



BUMPES

A study of position during
the late stages of labour in
women with an epidural

PROTOCOL

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labour in women with an epidural**

The BUMPES study

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1. Introduction

As the most effective form of pain relief in labour, epidural analgesia is chosen by up to 30% of women in the UK each year (1). Its uptake is greater in nulliparous women, with up to 40% of women having an epidural in large obstetric sites (2). However a systematic review of 21 randomised controlled trials which compared epidural analgesia with non regional or no analgesia in labour found that epidural was associated with an increased risk of instrumental vaginal delivery (IVD) (relative risk (RR) 1.38, 95% CI 1.24 to 1.53) (3).

The trials which made the most contribution to the evidence base were conducted with epidural techniques which caused dense neuraxial blockade. Significant peripheral motor blockade which can accompany conventional high-dose local anaesthetic epidural analgesia inhibits mobility or the adoption of upright positions in labour. "Low dose epidurals", which use low-dose local anaesthetic in combination with opioids (fentanyl), were introduced in the early 1990's and are now in widespread use in the UK. This approach has been shown to result in a lower risk of IVD (4) however, the rate of IVD is still higher than amongst women with no epidural (5).

Reducing the rate of IVD and increasing the spontaneous vaginal delivery (SVD) rate would reduce short and long term morbidity for women by reducing the risk of perineal trauma and the effects of surgical repair. The incidence of perineal pain, dyspareunia and incontinence following IVD could also be improved (6-11). Although mobile epidurals preserve motor function, allowing greater mobility throughout labour and can enable women to adopt upright positions, there is debate about whether an upright posture in the second stage of labour increases the SVD rate.

It is worth noting that the terms "ambulation" and "mobilisation" are often used interchangeably in the literature about epidural techniques which maintain motor function in the lower limbs. As the posture a woman adopts in labour is in part dependent on the motor power she retains, and this can be compromised by epidural pain relief it is clearly important to draw a distinction between *mobilisation*; the ability to move one's legs, change position or move around bed normally and *ambulation* which refers to the act of walking, during labour. The ability to adopt upright postures requires that women retain the capacity to mobilise, some of whom will be able to ambulate.

A systematic review of the impact of ambulation or upright positions in the first stage of labour (before full dilatation of the cervix) amongst women with epidurals on mode of delivery found no significant difference for IVD (RR 1.16, 95% CI 0.93 to 1.44) or caesarean section (RR 0.91, 95% CI 0.70-1.19) (12). The second stage of labour may represent a period during which the adoption of an upright posture could exert the greatest influence and affect delivery mode by facilitating descent of the fetal head. A Cochrane review of position in the second stage of labour in women **without** epidurals showed a reduction in IVD in the upright group (19 trials, RR 0.80, 95%CI 0.69 to 0.92) (13).

The aim of this pragmatic randomised controlled trial is to evaluate whether a policy of enabling upright position compared to a policy of lying down amongst nulliparous women

with a low dose epidural who enter second stage, decreases the incidence of IVD and increases the incidence of SVD.

Postnatal maternal and neonatal morbidity in the first week after birth will be evaluated and long-term maternal postnatal health and well-being assessed one year after birth. A concomitant prospective health economic evaluation of cost effectiveness will be conducted with the trial.

1.1 *Effectiveness of upright position in second stage for women with epidurals*

The incidence of SVD reported in the two randomised controlled trials (14, 15) which have evaluated the effectiveness of adopting an upright position during second stage for women with epidurals is given in Table 1.

Table 1. Upright position versus recumbent position for women with epidural in the second stage of labour and the incidence of spontaneous vaginal delivery

Study	Spontaneous vaginal delivery (%)		
	Upright	Recumbent	Relative risk (95% CI)
Golara <i>et al</i> 2002 [14] n = 66	16/25 (64%)	19/41 (46%)	1.50 (0.98 - 2.30)
Karraz 2003 [15] N = 215	117/141 (83%)	56/74 (76%)	1.10 (0.94 - 1.27)

A published systematic review of the above trials evaluated the effectiveness of maintaining upright positions (standing, walking, kneeling, squatting or sitting at >60 degrees to the horizontal) during the second stage of labour and identified no significant difference in the risk of IVD (RR 0.77, 95% CI 0.46-1.28) or caesarean section (RR 0.57, 95% CI 0.28-1.16) (16). However, there was heterogeneity between the studies, most importantly in the way that the study groups were described. In one trial, women who were sitting in a chair were considered to be in the “upright” group whilst in the other this position was categorised as “recumbent”. This heterogeneity of intervention limits the validity of conclusions based on pooling these studies, systematically or otherwise.

