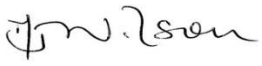
RESPITE TRIAL

END OF TRIAL REPORT

Title	The RESPITE Trial: A Randomised Controlled Trial of Remifentanil intravenous patient Controlled analgesia (PCA) versus intramuscular pethidine for pain relief in labour
EudraCT number	2012-005257-22
Sponsor protocol code	RG_12-151
ISRCTN number	29654603
Sponsor details	University of Birmingham
REC reference number	13/EM0239
Details of IMP	Remifentanil and Pethidine
Arms	This was a two-arm trial. Patients were randomised in a 1:1 ratio to receive either intramuscular pethidine or remifentanil PCA
Analysis stage	Final
Date of end of trial declaration	18th October 2016
Primary completion date	3rd September 2016
Global end date of trial reached?	Yes

Chief Investigator	Dr Matthew Wilson
Signature	
Date	18th October 2017

This report was prepared by the Chief Investigator and Trial Coordinator on behalf of the Sponsor.

Public and Scientific Contact:
Dr Matthew Wilson
School of Health and Related Research
University of Sheffield, Regent Court
30 Regent Street, Sheffield, S1 4DA

E-mail: Matthew.Wilson@sth.nhs.uk

GENERAL INFORMATION ABOUT THE TRIAL

Background and Rationale

Childbirth can be extremely painful and the majority of women who deliver in modern obstetric units choose a pharmacological method of pain relief. The commonest opioid used in labour is intramuscular pethidine, however, its effectiveness in providing pain relief has long been challenged and has known side effects including maternal sedation, nausea and potential transfer across the placenta to the foetus. More than a third of women who receive pethidine subsequently require an epidural due to inadequate pain relief. Epidurals provide highly effective pain relief, but increase the risk of a forceps or suction delivery which may extend hospital stay and produce long term consequences, such as incontinence or sexual dysfunction. Therefore there is a clear need for a safe, effective, easy to administer analgesic alternative.

Epidural pain relief is the most effective form of analgesia for childbirth but is associated with an increased prevalence of instrumental vaginal delivery. Remifentanil PCA is gradually entering clinical practice and its utility expanding. There is evidence to suggest that remifentanil PCA may reduce the requirement for epidural pain relief when compared to current standard systemic opioid administered for labour; intra-muscular pethidine. If this effect can be proven, the burden of excess intervention associated with epidural analgesia may be alleviated. A reduction in instrumental vaginal delivery rates has the potential to reduce maternal morbidity and hospital stay.

Although several studies have examined the effectiveness of PCA remifentanil relative to other analgesic regimen, no trial has been conducted with progression to epidural as a primary end-point. Whilst there may be no direct benefit to individual patients taking part in this trial, beyond effective pain relief in labour, the end results may result in a new way of delivering pain relief for women in labour and benefit future generations.

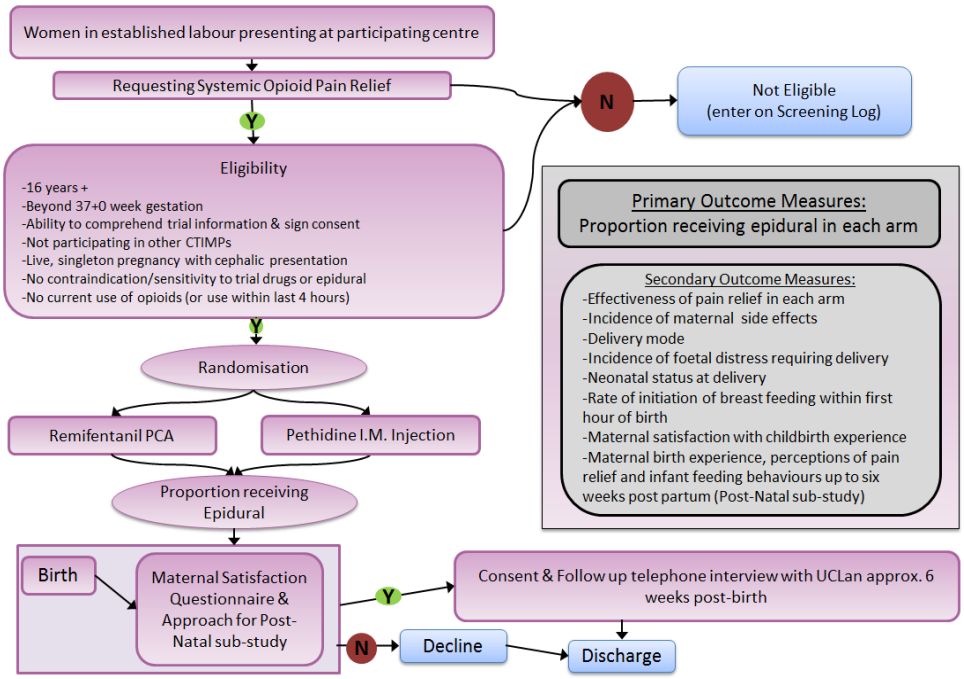
The “null hypothesis” was that the proportion of women requesting epidural pain relief after i.m. pethidine (control) and PCA remifentanil (intervention) will be the same. The objective was to prove the null hypothesis incorrect by demonstrating a significantly lower prevalence of epidural requirement in women randomised to PCA remifentanil, relative to i.m. pethidine.

