (this is a threshold above which the risks of neurological damage increase)
- Presence of meconium stained liquor
- Apgar score <4 at 5 minutes
- Resuscitation at birth
- Skin to skin contact within the first hour of birth
- Initiation of breastfeeding within the first hour of birth
- Duration of in-patient stay
- Admission to neonatal unit and duration of stay

1 year after birth - Woman

- Urinary incontinence
- Faecal incontinence
- Other bowel ‘problems’
- Dyspareunia
- General physical and psychological health

1 year after birth - Infant

Major morbidity e.g. gross neurodevelopmental delay including cerebral palsy (if a diagnosis has been made)

Hospital admissions

Cost effectiveness – see separate document

Data Collection Schedule

Woman and Infant Data Collection Booklet (DCB) – completed by the attending midwife during labour and immediately after delivery.
For all participating women and infants

Higher Level of Care Form: Woman – completed by the attending midwife during the woman's admission and/or immediately after discharge from hospital; checked by the local Principal Investigator.
For women receiving a higher level of care following delivery

Higher Level of Care Form: Infant – completed by the attending midwife during the infant's admission and/or immediately after discharge from hospital; checked by the local Principal Investigator.
For infants receiving a higher level of care following birth

Maternal Satisfaction Form – completed by the woman as soon as possible after delivery.
For all participating women

One Year Form – postal questionnaire completed by the woman.
For all women for whom their babies are alive and both are resident at the same address

Withdrawal Form - completed by the attending midwife at the time of withdrawal from the study.
For women who decide to withdraw from BUMPES after study entry

Sample Size and Power

The proposed sample size was a total of 3,000 women.

At the time of writing the funding application an assumed rate for the primary outcome spontaneous vaginal delivery (SVD) was made as 55% in the control group derived from data published on the COMET trial. [5] A total sample size of 3,000 women (1,500 in each arm) would have 90% power to detect a clinically significant (absolute) difference of 6% in the SVD rate between the two policies (with 95% confidence). The cost of implementing this technology is low, therefore even modest differences in outcome are likely to be cost-effective. Detecting the smallest and clinically relevant effect size possible is therefore desirable. A 6% absolute risk difference, which equates to a 10% relative risk reduction (approximately) is well within the uncertainty of the existing evidence (despite the existing trials' heterogeneity) and is considered sufficient to change clinical practice.

The proportion in the 'upright' group achieving a spontaneous vaginal delivery (SVD) was anticipated to be 0.61 (61%) under the null hypothesis and the proportion in the 'control' group was 0.55 (55%). The test statistic used is the two-sided Z test with pooled variance. The significance level of the 2-sided test was targeted at 5%. A trial of this size will also give more than 80% power to detect important differences in secondary outcomes, such as faecal incontinence at 1 year after birth which affects around 6% of women.

On collation of the pilot data for an interim analysis presented to the Data Monitoring Committee in 2011, it was recognised that the combined primary outcome event rate was lower than anticipated. As at 6th December 2011 the overall SVD rate for BUMPES (combining upright and lying down groups) was 33.8%; 95% CI 26.1% to 42.1% (based on 49/145 events). With a reduction in the control group event rate (from an anticipated 55% to between 30% and 40%), keeping the sample size fixed at 3000 would mean that a relative risk of between 1.13 and 1.19 would be detectable, equivalent to an absolute risk reduction of 5-6%. Although there is not sufficient power to detect a relative risk as small as the planned 1.11, the absolute risk detectable is similar and the Trial Steering Committee (TSC) agreed that changes to the target sample size were unnecessary.

Intervention Allocation

When a woman in a participating centre had an effective epidural established during the first stage of labour written informed consent was obtained by a health professional. The woman had to meet most of the eligibility requirements at this stage, though did not have to be in second stage to give consent.

When a woman with an effective low dose epidural was diagnosed as being in the second stage of labour and she fulfilled all of the eligibility criteria outlined above, and she gave consent, she was randomised.