Another trial (17), which was published after the systematic review, was carried out in a single centre and included 107 women, compared a policy of lateral with a policy of sitting position in second stage. No statistically significant difference in IVD was observed between the groups (upright 52% vs recumbent 33%, RR 1.58, 95% CI 0.99-2.54).

1.2 *Effects on short and longer term maternal morbidity*

An intervention that increases SVD by reducing IVD or caesarean section would also be expected to have an effect on short and longer term maternal morbidity. Faecal incontinence is clearly documented as being associated with forceps (10, 18), including ongoing symptoms in women who only ever have one forceps birth (19). There may also be

an increased risk of urinary incontinence, although this may be more closely associated with longer second stage (20, 21), however, women who have a caesarean section have a lower risk of symptoms (22, 23). Other bowel problems of haemorrhoids (20, 21, 24) and constipation (25) are more common after IVD, as are perineal pain and dyspareunia (25, 26). Caesarean section has many adverse sequelae but, with the clear exception of faecal incontinence, most of these symptoms are less likely to occur in association with this delivery mode. It is therefore important to investigate positive as well as any possible negative impacts of upright positions in second stage on maternal health outcomes.

There is increasing interest in obtaining maternity service users views of satisfaction with their experience of birth, as an indicator of the quality of their care and to inform organisational and policy changes (27). Satisfaction is poorly defined, although it is generally agreed that it is a multidimensional concept (28, 29). In one recent systematic review of factors influencing women's satisfaction with birth, with a focus on the role of pain and pain relief, four factors (caregiver support, participation in decision making, personal expectations and caregiver-patient relationship) were identified as important influences (29). As position for second stage could influence a woman's perceptions of the support she receives, her feelings of control and her expectations and experiences of labour and birth, satisfaction is an important consideration. Negative consequences of the position adopted for second stage on these perspectives should also be identified.

2. Current policy and practice

Up to 30% of women in the UK use epidural analgesia for pain relief at some point in labour (1). There is wide variation in the rate of epidural use between units. In a survey of units regarding epidural analgesia for labour usage in the United Kingdom, the epidural rate, including 'low dose' epidurals, ranged from 0 to 85% with an average rate of 24%. Of the 190 units that replied to the survey, 45 (24%) offered 'low dose epidurals' in 1999 (30). There is variation in epidural technique employed to provide pain relief in labour and hospital policies governing maternal ambulation with an epidural in situ. A recent UK survey was conducted via the Obstetric Anaesthetists' Association (OAA) (31) to characterise national epidural practice and policy, with a response rate from lead clinicians of 80%. It found that 95% of respondent units employ various epidural techniques consistent with the adoption of a range of upright positions including ambulation and that fewer than 50% of mothers actually did ambulate. Findings from the BUMPES trial would therefore be widely generalisable to the majority of the nulliparous population who choose epidural pain relief. With regard to reported hospital policies, 34% currently allow maternal ambulation with low dose epidural analgesia in situ. Of those units that prohibit ambulation, 37% cited lack of evidence for a beneficial effect as a reason for this policy. This reluctance may reflect the current uncertainty in this field and that in general midwives have less experience of enabling women with epidurals to ambulate in second stage rather than being in bed.

The NICE Guidelines on Intrapartum Care published in 2007 (32) noted that there is *"No effect of mobilisation following epidural analgesia on any maternal or neonatal outcomes"* and recommended that *"women with regional analgesia should be encouraged to move and adopt whatever upright positions they find comfortable throughout labour"* (Section 1.5.7,

page 22). This guidance is likely to lead to an increase in the use of upright positions hence the need to compare upright position with “lying down” rather than with usual care, given that usual care will increasingly include women assuming an upright position. Good quality evidence is needed on whether upright positions in the second stage of labour in women with epidural analgesia have any beneficial effect on delivery mode and other important outcomes. It is crucial that the policies for the upright and the comparison groups are clearly defined and monitored to ensure separation of the two approaches and provide robust evidence about whether upright position does improve outcomes for women and their babies.

3. Research objectives

The objectives of this trial are:

1. 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.
2. 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.
3. To evaluate cost-effectiveness of the two policies for position during second stage from an NHS perspective.
4. To measure women's satisfaction with, and experience of, labour and delivery.

4. Research methods

A multicentre randomised controlled trial.