RESPITE compared remifentanil intravenous PCA to intramuscular pethidine (normal care) in a randomised controlled trial. Women in established labour, requesting systemic opioid pain relief were randomised to either remifentanil intravenous PCA or pethidine intramuscular injection (im). The primary aim was to determine the proportion of women who have an epidural placed for pain relief in labour, in each group. The effectiveness of pain relief by visual analogue score, maternal sedation and any effects on the baby and mother at delivery were also considered. This multicentre study had a target of 400 women to recruit over approximately 24 months. The results will be used to make recommendations on the use of remifentanil in childbirth via publications and clinical guidelines.

Main Objective

The primary aim was to determine the proportion of women who had an epidural placed for pain relief in labour, in each group.

Trial Schema



Trial Design

RESPITE was a multi-centre, open, Phase IV randomised controlled trial.

Background Therapy

After the administration of analgesia, all women received one-to-one midwifery care and had observations recorded including:

- Respiratory rate and continuous oxygen saturation monitoring by pulse oximetry
- Sedation score every 30 minutes
- Visual analogue pain score every 30 minutes

SUBJECT DISPOSITION

Eligibility Criteria

Women who were admitted to labour ward and fulfilled all the following criteria were eligible to be randomised:

- Requesting systemic opioid analgesia
- 16 years of age or older
- Beyond 37+0 weeks' gestation
- In established labour, defined as regular painful contractions, irrespective of cervical dilatation, with vaginal birth intended
- Able to understand all information (written and oral) presented (using an interpreter if necessary) and provide signed consent.
- Not participating in any other clinical trial of a medicinal product
- Live, singleton pregnancy with cephalic presentation.

Any women, who at the point of randomisation, exhibited any of the following were not eligible for the trial:

- Contraindication to epidural analgesia
- Contraindication to intramuscular injection
- History of a previous adverse reaction to Pethidine or Remifentanil
- Patients taking any long term opioid drug therapy including Methadone
- Systemic opioid pain relief in the last 4 hours administered by intravenous or intramuscular injection. (Oral medications comprising opioids alone or in combination preparations, administered in this 4 hour period, are permitted).

Recruitment

The first patient was recruited and randomised into the trial on 13/05/2014 and the last patient was randomised into the trial on 02/09/2016.

The study was open in the UK only and was open in 16 centres in total. 2 centres closed prematurely after failing to recruit any women and 1 centre closed prematurely after only recruiting one woman.

Population of Trial Subjects

A total of 401 women were randomised into the study, all aged between 16-51 years old.

Allocation Method and Blinding

Patients were recruited into the trial via an unblinded 1:1 individual randomisation. A minimisation procedure using a computer-based algorithm was used. The stratification variables were:

1. parity: nulliparous vs. multiparous.
2. maternal age: <20, 20-<30, 30-<40, 40+.
3. ethnicity: South Asian (Pakistani/Indian/Bangladeshi) vs Other.
4. induced vs spontaneous labour.