Randomisation to the allocated intervention (allocation ratio 1:1) used a web-based central service. To confirm eligibility investigators needed to confirm the woman's gestation, age, that this was the woman's first birth and that the fetus was a singleton with cephalic presentation, and that an effective epidural was *in situ*, as well as signed consent.

The randomisation software used random permuted blocks of variable sizes to ensure that the staff recruiting women to the trial could not reliably predict the next allocation. Because of the large numbers of women recruited in each centre, no stratification by clinical characteristics was planned although there was stratification by centre. The procedures for randomisation were fully documented and tested prior to the start of the trial and monitored by the co-ordinating centre during the trial.

Interim analyses: The Independent Data Monitoring Committee

An independent Data Monitoring Committee (DMC) was established for the trial and met as and when the DMC requested. The terms of reference for the DMC were agreed at their first meeting. A DMC charter was completed following the recommendations of the DAMOCLES Study. [32]

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 may request. The data were supplied to the Chair of the DMC as frequently as they requested. Meetings of the committee were arranged periodically, as considered appropriate by the Chair. In the light of interim data, and other evidence from relevant studies (including updated overviews of the relevant randomised controlled trials), the DMC would inform the TSC, if in their view there was proof beyond reasonable doubt that the data indicated that any part of the protocol under investigation was either clearly indicated or contra-indicated, either for all women or for a particular subgroup of trial participants. A decision to inform the TSC would be based on statistical, clinical and ethical considerations.

Appropriate criteria for proof beyond reasonable doubt cannot be specified precisely. A difference of at least 3 standard errors in the interim analysis of a major endpoint may be needed to justify halting, or modifying, such a study prematurely. If this criterion were to be adopted by the DMC, it would have the practical advantage that the exact number of interim analyses would be of little importance, and so no fixed schedule was proposed. 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) remained blind to the results of the interim analysis. Collaborators and all others associated with the study could write through the trial office to the DMC, to draw attention to any concern they may have had about the possibility of harm arising from the treatment under study, or any other matters that may have been relevant.

Independent Data Monitoring Committee Membership

Dr Steve Yentis (chair) - Consultant Anaesthetist, Chelsea & Westminster Hospital

Mr Stephen Walkinshaw - Consultant in Maternal and Fetal Medicine, Liverpool Women's NHS Foundation Trust

Dr Pat Yudkin - Emeritus Reader in Medical Statistics, University of Oxford

Professor Christine Kettle - Professor of Women's Health, University Hospital of North Centre

Trial reporting

The trial will be reported according to the principles of the CONSORT statement. [63]

DATA MANAGEMENT

Data Collection

Information at trial entry, including eligibility and maternal characteristics, were collected from hospital notes onto the Data Collection Booklet (DCB). The position to which the woman was allocated was recorded on the DCB in two places – once in the eligibility section and again on the worksheet used to record the woman's actual positions. As soon as possible after the woman was randomised, the attending midwife encouraged her into the allocated position and started recording in the DCB what position the woman was in "for the majority of the time in the last 15 minutes" and if this position had changed from the allocated position and the reasons for this. Information on drugs taken after study entry and during labour were also recorded, as well as other clinical information about the labour. The DCB also collected clinical outcome information on the delivery as well as neonatal outcomes and hospital stay.

If either the woman or infant received a higher level of care, the relevant Higher Level of Care form was completed by the attending midwife.

As soon as possible after delivery, the woman was asked to complete a one page questionnaire asking about her satisfaction with her birth experience, as well as asking her to provide an overview of what position she was in most of the time after study entry.

Women with surviving infants are followed up at one year with a self-administered postal questionnaire asking about their general health and wellbeing, with specific questions relating to any urinary and bowel problems. This questionnaire also requests information on the use of health services for themselves or their child. Prior to contact, mortality status and place of residence of both mother and infant is checked using NHS Summary Care Records. Only women whose infants reside at the same address are contacted.