5. Trial eligibility

Women who are admitted to a participating labour ward who fulfil all of the following criteria will be 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

6. Randomisation process

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

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

7. Planned interventions

Women will be allocated to a policy of either:

1. Upright maternal position (intervention group) 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

or

2. Lying down maternal position (control group) 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.

** 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*

Women allocated the upright group will be encouraged by their midwife to adopt positions which are as upright a posture as possible (this would include walking, standing, sitting out of bed, supported kneeling or bolt upright in an obstetric bed - see Figure 1), for as much of second stage as possible.



Figure 1: Possible positions for women randomised to the upright maternal position

Women allocated the lying down position (control group) will be 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 (see Figure 2).



Figure 2: Possible positions for women randomised to the lying down maternal position

These pictures are only for illustration.

7.1 ***Preparing and supporting midwives for participation in the trial***

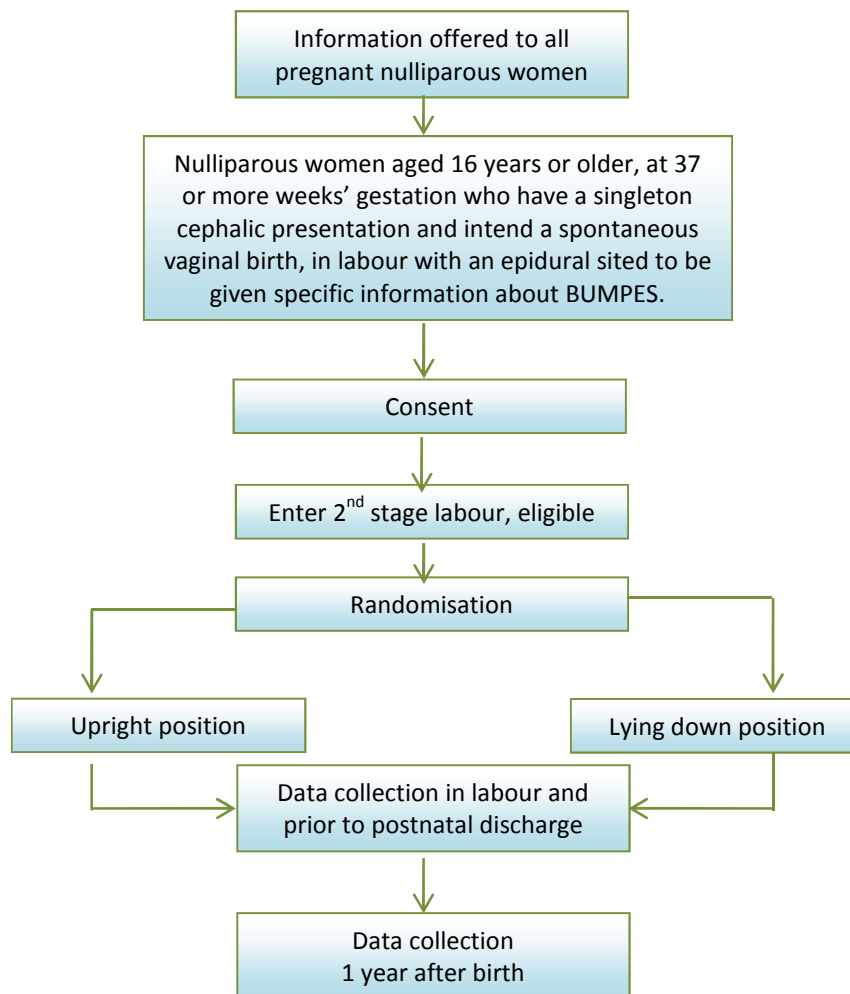
Midwifery staff will need to be willing and able to support women to either adopt a lying down or upright position. Current national guidelines advise that midwives, usually the health care professionals with women during labour, should encourage women with epidurals to mobilise and adopt upright positions in labour (32). However, evidence from the recent OAA national survey of epidural policy and practice indicated that policy in most units (66%) did not allow women with epidurals to mobilise, although upright positions are not prohibited (31). However, the majority of women who deliver vaginally do so in a semi-recumbent position (33). This is partly because women who have epidural analgesia are likely to have their movements restricted by electronic fetal monitoring.

The experience of a team who undertook a trial to compare the effect of lateral or sitting position in the “passive” second stage of labour on the rate of SVD amongst nulliparous women with epidural analgesia (34) has demonstrated the importance of such education, preparation and sustained support.