Drug Treatment Schedule

At randomisation women either received intramuscular pethidine or intravenous remifentanil PCA.

Women who were allocated pethidine received 100mg dose by intramuscular injection, up to 4 hourly in frequency (up to a maximum of 4 doses). The maximum dose being 400mg in 24 hours.

Women who were allocated remifentanil PCA received a 40µg dose with a lock out interval of 2 minutes. A dedicated intravenous cannula was also used for remifentanil administration. PCA pump programming was pre-set by anaesthetic staff in accordance to the single protocol indicated above. This dose regime was based on sample guidelines adapted from those used in the introduction of Remifentanil PCA into clinical practice in the applicant's own labour ward and reflect those used in the largest study up to 2010-11. In the event of excess sedation being recorded by regular observation of respiratory function the regimen was altered by reduction of the remifentanil bolus dose to 30µg with a lock-out interval of 2 minutes.

Following delivery, the mother and her baby were managed as appropriate by the clinical staff and no trial specific procedures were required. Women were invited to complete a Maternal Satisfaction questionnaire prior to hospital discharge.

Withdrawals, Deaths and Losses to Follow-Up

A total of 401 patients entered the trial, with 201 patients entered into the remifentanil PCA group and 200 in the pethidine group.

There were 201 women contributing to the primary outcome in the remifentanil PCA group and 199 in the pethidine group, 99.8% overall. One woman in the pethidine group withdrew consent to use her data. There were no maternal or neonatal deaths.

There was no routine follow up required after hospital discharge of mother and baby. Women were required to complete a Maternal Satisfaction questionnaire following birth but prior to hospital discharge. The completion rates for this questionnaire were 92% in the remifentanil arm and 88% in the pethidine arm.

BASELINE CHARACTERISTICS

Table 1: Patient characteristics at baseline

	Remifentanil (N=201)	Pethidine (N=199)	All Subjects (N=400)
Minimisation			
Parity			
Nulliparous	121 (60%)	118 (59%)	239 (60%)
Multiparous	80 (40%)	81 (41%)	161 (40%)
Ethnicity			
South Asian†	31 (15%)	30 (15%)	61 (15%)
Other	170 (85%)	169 (85%)	339 (85%)
Type of labour			
Induced	137 (68%)	136 (68%)	273 (68%)
Spontaneous	64 (32%)	63 (32%)	127 (32%)
Age At Randomisation			
<20	12 (6%)	13 (7%)	25 (6%)
20–29	99 (49%)	97 (49%)	196 (49%)
30–39	80 (40%)	80 (40%)	160 (40%)
≥40	10 (5%)	9 (4%)	19 (5%)
Patient Characteristics			
Age At Randomisation			
Mean (SD, N)	29.4 (6.1, 201)	29.3 (6.1, 199)	29.3 (6.1, 400)
Range	17-51	16-44	16-51
Full Ethnicity Categories			
White	146 (73%)	157 (79%)	303 (76%)
Black/Black British	8 (4%)	7 (3%)	15 (4%)
Chinese/East Asian	4 (2%)	0 (-)	4 (1%)

	Remifentanil (N=201)	Pethidine (N=199)	All Subjects (N=400)
Asian (Indian)	7 (4%)	12 (6%)	19 (5%)
Asian (Pakistani)	23 (11%)	17 (9%)	40 (10%)
Asian (Bangladeshi)	1 (1%)	1 (1%)	2 (<1%)
Mixed	3 (1%)	0 (-)	3 (1%)
Other	9 (4%)	5 (2%)	14 (3%)
Weight (kg)			
Mean (SD, N)	73.1 (18.4, 194)	74.0 (17.2, 192)	73.6 (17.8, 386)
Range	45-147	38-125	38-147
Height (cm)			
Mean (SD, N)	164.2 (7.4, 193)	164.3 (7.4, 191)	164.3 (7.4, 384)
Range	138-188	145-183	138-188
Current Pregnancy and Labour			
Gravidity			
Median [IQR, N]	2 [1-3, 201]	2 [1-3, 199]	2 [1-3, 400]
Range	1-8	1-7	1-8
Parity			
Median [IQR, N]	0 [0-1, 201]	0 [0-1, 199]	0 [0-1, 400]
Range	0-4	0-4	0-4
Previous Live Births			
Median [IQR, N]	0 [0-1, 201]	0 [0-1, 199]	0 [0-1, 400]
Range	0-4	0-4	0-4
Previous Term Births (>37 weeks)			
Median [IQR, N]	0 [0-1, 201]	0 [0-1, 199]	0 [0-1, 400]
Range	0-4	0-4	0-4
Previous Pre-term Births (34-37 weeks)			
Median [IQR, N]	0 [0-0, 201]	0 [0-0, 199]	0 [0-0, 400]