Data Entry, Cleaning and Validation

Data will be double entered at UCL CTU using MACRO, by independent data clerks. Validation routines will check for missing data and inconsistencies on an ongoing basis. This will include screening for out-of-range data, with cross-checks for conflicting data within and between data collection forms using computerised logic checking screens. Any validation errors on the DCB and Higher Level of Care Forms will be queried and documented. Queries will be communicated as soon as possible to the appropriate centres by the Trial Co-ordinator. Errors on the Maternal Satisfaction Questionnaire and the One-Year Follow-up form are not queried with the woman.

Derivation of Variables

See Table 2.

Process outcomes

As described in 3.1 above, every 15 minutes a record was made of what position the woman was in "for the majority of the time since the last assessment" and if this position had changed from the previous assessment with the reasons for this. These data will be used to assess to what extent the women were able to adhere to the allocated intervention during (i) the passive second stage (i.e. before pushing commenced); (ii) the active second stage (i.e. pushing) and (iii) the whole of the second stage. These data will be summarised to indicate what proportion of time of each of these three stages women adhered to the intervention. Reasons for a change from a woman's allocated position are recorded as text which will be coded into categories.

Positions recorded on DCB V9 Part 1 Question 4.1 are categorised according to whether they are 'lying down', 'upright' or 'other' positions for each 15 minute interval. For each interval the categorised position is compared to the position allocated for the woman, and where the allocated position is the same as the categorised position, this is coded as 'adherent' for that 15 minute interval. All other positions are coded as 'non-adherent'. Some manual coding will be required for positions recorded as text. Positions recorded as lithotomy will be categorised as 'lying down' since the pelvis is in a horizontal position.

See section 8.5 for details on the analysis of the process outcomes.

Reliability

All outcome data, except for Maternal Satisfaction Questionnaire data and 1 Year Form data, are recorded in women's hospital notes. Site monitoring visits verified a random sample of data collected on the DCBs and Higher Level of Care Forms, by making comparisons with information recorded in hospital notes. Self-administered forms were not verified.

Data relating to the calculation of the process outcomes (i.e. maternal position at 15 minute intervals since study entry) was recorded by the midwife on the DCB only and is itself the source documentation and can therefore not be verified directly with any other source. The Maternal

Satisfaction Questionnaire aims to confirm these data with a question asking the woman to record what position they were in for the majority of the time during the passive and active stages of labour.

The coding of position data and reasons for a change from allocated position recorded as text will be validated by an independent clinician.

SERIOUS ADVERSE EVENT REPORTING

Serious Adverse Events (SAE) should be reported to the UCL BUMPES Trial Office within 48 hours. The BUMPES Trial Office would then notify the Chair of the DMC and the Research Ethics Committee. All SAEs occurring during the trial observed by the investigator or reported by the participant, whether or not attributed to the trial, would be reported on the data collection form. SAEs considered to be related to the trial by the investigator would be followed up until resolution or the event is considered stable. The investigator could have been asked to provide follow-up information. All related SAEs that could have resulted in a participant's withdrawal from the trial or are present at the end of the trial, should be followed up until a satisfactory resolution occurs.

The Chief Investigator shall submit, once a year throughout the clinical trial, or on request, a safety report to the Research Ethics Committee that includes all SAEs.

Although no serious adverse events were anticipated, it was possible that these could have occurred, for example, in the upright group, if ambulation was allowed and encouraged in the participating centre, it is possible that women could fall. This would be considered a serious adverse event.

PROTOCOL VIOLATIONS AND DEVIATIONS

Protocol Violation

A protocol violation is the failure to comply fully with the final study protocol as approved by the Research Ethics Committee and Research Department, for example, a serious non-compliance with the protocol resulting from error, fraud or misconduct and results in the exclusion of a patient from the analysis for the study. Any violations would be reported to the Sponsor and Research Ethics Committee as soon as possible.

Protocol Deviation

A protocol deviation is an allowable departure from the final study protocol as approved by the Research Ethics Committee, with minor consequences on the integrity of the data. Protocol deviations would be reported in the final publication but not excluded from the analysis.

