The RESPIE Trial: A Randomised Controlled Trial of Remifentanil intravenous patient Controlled analgesia (PCA) versus intramuscular pethidine for pain relief in labour

PROTOCOL

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 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. Therefore there is a clear need for a safe, effective, easy to administer analgesic alternative.

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

Sponsor: The University of Birmingham, Dr Sean Jennings Research Governance & Ethics Manager, Research Support Group

Chief Investigator: Dr Matthew J.A Wilson

The University of Birmingham is responsible for obtaining necessary approvals and for pharmacovigilance. The Trial Management Committee is jointly responsible for overseeing good clinical practice and the Investigators are responsible for obtaining informed consent and care of the participants.

Signatures

The investigators and the sponsor have discussed this protocol. The investigators agree to perform the investigation and to abide by this protocol except in case of medical emergency or where departures from it are mutually agreed in writing.

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Dr Matthew J. A. Wilson

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Abbreviations

AE  Adverse event  
AR  Adverse reaction  
BCTU  Birmingham Clinical Trials Unit at the University of Birmingham  
CI  Chief Investigator  
DMEC  Data Monitoring and Ethics Committee  
EudraCT  European Clinical Trials Database  
GP  General Practitioner  
HEFT  Heart of England Foundation Trust  
IMP  Investigational Medicinal Product  
IM  Intramuscular  
ISRCTN  International Standard Randomised Controlled Trial Number  
LVLS  Last Visit of Last Subject  
MHRA  Medicines and Healthcare Products Regulatory Authority  
MRC  Medical Research Council  
MREC  Multicentre Research Ethics Committee  
PCA  Patient Controlled Analgesia  
PI  Principal Investigator – the local lead investigator for the RESPITE Trial  
REC  Research Ethics Committee  
SAE  Serious Adverse Event  
SAR  Serious Adverse Reaction  
SmPC  Summary of Product Characteristics  
SUSAR  Suspected Unexpected Serious Adverse Reaction  
TMG  Trial Management Group  
TSC  Trial Steering Committee
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1. BACKGROUND

1.1. Pain relief in labour: current practice

Childbirth can be extremely painful and the provision of pain relief during labour is a vital component of a positive maternal experience. The majority of women who deliver in modern obstetric units choose a pharmacological method of pain relief, including Entonox, the injection of opioids or epidural placement. The commonest opioid used in labour is pethidine, administered by intramuscular (im) injection.(1) However, the effectiveness of pain relief provided by pethidine has long been challenged(2). Its shortcomings are more serious when set against known side effects including maternal sedation, nausea and potential transfer across the placenta to the foetus.(3) More than a third of women who receive pethidine subsequently require an epidural due to inadequate pain relief.(4) Epidurals provide highly effective pain relief, but increase the risk of a forceps or suction delivery which may extend hospital stay(5-7). Therefore there is a clear need for a safe, effective, easy to administer analgesic alternative. A national survey of intravenous patient controlled analgesia for labour conducted in 2005 reported that 95.4% of UK maternity units used either intramuscular pethidine or diamorphine as their primary method of systemic opioid analgesia in labour, with the majority using pethidine alone and this remains the contemporary situation(1). Therefore it is reasonable to assert that intramuscular pethidine represents current practice.

1.1.1 New options in obstetrics: patient controlled analgesia

Patient Controlled Analgesia (PCA) comprises drug administration into an intravenous drip with a small dose given each time a woman presses a button, giving her control over her own pain relief. The pump is programmed to ensure that the maximum dose allowable is within the safe range. This form of delivery of pain relief matches the drug dose to pain sensation within the relevant time frame, which is not possible using a single dose intramuscular injection.(8) Whilst PCA is in widespread use for acute pain relief it has only a limited role in obstetrics. The most common drug given by PCA is morphine, however, since it has a long duration of action and crosses the placenta, the potential for accumulation in the foetus and consequent neonatal sedation at delivery restricts its utility (within obstetrics) to contexts where neonatal status is not relevant, such as intrauterine foetal death or foetal abnormality incompatible with survival(1).