	Remifentanil (N=201)	Pethidine (N=199)	All Subjects (N=400)
Range	0-1	0-1	0-1
Previous Pre-term Births (<34 weeks)			
Median [IQR, N]	0 [0-0, 201]	0 [0-0, 199]	0 [0-0, 400]
Range	0-1	0-1	0-1
Previous Miscarriages			
Median [IQR, N]	0 [0-1, 201]	0 [0-1, 199]	0 [0-1, 400]
Range	0-5	0-5	0-5
Previous Still Births			
Median [IQR, N]	0 [0-0, 201]	0 [0-0, 199]	0 [0-0, 400]
Range	0-1	0-1	0-1
Previous Delivery Modes			
Spontaneous Vaginal Delivery	58 (74%)	50 (63%)	108 (69%)
Instrumental Vaginal Delivery	14 (18%)	19 (24%)	33 (21%)
Elective Caesarean Section	7 (9%)	2 (3%)	9 (6%)
Emergency Caesarean Section	12 (15%)	15 (19%)	27 (17%)
Events Pre-Study Entry			
Pre-eclampsia			
Yes	8 (4%)	8 (4%)	16 (4%)
No	193 (96%)	191 (96%)	384 (96%)
Continuous Electronic Fetal Monitoring			
Yes	188 (94%)	184 (92%)	372 (93%)
No	13 (6%)	15 (8%)	28 (7%)
Syntocinon Commenced			
Yes	100 (50%)	103 (52%)	203 (51%)
No	101 (50%)	96 (48%)	197 (49%)
Events Post-Study Entry			

	Remifentanil (N=201)	Pethidine (N=199)	All Subjects (N=400)
Syntocinon Augmentation			
Yes	101 (50%)	105 (53%)	206 (52%)
No	100 (50%)	94 (47%)	194 (48%)
Fetal Blood Sampling			
Yes	23 (11%)	21 (11%)	44 (11%)
No	178 (89%)	178 (89%)	356 (89%)
Fetal Scalp Clip Applied for the First Time			
Yes	35 (17%)	39 (20%)	74 (18%)
No	166 (83%)	160 (80%)	326 (82%)

†Pakistani/Indian/Bangladeshi.

END POINTS

Primary End Point

The primary outcome measure was the proportion of women who had an epidural placed for pain relief in labour, in each group.

Secondary End Points

Secondary measures were:

- The effectiveness of pain relief provided by each technique, quantified by Visual Analogue Scale taken every 30 minutes after time zero, until epidural placement, delivery or transfer to theatre.
- The incidence of maternal side effects, up to the end of 3rd stage, including
    - Excessive sedation score (not rousable to voice)
    - Oxygen Saturation <94% whilst breathing room air
    - Nausea requiring anti-emetic administration
    - Requirement and indication for supplemental oxygen
    - Respiratory depression (respiratory rate < 8 breaths/minute)
- Delivery mode (Spontaneous vaginal, Instrumental vaginal, Caesarean Section)
- Incidence of foetal distress requiring delivery
- Neonatal status at delivery:
    - Apgar score at 5 minutes
    - Incidence of foetal acidosis determined by umbilical cord gas analysis (if performed)
    - Requirement for neonatal resuscitation

    - Incidence of and indication for admission to neonatal care
- Rate of initiation of breast feeding within the first hour of birth
- Maternal satisfaction with childbirth experience determined by postpartum questionnaire prior to discharge from the delivery ward

Statistical Analyses

All patients with available data were included in the analyses and were analysed in the group to which they were randomised (intention-to-treat analysis).