UNBLINDING OF RANDOMISED INTERVENTIONS

Due to the nature of the intervention all recruiting and attending midwives and clinicians as well as the trial participant and staff at the UCL trial co-ordinating centre are aware of the allocation of each woman. All persons involved in the trial (except for the Trial Statistician and Trial Programmer), including the UCL trial co-ordinating centre, do not have access to the aggregate list of

randomisation codes. The data entry and storage system (OpenClinica and Macro) does not allow data to be aggregated, and all forms are filed according to study number.

PATIENT GROUPS FOR ANALYSIS

Post-randomisation Exclusions

Losses to the trial post randomisation are defined as any of the following:-

- Women for whom a valid consent was not received;
- Women for whom consent to use their data was withdrawn;
- Women not in second stage of labour when randomised and didn't reach second stage before delivery
- Women not in labour or without an epidural in place at the time of randomisation

The numbers (with percentages of the randomised population) of post-randomisation exclusions will be reported by randomised treatment group, and reasons summarised.

Women can specify whether data collected up to the point of withdrawal can be used. If the response is 'No', then they will be considered post-randomisation exclusions. If the response is 'Yes', then they will be reported as 'missing' for any data not collected after withdrawal.

Primary Analysis Strategy

For the primary analysis, participants will be analysed in the groups into which they were randomly allocated, i.e. comparing the outcomes of all women and infants for women allocated to a policy of enabling upright position with a policy of lying down, regardless of position recorded at any time during the second stage of labour (see section 10.3 for a description of sensitivity analyses according to adherence to position). Post-randomisation exclusions, as set out in section 7.1, will be excluded from all analyses.

The unit of analysis is the woman for all maternal outcomes and the infant for all infant outcomes. Women with multiple births are not eligible for the trial and hence non-independence of observations is not a cause of concern.

Descriptive analysis population

Baseline demographic and clinical characteristics will be reported for all women randomised for whom we have data available excluding post-randomisation exclusions (see section 7.1).

Comparative analysis population

- Maternal outcomes
  All women randomised for whom we have data available, excluding post-randomisation exclusions (see section 7.1).

- Short term neonatal outcomes
  All infants born to women randomised for whom we have data available, excluding post-randomisation exclusions (see section 7.1).

- 1 year maternal health outcomes
  All women randomised for whom we have data available, excluding post-randomisation exclusions (see section 7.1).

- 1 year infant health and development outcomes
  All infants born to women randomised for whom we have data available, excluding post-randomisation exclusions (see section 7.1).

Interim analysis population

Different denominators will be used for each of the interim analyses, based on the number of women randomised and data available:

- The total number of trial participants randomised at the time of data freeze, excluding post-randomisation exclusions (see section 7.1).
- The number of women and infants with 1 year follow up data available, excluding post-randomisation exclusions (see section 7.1).

Safety reporting analysis population

All women randomised, excluding women for whom a valid consent was not received and women who withdrew and did not consent to use of their data.

DESCRIPTIVE ANALYSES

Representativeness of Trial Population and Participant Throughput

The flow of participants through each stage of the trial will be summarised using a CONSORT diagram.[68] Specifically, for each intervention group we will report the numbers of women randomly assigned and women for whom the incorrect allocation was recorded in the eligibility section of the DCB (Part 1, section 2 of the DCB). The number of ineligible women randomised, if any, will be reported, with reasons for ineligibility. The number of post-randomisation exclusions and women analysed for the primary outcome will also be reported. We will also report numbers for the 1 year follow-up, women lost to follow up, women who withdrew before 1 yr, or withdrew after 1 year and did not consent to use of their data.

The total number of eligible women was not collected during the conduct of this study as it was considered heavy on resources and would not be sufficiently reliable.