1.2. Current therapy for pain relief in labour

Remifentanil is a novel synthetic opioid with a very rapid onset (blood-brain equilibration 1.2-1.4 minutes) and short duration of action (context specific half-life 2-3 minutes), giving it an analgesic profile which potentially makes it ideal for providing pain relief over 1-2 uterine contractions after a single intravenous dose. It is subject to rapid redistribution and metabolism by non-specific blood and tissue esterases, negating the potential for accumulation in mother or foetus(9). Administration of remifentanil by PCA has been investigated in several small studies in comparison to pethidine and shown to provide useful, although not complete, pain relief in labour(10-12). Thus far, there is no evidence of detrimental neonatal effects in comparison to other opioids(9;11;13).

Some units are starting to offer this form of pain relief in cases where pain relief is requested, but an epidural is contraindicated, for example in the case of maternal clotting abnormality or platelet dysfunction. However the use of remifentanil PCA is not currently widespread or routine(14). Crucially, there is some evidence from the studies performed thus far that the proportion of women who require rescue pain relief with an epidural after remifentanil PCA is reduced in comparison to pethidine(9), although no study has yet investigated this as a primary end-point. If such an effect were proven and remifentanil demonstrated to be at least as safe and effective as pethidine, the number of women requiring an epidural in labour could potentially be reduced with a concomitant beneficial reduction in instrumental vaginal delivery(5-7) and associated morbidity including incontinence(15) and sexual dysfunction, relative to spontaneous delivery(16;17).
1.3. Literature review
Numerous clinical studies have examined the effectiveness of pain relief in labour provided by Remifentanil PCA. These studies have resulted in the refinement of dose administration techniques to provide the optimum balance between effectiveness and maternal safety.

The table below summarises pertinent remifentanil studies to date and gives details on study size, comparator and the epidural “Conversion” rate, if reported. The heterogeneity of dosing regimen and the opioid techniques used for comparator are immediately apparent, however, a degree of consistency in epidural conversion rate in direction and proportion emerges. It is notable that the only study which reported a higher epidural conversion rate with Remifentanil used a substantially smaller drug dose than those in more recent studies. Thus, inadequate pain relief may have influenced maternal decisions to request neuraxial blockade.

<table>
<thead>
<tr>
<th>Study &amp; Remifentanil technique</th>
<th>N</th>
<th>Comparator</th>
<th>Conversion Comparator</th>
<th>Conversion Remifentanil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blair (Infusion 0.25-0.5 µg/kg/min)</td>
<td>21</td>
<td>None</td>
<td>na</td>
<td>0.19</td>
</tr>
<tr>
<td>Thurlow (PCA 20 µg, lockout 3 min)</td>
<td>36</td>
<td>im pethidine</td>
<td>0.17</td>
<td>0.38</td>
</tr>
<tr>
<td>Blair (PCA 40 µg, lockout 2 min)</td>
<td>39</td>
<td>Pethidine PCA</td>
<td>0.32</td>
<td>0.1</td>
</tr>
<tr>
<td>Evron (Infusion 0.27-0.93 µg/kg/min)</td>
<td>88</td>
<td>Pethidine infusion</td>
<td>0.39</td>
<td>0.11</td>
</tr>
<tr>
<td>Volikas (PCA 0.5 µg/kg lockout 2)</td>
<td>50</td>
<td>None</td>
<td>n/a</td>
<td>0.1</td>
</tr>
<tr>
<td>Balki (Bolus 0.25 µg plus infusion)</td>
<td>20</td>
<td>Variable bolus/infusion Epidural</td>
<td>n/a</td>
<td>0.05</td>
</tr>
<tr>
<td>Douma (PCA 40 µg, lockout 2 min)</td>
<td>20</td>
<td>PCA pethidine/fentanyl</td>
<td>0.34/0.15</td>
<td>0.13</td>
</tr>
</tbody>
</table>

Epidural conversion rates of approximately 10% (range 5% to 19%) are commonly reported after Remifentanil. This compares to conversion rates of greater than 30% (range 17% to 39%) being representative in women receiving Pethidine.

1.4. The choice of questions to be asked
The central question addressed by this trial is whether remifentanil PCA administered for pain relief in childbirth, reduces the requirement for progression to epidural analgesia, relative to intramuscular pethidine injection “standard care”. Secondary questions regarding the relative effectiveness of pain relief, maternal and neonatal indices of well-being and maternal satisfaction will be answered.