The primary analysis of the primary outcome was a comparison of the rate of conversion to epidural between Remifentanil PCA and Pethidine (usual care) using a log-binomial model. The primary analysis was unadjusted and by intention to treat. A further log-binomial model was fitted adjusting for minimisation variables.

In addition to the primary unadjusted ITT analysis two 'per-protocol' analyses were undertaken for the primary outcome only as a sensitivity analysis to explore the potential effect of non-adherence to the randomised allocation and cross-over between treatment arms.

The effectiveness of pain relief quantified by visual analogue scale (VAS) was recorded on the maternal observations form every 30 minutes from time of randomisation until delivery, transfer to theatre or placement of epidural. VAS scores were reduced to two values; maximum and median. Each were analysed separately using t-tests to compare Remifentanil PCA and Pethidine (usual care).

The requirement for supplemental oxygen was compared between Remifentanil PCA and Pethidine (usual care) using a chi-squared test. The CRF used to capture data regarding supplemental oxygen was changed part way through the trial to acquire a more detailed summary of reasons why supplementary oxygen was administered.

Respiratory rate (breaths/minute) was recorded on the maternal observations form every 30 minutes from time of randomisation until delivery or transfer to theatre. Respiratory rate was reduced to a single response- respiratory depression, defined as <8 breaths per minute. The proportion of women who experienced respiratory depression was compared between Remifentanil PCA and Pethidine (usual care) using a chi-squared test or Fishers exact test where appropriate.

Oxygen saturation (%) was recorded on the maternal observations form every 30 minutes from time of randomisation until delivery or transfer to theatre. Oxygen saturation was reduced to a single response-low oxygen saturation, defined as <94% whilst breathing room air. The proportion of women who experienced low oxygen saturation was compared between Remifentanil PCA and Pethidine (usual care) using a chi-squared test.

Sedation score (1-5, 1=fully awake, 5=eyes closed and not rousable) was recorded on the maternal observations form every 30 minutes from time of randomisation until delivery or transfer to theatre. Sedation score was reduced to a single response-excessive sedation, defined as a score ≥4. The proportion of women who experienced excessive sedation was compared between Remifentanil PCA and Pethidine (usual care) using a chi-squared test.

Maternal sedation as a reason for discontinuation of Remifentanil was recorded on the pain relief form and was tabulated with corresponding proportions. No formal hypothesis tests were implemented.

Anti-emetic administration, delivery mode, incidence of admission to higher level care and initiation of breast feeding within the first hour of birth were compared between Remifentanil PCA and Pethidine (usual care) using a chi-squared test.

For women who have an assisted birth, the primary reason for assistance was recorded. The proportion of women who indicated foetal distress as the primary reason for assisted birth was compared between Remifentanil PCA and Pethidine (usual care) using a chi-squared test.

Apgar score (0-10) was recorded at 5 minutes post birth. Apgar score was dichotomised to <4 and ≥4. The proportion of infants who had an Apgar score <4 was compared between Remifentanil PCA and Pethidine (usual care) using a chi-squared test.

Umbilical cord pH and base deficit were recorded at birth. Foetal acidosis was defined as a PH < 7.05 and a base deficit ≥ 12 (or ≤-12). The proportion of infants who had foetal acidosis was compared between Remifentanil PCA and Pethidine (usual care) using a chi-squared test.

The proportion of infants who required neonatal resuscitation was compared between Remifentanil PCA and Pethidine (usual care) using a chi-squared test. The method of resuscitation was tabulated with corresponding proportions.

Data regarding maternal satisfaction was collected by a postpartum questionnaire prior to discharge. This was not a validated questionnaire. Responses to each question of the maternal satisfaction questionnaire were compared between Remifentanil PCA and Pethidine (usual care) using chi-squared tests or fishers exact test where appropriate.

ADVERSE EVENTS

Adverse event information

SAEs were collected for all patients in the study from randomisation until hospital discharge.

There were a total of 16 reported SAEs in RESPITE as shown in the table below.