It will therefore be crucial to the success of this trial that midwives are equally well-prepared to support women to adopt either of the allocated positions. Before randomisation begins, a programme will be implemented in every participating site to provide staff with information and training. This will include explanation and discussion of the importance of protocol adherence and the impact of contamination between allocated groups. Throughout the whole of the period of recruitment, staff will be given regular information and support to ensure that the maximum number of eligible women are randomised and that midwives are able to adhere to the protocol.

Other than the position during the second stage of labour, no other aspect of the clinical management of women participating in this trial will be altered by their participation.

8. Information, randomisation and data collection flow diagram



8.1 *Information for women and obtaining informed consent*

Information about the trial will be provided to all women during the antenatal period, after their booking appointment. This process will be individualised for each participating centre depending on their routine practice to ensure that the maximum number of women are offered information well in advance of labour. For example, in some sites, women will be provided with information about the trial at their routine anomaly scan appointment (18-22 weeks). All women will have the opportunity to ask questions.

When a woman in a participating centre has an effective epidural established during the first stage of labour she can be given a participant information leaflet on the study. If, after reading this and having the opportunity to ask questions, she is willing to take part in the study then informed consent may be taken. The woman must meet most of the eligibility requirements at this stage, though does not have to be in second stage to give consent. It will be clearly stated that she is free to withdraw from the trial at any time for any reason without prejudice to her future care, and with no obligation to give a reason for the withdrawal. Written informed consent will be obtained by a health professional (midwife, obstetrician, anaesthetist) with delegated authority from the Principal Investigator. Consent

will comprise a dated signature from the woman and a dated signature of the person who obtained informed consent.

A copy of the signed informed consent document will be given to the woman. A copy will be retained in the woman's medical notes, a copy retained in the study site file and a copy will be sent to the Trial Co-ordinating Centre, UCL Clinical Trials Unit, University College London.

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

When a woman with an effective low dose epidural is diagnosed as being in the second stage of labour and she fulfills all of the eligibility criteria outlined above she will be randomised.

Information about the trial will continue to be offered to women after they leave the hospital.

9. Outcome measures

9.1 Primary outcome

Incidence of spontaneous vaginal delivery (SVD).

9.2 Secondary outcomes

9.2.1 Mode of delivery

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

9.2.2 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

9.2.3 **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

9.2.4 **Postnatal period – Woman**

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

9.2.5 **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

9.2.6 **1 year after birth - Woman**

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

9.2.7 **1 year after birth - Infant**

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

9.3 ***Process outcomes***

When evaluating a non-discrete intervention such as maternal position during labour, it is important to be able to describe the adherence to the intervention to (a) explain a null-finding, if that is the result, and (b) explore the relationship between adherence and outcome if there is a relationship between maternal position and outcome. There are no accepted and validated methods of measuring adherence with the allocated position in the

second stage of labour and the existing trials have used a variety of methods. Tools such as direct observation of all labours or videoing all labours are impractical and likely to be unacceptable to women and care providers. In the UK all women in the second stage of labour have observations recorded every 15 minutes. We will include at each of these assessments a record 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, the reasons for this.

These data will be used to indicate to what extent the women were able to comply with the allocated intervention during (i) the whole of the second stage; (ii) the “passive” second stage (i.e. before pushing commenced); and (iii) the active second stage (pushing). These data will be summarised, initially to indicate what proportion of women “adhered” to the intervention to produce a dichotomous variable. “Adherence” will be defined when women were able to assume the allocated position for (i) more than 60% of the duration of the whole second stage; (ii) the whole of the “passive” second stage; and (iii) more than half of the duration of the active second stage. This will be used to explore in a “per-protocol” analysis whether adherence with the allocated intervention is associated with a greater chance of SVD. Further analyses will be undertaken to explore whether there appears to be a threshold duration of adherence (absolute or relative) which is associated with achieving a SVD.

9.4 ***Data collection***

For all participating women and babies, information related to labour and the immediate postnatal period will be collected in a specially designed data collection booklet (DCB), which will be completed by the attending midwife. The DCB’s will be checked for completeness. Any missing information will be obtained using medical records. The woman will also be asked to complete a questionnaire before she goes home.

At one year after recruitment, the UCL Clinical Trials Unit will check the status of the mother and baby and their contact details using the National Health Service (NHS) Information Centre (IC) system. Every participating woman will then be sent a self-administered questionnaire with a pre-paid and addressed return envelope. Each woman will be asked to complete a maternal satisfaction questionnaire which will assess her health and wellbeing and that of her baby.