A central challenge to randomised methodology is the obvious difference in the techniques under scrutiny. Using a PCA may exert an influence on maternal perception of pain, irrespective of the drug used, as a result of the greater control provided. This may in turn effect progression to other forms of pain relief including epidural. The ideal design would be a double blind individual randomised controlled trial of remifentanil PCA compared to placebo PCA. However, the administration of placebo PCA alone is not ethically justifiable, and would be immediately obvious to the woman and health professional, negating the benefit of blinding. A double dummy trial design would be required, whereby intramuscular pethidine or placebo is given to the placebo PCA and remifentanil PCA groups, respectively. This too raises ethical issues regarding placebo injections, with inherent risks of injury, and may impact on trial acceptance and compliance. A double dummy design would be difficult to implement on a busy delivery suite.
The alternative is to have an open, randomised trial, whereby the randomised allocation is apparent to both participant and healthcare provider. This removes the ethical issues of placebos, reduces complexity and the control group represents current practice. The disadvantage is that the knowledge of the intervention may influence the decision to implement epidural pain relief, introducing performance bias. In the context of this clinical situation, performance bias is not considered to be an issue as use of epidural analgesia will be driven by maternal and clinical need.

1.4.1 Rationale

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 endpoint. 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" is that the proportion of women requesting epidural pain relief after i.m. pethidine (control) and PCA remifentanil (intervention) will be the same. The objective is 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.

2. TRIAL DESIGN

2.1. Design

Women in established labour, requesting systemic opioid pain relief will be randomised to either remifentanil PCA or pethidine intramuscular injection in a unblinded, 1:1 individual randomisation.

3. ELIGIBILITY

3.1. Inclusion and Exclusion Criteria

Women who are admitted to labour ward who fulfll all the following criteria will be eligible to be randomised:

- Requesting systemic opioid analgesia
- 16 years of age or older
- Beyond 37+0 weeks' gestation
- In established labour 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.

3.2. Exclusion criteria

- Contraindication to epidural analgesia
- Contraindication to intramuscular injection
- History of drug sensitivity to Pethidine or Remifentanil
- Patients taking any long term opioid drug therapy including Methadone
- Systemic pain relief opioid in the last 4 hours.

3.3. Approaching potential participants for consent

Gaining consent from women in labour who are experiencing pain requires a pragmatic approach. All women booked to deliver at participating sites will receive information about the study at antenatal clinic, during their pregnancy. Further information will be made available on admission to hospital in labour. All women will have the opportunity to ask questions about the study. When a woman in labour decides that she wants an opioid method of pain relief, she will be approached for consent to participate. If she fulfils all of the criteria, she will be again offered information about the trial to support her decision about whether or not to take part. It will be clearly stated that she is free to withdraw from the trial at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal. A hospital interpreter will be utilised to assist a patient with difficulty in understanding English.

Written informed consent will be obtained by a health professional with delegated authority from the Principal Investigator. Consent will comprise a dated signature from the woman and the signature of the person who obtained informed consent. A senior investigator will be available at all times to discuss concerns raised by women or clinicians during the course of the trial. Women will be able to follow the progress of the trial and obtain a summary of the final results via the RESPITE trial website.

The time interval from obtaining consent to randomisation (and administration of pain relief) will progress as quickly as possible.

3.4. Ineligible patients

An anonymous record of women ineligible for randomisation and those approached for consent, who decline, may be kept on a screening log if practicable to do so at the centre involved. The log will collect women’s initials, age, ethnic group, parity, gestational age and ineligibility reason. The log should be kept in the centre site file and a copy returned to BCTU. If completed accurately, the logs will inform recruitment targets for RESPITE and give an indication of the external validity of the study.

4. RANDOMISATION

<table>
<thead>
<tr>
<th>Randomisation</th>
</tr>
</thead>
<tbody>
<tr>
<td><a href="https://www.trials.bham.ac.uk/RESPITE">https://www.trials.bham.ac.uk/RESPITE</a>.</td>
</tr>
<tr>
<td>Telephone 0800 953 0274</td>
</tr>
<tr>
<td>Fax 0121 415 9136</td>
</tr>
<tr>
<td>Telephone randomisations are available Monday-Friday, 09:00-17:00.</td>
</tr>
<tr>
<td>Online randomisation is available 24 hours a day, 7 days a week apart from short periods of scheduled maintenance and occasional network problems.</td>
</tr>
</tbody>
</table>

4.1. Randomisation

4.2. Randomisation method and stratification variables

Randomisation will be carried out via a web-based central service (with telephone back-up during office hours) based at Birmingham Clinical Trials Unit (BCTU). To confirm eligibility, investigators
will need to verify the woman’s gestation and age, confirm all eligibility criteria and provide baseline data items. Before assignment of a trial number and randomised allocation. At randomisation a confirmatory email will be sent to the randomising investigator, the local PI and the research midwife. A ‘minimisation’ procedure using a computer-based algorithm will be used to avoid chance imbalances in parity, an important prognostic variable, which will be considered as an ordinal variable.