Baseline Comparability of Randomised Groups

Participants in the two randomised groups will be described separately with respect to baseline demographics and clinical characteristics recorded on the Woman and Infant Data Collection Booklet. Data summarised will include:

- Centre
- Maternal age
- Gestational age at trial entry
- Index of Multiple Deprivation
- Ethnic group
- BMI at booking visit (if recorded)
- If woman had undergone Female Genital Mutilation
- Labour induction
- Diagnosis of pre-eclampsia
- First stage of labour history (duration of first stage, Electronic Fetal Monitoring, diagnosis of delay, opioids given)
- Epidural information (technique, PCEA, pain score, straight leg raise)

- Position prior to study entry
- study durations (from diagnosing second stage to randomisation, from randomisation to start of recording position).

Numbers (with percentages) for binary and categorical variables and means (and standard deviations), or medians (with lower and upper quartiles), or geometric means for continuous variables will be presented; there will be no tests of statistical significance performed nor confidence intervals calculated for differences between randomised groups on any baseline variable.

Losses to Follow-up

The number (with percentages) of losses to follow up among women selected for the 1 year assessment will be reported in the CONSORT flow chart (see section 8.1) by trial arm, and the reasons will be reported. Any deaths (and their causes) will also be reported in the CONSORT flow chart. Selected demographic and clinical characteristics, the primary outcome and selected short-term outcomes of women and their infants with 1 year data available will be compared with those for whom no follow-up data were received, using tests of statistical significance.

Description of Available Data

Missing data for primary and secondary outcomes, from baseline to the end of follow-up, will be summarised for the two trial arms.

Not all data may be routinely collected by all hospitals, e.g. BMI, cord artery pH and base deficit. The DCB allows midwives to tick “Data not recorded”. These data will be summarised by trial arm and reported separately to data missing or unknown.

Description of Adherence to Allocation

A summary of adherence to allocated position will be reported by trial arm for (i) the passive second stage (i.e. before pushing commenced); (ii) the active second stage (i.e. pushing) and (iii) the whole of the second stage. Summaries of adherence data will be presented calculated as the proportion of 15 minute intervals a woman spends in the position to which she was allocated out of the total number of 15 minute intervals recorded in the passive, active or whole of the second stage of labour. Medians and inter-quartile ranges will be presented due to the skewed distribution of the data. Data will be presented by randomised group and differences in medians will be calculated with corresponding 95% confidence intervals.

There are a variety of reasons why women change from their allocated position. Changing position to perform fetal blood sampling or to enable fetal heart rate monitoring is considered unavoidable. All reasons for change will be reviewed and classified as avoidable or unavoidable according to these criteria. The analysis will be performed for adherence treating periods where changes to a non-allocated position are considered necessary for unavoidable reasons as adherent.

Reasons for change from allocated position are recorded as free text on the DCB. These will be coded by the trial statistician and an independent assessor and presented by trial arm using counts and percentages.

The self-complete Maternal Satisfaction Questionnaire includes a question asking the woman to record what position they were in for the majority of the time during the passive and active stages of labour (see section 3.4) with responses “lying down”,“upright”, “other” and “can’t remember”.

These data will be summarised by trial arm using counts and percentages along with 95% confidence intervals for differences in percentages. A qualitative comparison will be made between these results and the results from the DCB data provided by the midwife, to ascertain the extent to which reporting bias may have occurred, if at all.

PRIMARY EFFECTIVENESS ANALYSES

Statistical Methods Used for Primary Analysis

Outcomes will be summarised by trial arm using counts and percentages for categorical variables, means and standard deviations for normally distributed continuous variables, or medians and interquartile ranges for other continuous variables. In addition geometric means will be presented for durations of stages of labour, as these are inherently highly skewed data.

An adjusted analysis will be performed on all comparative analyses adjusting for centre (the stratification factor at randomisation) as a random effect. [69] Binary outcomes will be analysed using log binomial regression models and results will be presented as adjusted risk ratios with corresponding confidence intervals (CI). If the model does not converge then log Poisson regression models with robust variance estimation will be used. [33] If the model is still unstable then centre will be removed and unadjusted risk ratios will be presented. Continuous outcomes will be analysed using linear regression models and results will be presented as adjusted differences in means with associated confidence intervals. Transformations will be applied for non-normal data if possible. Otherwise unadjusted median differences (plus CIs) for skewed continuous variable will be presented. In addition geometric mean ratios will be presented for durations of stages of labour.