9.5 ***Reporting procedures for serious adverse events (SAEs)***

Although no serious adverse events are anticipated, it is possible that these may occur and a system for reporting these promptly is required. For example, in the upright group, if ambulation is allowed and encouraged in the participating centre, it is possible that women may fall. This will be considered a serious adverse event.

All SAEs occurring during the trial observed by the investigator or reported by the participant, whether or not attributed to the trial, will be reported on the data collection form. SAEs considered to be related to the trial by the investigator will be followed up until resolution or the event is considered stable. The investigator may be asked to provide follow-up

information.

All related SAEs that result 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.

9.6 **Health economics**

A prospective economic evaluation will be conducted alongside the trial with the aim of estimating the cost-effectiveness of adopting either an upright or lying down position in the second stage of labour in nulliparous women who elect to have low dose epidural analgesia. The economic evaluation will be conducted from a health-service perspective. Information on hospital resource utilisation during the intrapartum, postpartum and neonatal periods will be collected using the trial data collection forms and hospital patient administration and maternity information systems. Observational research methods may be used to collect additional costs arising from either strategy.

Current UK unit costs will be applied to each resource item to value total resource use in each arm of the trial. A *per diem* cost for each level of care for the baby and mother will be calculated by sending a detailed questionnaire to the finance department of each centre participating in the trial. The unit costs of clinical events that are unique to this trial will be derived from the hospital accounts of the sites participating in the trial, although primary research may also be required.

Economic costing and preference-based quality of life (QoL) questionnaires at one year after the index birth will be completed by women to document subsequent health care use and health related QoL. The preference-based QoL instruments that will be used are the EQ-5D and the SF 12 (35) questionnaires; both of these instruments can inform the quality adjusted life years (QALYs) metric. The primary outcome of the economic evaluation will be incremental cost-effectiveness ratio, which will be expressed in terms of an incremental cost per QALY gained.

9.7 **Proposed sample size**

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

The following data sources and assumptions have been used in the calculation of the trial sample size:

9.8 **Incidence of primary outcome**

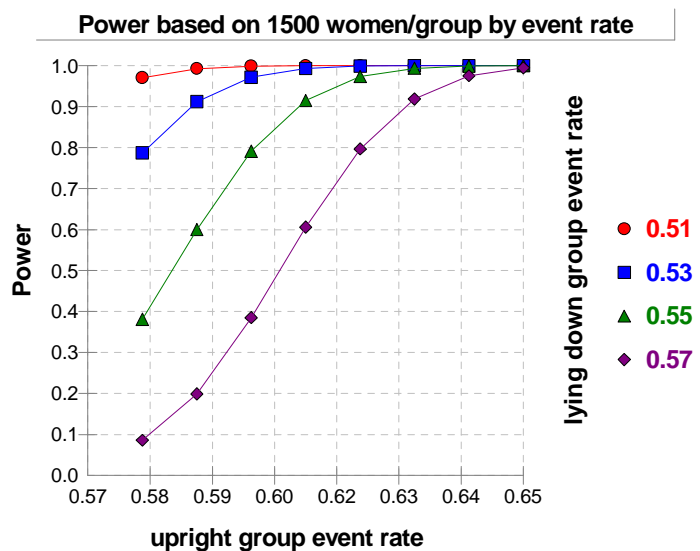
We had originally assumed a rate of the primary outcome spontaneous vaginal delivery (SVD) of 55% in the control group. In the COMET trial (4) undertaken by team members 1,054 women were randomised of whom 701 received an epidural technique consistent with mobilisation. Of those 701 women, 546 entered second stage of labour and experienced the following incidence of delivery mode: SVD: 300 (55%, 95%CI 51 to 59%); IVD: 200 (37%); caesarean section in second stage: 46 (8%) (Wilson, personal communication 2009).

A total sample size of 3000 women (1500 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 effect size possible is therefore desirable. However, this has to be balanced against the cost and practicality of undertaking a trial to detect a difference that is so small, it is not clinically relevant. 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 would be sufficient to change clinical practice in our view.

The proportion in the 'upright' group achieving a spontaneous vaginal delivery (SVD) is 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%. The graph (Figure 3) shows how the power of a sample size of 1500 women per arm changes in relation to the underlying 'upright' group event rate assumptions. Each line displays how the power changes for that particular control group event rate compared to the 'upright' group event rates of between 0.58 (58%) and 0.65 (65%).