Stratification variables will be:

1. parity: nulliparous vs. multiparous.
3. ethnicity: South Asian (Pakistani/Indian/Bangladeshi) vs Other.
4. induced vs spontaneous labour.

The procedures for randomisation will be fully documented and tested prior to the start of the trial and monitored by BCTU.

5. TREATMENT ALLOCATIONS

5.1. Remifentanil and Pethidine (IMPs)

Women will be randomly allocated to either:

1. Remifentanil PCA (intervention group)
2. Intramuscular injection of pethidine (control group).

5.1.1 Dose and route of administration

Remifentanil via PCA pump (18)

- Dedicated intravenous cannula for remifentanil administration
- PCA protocol
  - PCA bolus remifentanil 40 µg
  - Lockout interval 2 minutes

PCA pump programming will be pre-set by anaesthetic staff in accordance to the single protocol indicated above. This dose regime is 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 to date(19;20). In the event of excess sedation being recorded by regular observation of respiratory function (see Section 5.1.2), the regimen will be altered by reduction of the remifentanil bolus dose to 30 µg with a lock-out interval of 2 minutes.

Pethidine

- 100mg by intramuscular injection, up to 4 hourly in frequency (up to a maximum of 4 doses). The maximum dose being 400mg in 24 hours.

5.1.2 Intrapartum care

After the administration of analgesia, a trial participant will receive the following standards of care independent of group allocation:

- One-to-one midwifery care
- Observations including
  - Respiratory rate and continuous oxygen saturation by pulse oximetry
Indications for contacting an anaesthesia provider

- Excessive Sedation Score (not rousable to voice)
- Respiratory rate <8 breaths/minute
- Oxygen Saturation <94% whilst breathing room air

5.1.3 Supply of Remifentanil and Pethidine

No pharmacy provisions are required for drug utilization beyond established clinical protocols already in place at participating centres. The drugs compared in this trial are generic and not trial specific. They are in routine use and readily available from clinical hospital supplies. Trial drugs will therefore be sourced ‘off-the-shelf’ from normal labour wards, stored as standard hospital stock, and no additional trial specific labelling will be applied. All details of trial drug are as per the requirements of the Medicines for Human Use (Clinical Trials) Regulations 2004. The drugs will be administered according to trial and local protocols and in compliance with the national guidelines for the use of controlled drugs.

5.1.4 Study Treatment Accountability

A record will be kept of trial drugs dispensed. This is a standard requirement for dispensing controlled drugs for pain relief in labour. The attending clinician administering the randomised analgesic will be required to record each dose and batch number on the patient’s specific case report form. Any subsequent changes in dose, will be recorded on this form, along with the batch number(s) and the time/date.

5.2. Decision to convert to epidural anaesthesia

Participants are free to request epidural pain relief at any point after trial entry. A maternal request for epidural analgesia will be treated according to local labour ward practice including assessment by attending midwifery and anaesthetic staff. The precise details of epidural technique will be dictated by local labour ward protocols. In the rare instance of epidural placement being recommended for medical indications arising during labour, this will be recorded. There is no reason to expect an imbalance of such an event between allocated groups.

Once effective epidural is established, the administration of opioid drugs will be discontinued irrespective of trial group allocation. Recordings of maternal observations and neonatal status will be taken at delivery.

5.3. Withdrawal from treatment

Withdrawal from treatment is a decision of the participant however, withdrawn patients can bias trial results and reduce the power of the trial to detect important differences, so women should be encouraged to allow data collection to continue even if trial treatment ceases.

There are unlikely to be many instances of withdrawal from the trial on the grounds of inadequate analgesia since there is no restriction on the availability of pain relief after study entry. There will be occasions where study participants do not progress to the end of labour. The commonest foreseeable reason for this will be intervention by emergency caesarean section in the event of fetal distress necessitating expeditious delivery. Provision has been made in the study population to absorb the impact of such attrition. These women will remain in the study for the purposes of analysis. Withdrawal of treatment will also be necessitated in cases where a known serious adverse reaction to the trial drugs occurs or a suspected unexpected serious adverse reaction occurs.
There may be rare occasions when a woman decides to withdraw from the study for other reasons (such as refusal to take trial drugs). The patient is free to withdraw from the trial, at any time, for any reason, without prejudice to future care and with no obligation to give reason for withdrawal. These will be recorded and a request made to utilise the data accumulated prior to withdrawal.