Table 2: Cumulative Summary Tabulation of Serious Adverse Events

System Organ Class Preferred Term	Treatment	
	Remifentanil	Pethidine
Blood and Lymphatic Disorders		
Bone and Joint injuries		
Cardiac Disorders Hypertrophic cardiomyopathy (neonatal)		**1** 1†
Congenital, familial and genetic disorders		
Ear and labyrinth disorders		
Endocrine disorders		
Eye disorders		
Gastrointestinal disorders		
General disorders and administration site conditions		
Hepatobiliary disorders		
Immune system disorders		
Infections and infestations Sepsis (neonatal) Sepsis (post-delivery; maternal) Pyrexia (neonatal) Respiratory infection (neonatal)	**4** 2* 1 1*	**4** 1 (Pethidine not administered) 1 1

Pneumonia (neonatal)		1†
Injury, poisoning and procedural complications		
Investigations		
Metabolism and nutrition disorders		
Musculoskeletal and connective tissue disorders		
Neoplasms benign, malignant and unspecified		
Nervous systems disorders		
Pregnancy, puerperium and perinatal conditions Post-partum haemorrhage (maternal) Pre-eclampsia	**3** 3	**1** 1
Psychiatric disorders		
Renal and urinary disorders		
Reproductive system and breast disorders		
Respiratory, thoracic and mediastinal disorders Respiratory distress (neonatal) Tachypnoea (neonatal) Meconium aspiration (neonatal) Pulmonary hypertension (neonatal)	**2** 1 1	**4** 1 (Pethidine not administered) 2 1†
Skin and subcutaneous tissue		
Social circumstances		
Surgical and medical procedures		
Vascular disorders		

*1 x neonatal SAE included diagnosis of sepsis and pyrexia (Remifentanil arm)

† 1 x neonatal SAE included diagnosis of hypertrophic cardiomyopathy, pneumonia and pulmonary hypertension (Pethidine arm)

MORE INFORMATION

Substantial Amendments

Table 3: List of substantial protocol amendments requiring approval by the competent authority.

Date of amendment / amended protocol version submitted to the Competent Authority	Amendment description
Substantial amendment 2, dated 4th December 2013. Protocol updated to v1.2	Change in wording of eligibility criteria to make in line with the randomisation form. Section 5.1.2 'continuous' added to oxygen saturation monitoring and removal of '30 mins' from timing
Substantial amendment 5, dated 14th October 2014. Protocol updated to v1.3	Addition of TSC and DMC members, amended TMG members, updated BCTU address and addition of Clinicaltrials.gov NCT number. Section 3.3 wording amended so consent can be obtained once patient enters established labour up to and including the point that the patient requests opioid analgesia. Section 3.4 removed patient initials, parity and gestational age as these are not being collected on screening logs. Section 5.1.3 clarification that no additional temperature monitoring of trial drugs is required beyond established Trust protocols. Section 5.2 clarification that consenting investigator nor research midwife are party to the decision to progress to epidural. Section 6.1.3 list of anticipated SAEs added which are not considered to be related to Pethidine and/or Remifentanil
Substantial amendment 10, dated 15th October 2015. Protocol updated to v2.0	Various clarifications around eligibility assessment, delegated roles, SAE assessment, definition of established labour, scope for co-enrolment, data transferred to University of Aberdeen for randomisations performed via the 24/7 automated telephone system, drug storage and dispensing and the exclusion criteria regarding systemic opioids. Additional information has been added regarding breastfeeding with Pethidine and Remifentanil, incentives for sites in recognition of reaching recruitment targets and extending the recruitment end date. Addition of DMC member, addition of collaborator, change of details for Trial Coordinator

Substantial amendment 12, dated 25th July 2016. Protocol updated to v3.0	Change of BCTU logo, update to table 1 - list of previous studies of remifentanil for analgesia in labour, clarification of secondary outcomes and update to the reference list

Interruptions

Further clarification was required on governance aspects of the trial within protocol v1.4. This resulted in a temporary halt to the trial which was not related to safety of trial patients or data integrity. This was submitted to REC and MHRA via a substantial amendment (substantial amendment 10, dated 15th October 2015) and a serious breach regarding this was also reported to REC and MHRA.

Conclusions

For published outcome data, please see the final trial publication.

Publication and Dissemination

The final publication is in the final draft stages and will be submitted in late 2017.
The paper will initially be submitted to The Lancet.