For example, the green line (triangle symbols) charts the change in power for a control event rate of 0.55 (55%). It can be seen that when the 'upright' group event is 0.61 (61%), the power is over 0.9 i.e. 90% power. If the control group event rate ends up being higher than we anticipate e.g. 0.57 (57%) then this sample size still achieves 80% power for an absolute difference of 5%; this finding applies to other control event rates.

Figure 3 How the power of a sample size of 1,500 women per arm changes in relation to the underlying 'upright' group event rate assumptions



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 (29).

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 has agreed that changes to the target sample size are considered unnecessary.

10. Statistical analysis

10.1 Primary analysis

A detailed analysis plan will be developed and agreed by the Trial Steering Committee and the Data Monitoring Committee. Demographic factors and clinical characteristics will be summarised with counts (percentages) for categorical variables, mean (standard deviation [SD]) for normally distributed continuous variables, or median (interquartile [IQR] or entire range) for other continuous variables. The primary analysis will be a comparison of the management policies assigned at randomisation (intention-to-treat population). The risk of the primary outcome in the upright group will be compared with the lying down group and tested for significance at the two-sided 5% level of significance. Estimated risk ratios and 95% confidence intervals will be produced. An adjusted analysis of the primary outcome will be performed to investigate the impact of known prognostic factors.

Analysis of secondary outcomes will be clearly delineated from the primary analysis in any statistical reports produced. For secondary outcomes, 99% confidence intervals will be produced, in order to take account of the number of comparisons. Results will be reported according to the CONSORT statement (36).

10.2 Sub-group analysis

The following subgroup analyses have been pre-specified for the primary outcome: recruitment centre, gestational age, maternal age, augmentation in the first stage of labour and Index of Multiple Deprivation. The consistency of the treatment effect across subgroups will be explored using the statistical test of interaction.

Further exploratory analyses will also be undertaken after the main trial report is complete. These will include an exploration of whether there are specific prognostic factors for adverse outcomes. These analyses will be hypothesis-generating and the findings will be interpreted cautiously.

10.3 Economic evaluation

All analyses will be conducted on the basis of intention-to-treat. As the data for costs are likely to be skewed, we shall use non-parametric bootstrap estimation to derive 95% confidence intervals for mean cost-differences between the trial groups (37). Non-

parametric bootstrap methods will also be used to calculate 95% confidence intervals for incremental cost-effectiveness ratios. In the absence of stochastic data for all variables, a series of multi-way sensitivity analyses will be undertaken, to explore the implications of uncertainty on the base-case incremental cost-effectiveness ratios. In addition, cost-effectiveness acceptability curves will be constructed using the net-benefits approach (38).

10.4 *Loss to follow-up*

Loss to follow-up for the primary outcome will be negligible, as this information is collected at the end of labour and before the woman leaves the hospital where she has been recruited. Data on neonatal outcomes will be collected for the small number of babies admitted to the neonatal unit. For the rare instances where babies are transferred out of the recruiting hospital to another hospital for specialist care, data will be collected from the hospital(s) providing care for that child prior to discharge home or death. Data will also be collected on any woman who is admitted for higher level care.

At the time of entry to the trial all women will be asked for permission for their contact details to be collected so that they can be followed up at 1 year after birth.

11. Trial Management

11.1 *Project timetable and milestones*

The first 12 months of this trial includes a pilot phase in two centres during which a training programme for midwives will be developed and tested by the BUMPES team. The pilot allowed the team to develop and test data collection systems and methods. This pilot will be used to model the implementation of trial protocols and inform their roll-out to other recruiting centres. Once the trial infrastructure was determined then additional sites were established and a rolling programme of training and support for midwives implemented.

The original aim was to randomise 3,000 women to the trial over 24 months (after the pilot phase) in five obstetric units in England. Approximately 125 women per month would therefore need to have been recruited.

Following the pilot phase, where it was clear that recruitment expectations were unrealistic, the revised aim is to randomise 3,000 women to the trial over 24 months (after the pilot phase) in multiple obstetric units in the UK. Assuming there are an average of just over 1000 nulliparous women with epidural analgesia per annum per centre, with approximately 70% of these entering second stage of labour and therefore eligible for recruitment, with a 25% recruitment rate, approximately 15 women per month could be recruited once steady state is reached. Based on experience at the pilot centres, a steady state of 12 per centre is considered to be a reasonable monthly target. Again based on experience, recruitment in the first five months of a centre starting will increase gradually to reach a steady state at five months.