5.4. Protocol violation

Any incidences of study participants not receiving the specified treatment allocation by randomisation will be recorded in a similar way. For example, there may be very rare occasions on which emergency delivery by caesarean section, in the interests of fetal well-being, is indicated after randomisation, before administration of opioid pain relief. Women will be analysed according to group allocation, by intent-to-treat analysis.

6. SAFETY MONITORING PROCEDURES

There may be unexpected serious adverse reactions associated with Remifentanil and/or Pethidine when used in labour. Remifentanil and Pethidine used to treat pain relief have been associated with rare but serious adverse reactions (see Appendix E).

The Medicines for Human Use (Clinical Trials) Regulations 2004 define categories of adverse events, the responsibilities of the investigators to notify adverse events to the sponsor and for the sponsor to report to the regulatory authority and ethics committee. It is therefore imperative that all investigators have a thorough understanding of anticipated adverse events and the reporting process of these events.

6.1. General Definitions

6.1.1 Adverse Events (AEs)

An AE is:

- any unintentional, unfavourable clinical sign or symptom. This will include complications of Remifentanil or Pethidine.
- any new illness or disease or the deterioration of existing disease or illness.
- any clinically relevant deterioration in any laboratory assessments or clinical tests.

The following are not AEs:

- A pre-existing condition (unless it worsens significantly during treatment).
- Diagnostic and therapeutic procedures, such as Caesarean section (although the medical condition for which the procedure was performed must be reported if thought to be attributable to the study treatment)

6.1.2 Adverse Reactions (ARs)

An AR is an adverse event that is considered to have a “reasonable causal relationship” with trial drug.

Expected symptoms and recognised complication include, but are not limited to, the following:

Remifentanil.

- Skeletal Muscle Rigidity,
- Bradycardia
- Hypotension
- Hypertension
- Acute respiratory depression
- Apnoea
- Nausea, Vomiting, and Shivering

**Pethidine.**

- Respiratory depression and hypotension
- Light-headedness, dizziness
- Hypothermia
- Sedation
- Nausea, vomiting and sweating

Unless these meet the criteria for serious adverse events, these adverse reactions do not require expedited reporting.

### 6.1.3 Serious Adverse Events (SAEs)

An SAE is an untoward event which:

- Results in death
- Immediately threatens the life of participant*
- Results in hospitalisation or a longer than anticipated stay in hospital
- Results in a persistent or significant disability

*Life-threatening in the definition of a serious adverse event or serious adverse reaction refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe. Important adverse events/reactions that are not immediately life-threatening or do not result in death or hospitalisation, but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

In the definition of a SAE usually includes any congenital anomaly or birth defect in any pregnancy, but in RESPITE, the intervention is given briefly at delivery beyond 24 weeks' gestation where it cannot have any possible teratogenic effect. Any babies with congenital anomalies will not be considered to be SAEs.

Events NOT considered to be SAEs are:

- extended hospital stay of the mother due to complications of delivery not related to the analgesia eg post-partum infection.
- extended hospital stay of the mother due to the need to keep the baby in hospital

### 6.1.4 Expected SAEs

Expected SAEs are those listed in the current Summary of Product Characteristics (SmPC) for remifentanil and pethidine. These events do not meet the criteria of SUSAR unless for reason of their severity. For convenience, the current expected events for remifentanil and pethidine are listed in Appendix E. We will however always use the most recently updated Summary of Product Characteristics (SmPC). The BCTU will ensure that any SmPC updates are circulated to all investigators; in addition, up-to-date SmPCs of licensed products are available at [http://emc.medicines.org.uk/](http://emc.medicines.org.uk/).

**Suspected unexpected serious adverse reactions (SUSARs)**

A SUSAR is an SAE suspected to be related to a product, which is of a **type or severity** which is NOT consistent with the up-to-date product information (i.e. SmPC).
6.2. Reporting AEs

All adverse reactions, from the first administration of trial treatment until discharge from labour ward, whether observed directly or reported by the patient, will be collected and recorded in the RESPITE data collection forms. Non-serious adverse events, not directly linked to trial interventions, will not be reported.