Comparisons between randomised groups of all primary and secondary outcomes will be reported in full for completeness and transparency i.e. there will be no selective reporting of outcomes.

Adjustment for Multiplicity

In order to take account of the number of comparisons, 95% confidence intervals will be presented for the primary outcome and 99% confidence intervals for all other outcomes.

Missing Data

Missing data for the primary outcome are likely to be negligible. If any data items are missing on the data collection forms every effort will be made to extract these data from the hospital involved.

Statistical Software Employed

The most recent version of Stata/SE for Windows (version 13.1 at the time of writing this document) will be used for all analyses.

ADDITIONAL EFFECTIVENESS ANALYSES

Adjusted Analyses

The primary analysis will be adjusted further for the primary outcome to investigate the impact of the following known prognostic factors (in addition to centre) : age as a continuous variable, ethnicity, diagnosis of delay, onset of labour – induced vs. spontaneous.

Pre-specified Subgroup Analysis

To examine whether the effect of policy of position during the second stage of labour is consistent across specific subgroups of women, the following subgroup analyses will be undertaken:

- Gestational age (37+0 to 38+6; 39+0 to 40+6; and 41+0 or more)
- Maternal age (Up to 24, 25-29, 30-34, 35 and over)
- Augmentation with syntocinon in the first stage of labour (Yes/No)
- Index of Multiple Deprivation (population based quintiles 1 to 5)
  (derived using the postcode of the woman's last known address based on Office of National Statistic Indices of Multiple Deprivation 2010 and Ordnance Survey Code-Point Open Feb 2013).

For the trial primary outcome, results will be presented on forest plots showing the risk ratio plus 95% CI for each subgroup , [37] by intervention group, with the p value for the statistical test of interaction or test for trend where appropriate. [38]

Centre was included as a stratifying factor in the original protocol as we were expecting to recruit to target using 5 centres only. Recruitment rates were poor and we expanded the number of recruiting centres to 40. A subgroup analysis on 40 centres is therefore not considered relevant.

Pre-specified Sensitivity Analysis

A sensitivity analysis on the one year maternal outcomes will be carried out on a restricted dataset that excludes all women who are pregnant or have had another child at the time of completing the 1 year follow-up questionnaire.

In some cases women gave more than one response to a single question on the Maternal Satisfaction Questionnaire (MSQ). For the primary analysis, responses to these questions will be treated as missing. A sensitivity analysis will be undertaken if this occurs for more than 5% of the returned questionnaires for each individual question (i.e. if 2000 MSQs are received and for one question there are more than 100 responses treated as missing, then a sensitivity analysis will be performed on that question). This analysis will impute data according to the recorded worst and best case scenario.

Resource Use and Cost Data

See BUMPES Economic Evaluation Analysis Plan.

ADDITIONAL EXPLORATORY ANALYSES

The following further exploratory analyses will be performed to provide context to the results or to generate hypotheses for future testing:

To explore the relationship between adherence and outcome, an analysis will be undertaken to investigate whether there appears to be a threshold of duration of adherence (absolute or relative) which is associated with achieving a SVD. This will be performed for the passive stage only as this is the focus of the intervention. Receiver Operating Characteristic (ROC) curve analysis will be employed to determine a cut-off value of adherence using time as an absolute measurement, and proportion of time as a relative measurement. [70, 71, 72]The ROC curve will be used to provide a visual presentation of sensitivity versus specificity and a cut-off value of duration of adherence that maximises these will be examined. The accuracy of the measurement of duration of adherence as a predictor of SVD will be summarised using the area under the ROC curve. This analysis will be undertaken controlling for trial arm. Adherence will be defined according to the definition detailed in section 8.5.