Original project Plan

Project years	YEAR 1												YEAR 2												YEAR 3												YEAR 4												YEAR 5																																																										
Months	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57																																																		
Run in period (3 months)	Red																																																																																																										
Recruitment at pilot site (9 months)				Yellow																																																																																																							
Main recruitment period (24 months)													Light Green																																																																																														
Data cleaning				Light Blue																																																																																																							
Follow-up (1 year)																Blue																																																																																											
Final data cleaning																																																		Light Purple																																																									
Analysis & writing up																																																				Light Orange																																																							
Closure of dataset																																																				Blue																																																							
TSC & DMC joint meeting	Orange																																																																																																										
DMC meetings																Orange												Orange																																																																															
TSC meetings									Orange												Orange																																																																																						
Collaborators meetings										Orange												Orange																																																																																					

Revised Project Plan

11.2 ***Ethical arrangements***

The Investigators will ensure that this trial is conducted in full compliance with the current revision of the Declaration of Helsinki (last amended October 2008) and with relevant regulations and with the MRC GCP guidelines which are based on ICH Guidelines for GCP (CPMP/ICH/135/95) July 1996. The trial can only start after approval from a Research Ethics Committee and the local Research and Development departments at each of the participating sites.

11.3 ***Research Governance and Insurance***

The sponsor of the trial is the UCL. The trial will be run on a day-to-day basis by the UCL Clinical Trials Unit Project Management Group. This group reports to the Trial Steering Committee which is responsible to the trial sponsor (UCL). At each participating centre, local Principal Investigators will report to the Project Management Group via the project funded staff based at the UCL Clinical Trials Unit.

University College London holds insurance against claims from participants for injury caused by their participation in this clinical study. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, if this clinical study is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the clinical study. University College London does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or otherwise.

Hospitals selected to participate in this clinical study must provide clinical negligence insurance cover for harm caused by their employees and a copy of the relevant insurance policy or summary can be provided on request

11.4 ***Quality Control and Quality Assurance Procedures***

Compliance with the protocol will be ensured by a number of procedures:

11.4.1 ***Site set-up and training***

Start-up visits at each site, including training in trial procedures, will be performed before the first woman is enrolled.

Regular site visits will be made by the trial research midwife to ensure adherence to the protocol and to deal with any specific site issues. Midwife trial days will be undertaken to ensure that midwives involved with the trial are fully apprised of issues such as consent, compliance with the protocol, data collection and changing regulations.

An annual meeting for Principal Investigators and midwives will be organised when workshops to discuss protocol issues, data collection issues and trial specific procedures are conducted.

11.4.2 ***Data collection, processing and monitoring***

All trial data are:

- Collected using specific BUMPES data collection forms.

- Processed and monitored centrally for consistency, viability and quality at the Trial Co-ordinating Centre, UCL Clinical Trials Unit, UCL
- Screened for out-of-range data, with cross-checks for conflicting data within and between data collection forms using computerised logic checking screens
- Referred back to the relevant centre for clarification in the event of missing items or uncertainty
- Processed using a double data-entry system by independent data clerks.

11.4.3 **Central statistical monitoring**

All data are monitored using central statistical monitoring by the trial statistician based at the National Perinatal Epidemiology Unit CTU, University of Oxford, for consistency, viability and quality using bespoke data management systems. Central statistical monitoring is used to monitor patterns of recruitment at sites, characteristics of women, time of recruitment, etc. Central statistical monitoring can be utilised 'for cause' purposes if necessary.

The trial programmer runs trial-specific programs to extract certain fields from the database (as requested by the Chief Investigator, or Trial Statistician) and to cross-check certain information. These fields may include measures of eligibility criteria, management after trial entry and compliance but not by allocation.

The trial programmer and Chief Investigator will review the results generated for logic and for any patterns or problems. Outlier data will be investigated. The Chief Investigator and Trial Statistician will decide if any action needs to be taken.

11.4.4 **On-site monitoring**

- A random sample of cases are monitored at source when site visits are performed (Source Document Verification).
- The documents to be verified are randomly selected using computerised trial number generation. Any major discrepancies found at a site visit would trigger a more extensive audit of trial data at the site involved.

11.4.5 **National registration systems**

All women recruited into BUMPES, and their babies, will be 'flagged' after discharge. Information held by the NHS and records maintained by The NHS Information Centre and the NHS Central Register may be used to help contact participants and provide information about their and their baby's health status.

11.5 **Co-applicant Group**

The Co-applicant group comprises Peter Brocklehurst, Debra Bick, Janesh Gupta, Ed Juszcak, Christine MacArthur, Rona McCandlish, Phil Moore, Mary Nolan, Geraldine O'Sullivan, Stavros Petrou, Julia Sanders, Andy Shennan and Matthew Wilson.

11.6 ***Clinical Investigators Group***

The Clinical Investigators Group (CIG) comprises the Co-applicants, the Clinical Investigators from each Study site, the Study Clinical Consultant, the Study Health Economist, the Study Co-ordinator, the Study Statistician, the Senior Research Midwife and other project staff. The CIG will meet periodically (every 3-6 months) but more frequently during trial set-up.

11.7 ***Project Management Group***

The Project Management Group (PMG) comprises the Study Chief Investigator, the Study Health Economist, the Study Co-ordinator, the Study Statistician, the Senior Research Midwife and other project staff. The PMG staff based at the UCL Clinical Trials Unit will hold regular meetings (every 3-4 weeks).

11.8 ***Trial Steering Committee***

The trial will be supervised by an independent Trial Steering Committee (TSC). The specific tasks of the TSC are:

- (i) to approve the trial protocol;
- (ii) to approve necessary changes in the protocol based on considerations of feasibility and practicability;
- (iii) to receive the report from the Data Monitoring Committee;
- (iv) to resolve problems brought to it by the co-ordinating centre;
- (v) to approve trial reports and papers for publication.

11.9 ***Data Monitoring Committee***

An independent Data Monitoring Committee (DMC) will be established for the trial. This will be independent of the trial organisers and will meet yearly. During the period of recruitment to the trial, interim analyses will be supplied, in strict confidence, to the DMC, together with any other analyses the DMC may request. The data will be supplied to the Chair of the DMC as frequently as he or she requests. Other meetings of the committee may be 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 will inform the Trial Steering Committee, if in their view there is proof beyond reasonable doubt that the data indicate that any part of the protocol under investigation is either clearly indicated or contra-indicated, either for all women or for a particular subgroup of trial participants. A decision to inform the Trial Steering Committee will in part be based on statistical 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 trial 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 is proposed (39). Unless modification or cessation of the protocol is recommended by the DMC, the Trial Steering Committee, collaborators and administrative staff (except those who supply the confidential information) will remain blind to the results of the interim analysis. Collaborators and all others associated with the trial may write through the trial office to the DMC, to draw attention to any concern they may have about the possibility of harm arising from the treatment under study, or about any other matters

that may be relevant.

One interim analysis is planned for each year of recruitment.

11.10 **Local Co-ordination**

Each participating site will identify a site specific Principal Investigator who will nominate a local co-ordinator for that site (this may be him/herself) whose responsibilities will be to:

- be familiar with the Trial
- liaise with the Trial Co-ordinating Centre at the UCL Clinical Trials Unit
- ensure that all staff involved in the care of eligible women are informed about the Trial and have received requisite training
- ensure that mechanisms for recruitment of eligible women, including the ready availability of parent information, are in place; monitor their effectiveness and discuss the reasons for non-recruitment with relevant staff
- notify the Trial Co-ordinating Centre of any serious adverse events
- make data available for verification, audit and inspection processes as necessary
- ensure that the confidentiality of all information about Trial participants is respected by all persons

11.11 **Publication policy**

The Chief Investigator will co-ordinate dissemination of data from this trial. All publications using data from this trial to undertake original analyses will be submitted to the TSC for review before release.

To safeguard the scientific integrity of the trial, data from this trial will not be presented in public before the main results are published without the prior consent of the TSC. The success of the trial depends on a large number of midwives and obstetricians. For this reason, credit for the results will not be given to the committees or central organisers, but to all who have collaborated and participated in the trial. Acknowledgement will include all local co-ordinators and collaborators, members of the trial committees, the Trial Co-ordinating Centre and trial staff.

Authorship at the head of the primary results paper will take the form “The Epidural and Position Trial Collaborative Group”. This avoids giving undue prominence to any individual. All contributors to the trial will be listed at the end of the report, with their contribution to the trial identified.

Those responsible for other publications reporting specific aspects of the trial may wish to utilise a different authorship model, such as “[name], [name] and [name] on behalf of the Epidural and Position Trial Collaborative Group”. Decisions about authorship of additional papers will be discussed and agreed by the trial investigators and the TSC.

The women participating in the trial will be sent a summary of the final results of the trial, which will contain a reference to the full paper. A copy of the journal article will be available on request from the UCL Clinical Trials Unit.

Appendix: Original Projected Recruitment

Assumptions:

Recruitment lasts 33 months – 9 months in a pilot site, 24 months at 5 sites.



Revised Projected Recruitment



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