Further exploratory analyses will also be undertaken after the main trial report is complete. These will include an exploration of whether there are other prognostic factors for the primary outcome (e.g. duration of passive second stage, time from first dose of epidural to randomisation). These analyses will be hypothesis-generating and pre-specified in a separate document, and the findings will be interpreted cautiously.

SAFETY DATA ANALYSIS

Serious Adverse Events

Any serious adverse event occurring whilst a woman is in the study (until discharge), will be recorded and tabulated in full.

DEVIATION FROM ANALYSIS DESCRIBED IN PROTOCOL

Centre was included as a stratifying factor in the list of subgroup analyses in the original protocol as we were expecting to recruit to target using 5 centres only. Recruitment rates were poor and we expanded the number of recruiting centres to 40. A subgroup analysis on 40 centres is therefore not considered relevant.

Table 1 Document History

Date	Version	Name	Details
27 May 2012	i	Pollyanna Hardy	First draft
29 July 2014	ii	Pollyanna Hardy	Reviewed and updated by PH and sent to PB for review.
13 August 2014	iii	Pollyanna Hardy	Incorporating PB's edits and comments for review by the CiG.
10 November 2014	iv	Pollyanna Hardy	Incorporating discussion from CiG held on 8th Sept 2014 – not finished
11 November 2014	v	Pollyanna Hardy	Incorporating Beth Howden's changes and finishing edits from CiG
14th May 2015	vi	Pollyanna Hardy	Accepting changes, incorporating PB's edits and amending methods for dose-response analysis
18th May 2015	vii	Pollyanna Hardy	After discussion with PB on 18th May 2015, changes accepted and minor amendments made. CACE analysis considered and not thought relevant for this study.
26th May 2015	viii	Pollyanna Hardy	Edited analysis of Maternal Satisfaction Questionnaire based on advice from Debbie Bick and PB.
27th May 2015	1	Pollyanna Hardy	Version 1 saved for sign off

TABLE 2: DERIVATION OF VARIABLES

According to version 9 of the Data Collection Booklet (DCB)
Version 5 of the Maternal Satisfaction Questionnaire (MSQ)
Version 2 of the Higher Level of Care Forms (Infant and Mother)
Version 3 of the One Year Follow-up forms

Outcome	**Part no./Question reference**	**Comments**
Primary outcome		
Incidence of spontaneous vaginal delivery (SVD)	DCB P2 Q 3.3, 'Spontaneous vaginal birth'	Exclude if 'Breech presentation' ticked for P2 Q 3.4
Secondary outcomes		
Mode of delivery		
Instrumental delivery (forceps and ventouse)	DCB P2 Q 3.3, 'Forceps' or 'Ventouse'	
and primary indication	DCB P2 Q 3.4	
Caesarean section	DCB P2 Q 3.3, 'Caesarean section'	
and primary indication	DCB P2 Q 3.4	
Outcomes from randomisation until delivery		
Augmentation with syntocinin	DCB P2 Q 2.2, 'Yes'	
Major interventions to maintain blood pressure (eg Vasopressors)	DCB P2 Q 2.7, 'Yes'	
Hypotension (systolic BP < 100 mmHg prior to delivery)	DCB P2 Q 2.6, 'Yes'	
Application of fetal scalp clip	DCB P2 Q 2.4, 'Yes'	
Fetal blood sampling	DCB P2 Q 2.3, 'Yes'	
Total doses of epidural local anaesthetic and opioids administered after randomisation	DCB P1 3.3, pump reading DCB P1 5.1, pump reading DCB P2 Q 2.1	Separate outcomes for each type of anaesthetic using the general formula: Dose in milligrams = Local anaesthetic concentration in percent x volume in millilitres x 10 (e.g. 10 mls of 1% lignocaine, dose = 1 x 10 x 10 = 100mg of lignocaine). The opioid amount is calculated separately by multiplying the concentration by the volume.
Duration of active second stage *Time from when pushing commenced to when baby was born*	DCB P2 Q 3.2 – DCB P2 Q 3.1	Presented as minutes
Duration of second stage of labour	DCB P2 Q 3.2 – Date and time taken from randomisation	Presented as minutes

Time from entry into the study to when baby was born	data	
Additional anaesthesia used for operative delivery	DCB P2 Q 3.5, 'Yes'	
Immediate post delivery outcomes		
Active management of the third stage	DCB P2 Q 3.6, 'Yes'	
Episiotomy	DCB P2 Q 3.7, 'Yes'	
Pain during delivery	DCB P1 Q 5.2, Score from 0 to 100	
Genital tract trauma (location and severity)	Perineal tear: DCB P2 Q 3.8, 'Yes'(Perineal tear evident) Severity - degree 1, 2, 3a, 3b, 3c, 4 Sutured - DCB P2 Q 3.9 'Yes'(Perineum sutured) Anterior tear: DCB P2 Q 3.10, 'Yes'(Anterior tear evident) Sutured - sutured ticked 'Yes'	
Manual removal of the placenta	DCB P2 Q 3.11, 'Yes'	
Primary PPH requiring blood transfusion	DCB P2 Q 3.12, 'Yes' AND Units transf>0	
Postnatal period – Woman		
Duration of in-patient stay after delivery	DCB P2 Q 4.1 - DCB P2 Q 3.2	Days from date of delivery to date of maternal discharge from hospital
Satisfaction with experience of birth	The individual items from the MSQ Q 3.	Multiple responses to one question to be treated as missing for the primary analysis.
Postnatal period – Infant		
Cord-artery pH <7.05 in second stage with base deficit ≥ 12 mmol/l	DCB P2 Q 3.19, pH<7.05 AND (base deficit ≥ 12 OR base deficit ≤ -12)	A pH <7.4 will always produce a base deficit (rather than a base excess)
Presence of meconium stained liquor	DCB P2 Q 3.20, 'Yes'	
Apgar score <4 at 5 minutes	DCB P2 Q 3.17, Apgar<4	
Resuscitation at birth	DCB P2 Q 3.21, 'Yes'	
Skin to skin contact within the first hour of birth	DCB P2 Q 3.22, 'Yes'	
Initiation of breastfeeding within the first hour of birth	DCB P2 Q 3.23, 'Yes'	
Duration of in-patient stay	DCB P2 Q 4.2 - DCB P2 Q 3.2	Days from date of delivery to date of infant discharge from hospital
Admission to neonatal unit and duration of stay	DCB P2 Q 3.24, 'Neonatal Unit' Higher Level of Care Form – Infant, Q 1.1, Total number	

	of days in 'Special Care', 'High Dependency Intensive Care' and 'Intensive Care'	
1 year after birth – Woman		
Urinary incontinence	1 Yr Form Qs 4.1 to 4.5. (ref 11) Leaking in first 3 months - Q 4.1 Overall ICIQ-UI score is sum of Qs 4.2, 4.3 x 2 and 4.4 When does Urine leak - Q 4.5	
Faecal incontinence	Individual items from 1 Yr Form Q 4.6	
Other bowel 'problems'	1 Yr Form Q 4.7 (constipation), nvr/frst 3 mnths/lst 4 wks/other time 1 Yr Form Q 4.8 (haemorrhoids), nvr/frst 3 mnths/lst 4 wks/other time	
Dyspareunia	1 Yr Form Q 4.9 (pain on intercourse), nvr/frst 3 mnths/lst 4 wks/other time/no intercourse	
General physical and psychological health	1 Yr Form Qs 2.1 to 2.6 (EQ-5D) (ref 12) – Overall score and overall health state 1 Yr Form Qs 3.1 to 3.7 (SF-12 V2) (ref 13)	See Health Economics Analysis Plan for details on scoring.
1 year after birth – Infant		
Major morbidity e.g. gross neurodevelopmental delay including cerebral palsy (if a diagnosis has been made)	1 Yr Form Q 7.1 (CP) AND/OR Question 7.2 (Other major health problem)	
Hospital admissions	1 Yr Form Q 6.1, 'Yes' and no. of admissions	