6.3. Reporting SAEs

All SAEs must be recorded on the SAE Form (Appendix D) and faxed to the BCTU on 0121 415 9136 within 24 hours of the research staff becoming aware of the event. The Principal Investigator (or other nominated clinician) has to assign seriousness, causality and expectedness to the SAE before reporting. All SAEs should be assessed for seriousness, causality and expectedness according to the analgesia received, whether or not this was the randomised allocation.

For each SAE, the following information will be collected:

- full details in medical terms with a diagnosis, if possible
- its duration (start and end dates; times, if applicable)
- action taken
- outcome
- causality, in the opinion of the investigator*
- whether the event would be considered expected or unexpected* (refer to the most recent and relevant Summary of Product Characteristics)

*Assessment of causality and expectedness must be made by a doctor. If a doctor is unavailable, initial reports without causality and expectedness assessment should be submitted to the BCTU by a healthcare professional within 24 hours, but must be followed up by medical assessment as soon as possible thereafter, ideally within the following 24 hours. An SAE which is assessed as possibly, probably or definitely related to trial treatment is classified as a Serious Adverse Reaction (SAR)

The local investigator and others responsible for patient care should institute any supplementary investigations of SAEs based on their clinical judgement of the likely causative factors and provide further follow-up information as soon as available. If a participant dies, any post-mortem findings should be provided to the BCTU. Neonatal deaths should also be reported to the BCTU (although these will not be considered as SAEs). The BCTU will report all deaths to the DMEC for continuous safety review.

SAEs still present after delivery must be followed up at least until the final outcome is determined. The BCTU will report all SAEs to the DMEC approximately 6-monthly. BCTU will also report all SAEs to the main REC and MHRA annually, and to the Trial Steering Committee 6-monthly. Local Investigators are responsible for reporting SAEs to their host institution, according to local policy, but they do not need to inform MHRA or main REC as this will be done by the BCTU as detailed below.

6.4. Reporting SUSARs

SAEs categorised by the local investigator as both suspected to be related to the trial drug and unexpected are SUSARs, and are subject to expedited reporting. For the purposes of this trial, events considered to be related to either remifentanil or pethidine will be considered to be SUSARs and will be reported expeditiously.

All SUSARs must be recorded on the SAE Form (Appendix D) and faxed to the BCTU on 0121 415 9136 immediately or within 24 hours of the research staff becoming aware of the event. The Chief Investigator (CI) or nominated individual will undertake urgent review of SUSARs within 24 hours of reporting and may request further information immediately from the patient’s clinical team. The CI will not overrule the causality, expectedness or seriousness assessment given by the local
investigator. If the CI disagrees with the local investigator’s assessment, further clarification and discussion should take place to reach a consensus. If a consensus cannot be reached, both the opinion of the local investigator and the CI should be provided in the report to the Medicines and Healthcare and Regulatory Agency (MHRA) and the MREC.

The BCTU will report all SUSARs to the MHRA and the main REC. If the SUSAR resulted in death or was life-threatening this will be done within 7 days of the initial report being received, or within 15 days for any other SUSAR. If information is incomplete at the time of initial reporting, or the event is ongoing, the BCTU will request follow-up information, including information for categorisation of causality, from the local investigator and will send the follow-up information to the MHRA and main REC within an additional 8 days for fatal or life-threatening SUSARs and as soon as possible for any other events.

6.5. Pharmacovigilance responsibilities

6.5.1 Local Principal Investigator (or nominated individual in PI’s absence):

- To record all ARs occurring in the subjects taking part in the trial in RESPITE data collection forms. This includes non-serious ARs and SAEs, whether expected or unexpected.
- Medical judgement in assigning seriousness, expectedness and causality to AEs.
- To fax SAE forms to BCTU within 24 hours of becoming aware, and to provide further follow-up information as soon as available.
- To report SAEs to local committees if required, in line with local arrangements.
- To sign an Investigator’s Agreement accepting these responsibilities.

6.5.2 Chief Investigator (or nominated individual in CI’s absence):

- To assign causality and expected nature of SAEs where it has not been possible to obtain local assessment
- To review all events assessed as SAEs in the opinion of the local investigator
- To review all events assessed as SUSARs in the opinion of the local investigator. In the event of disagreement between local assessment and Chief Investigator with regards to SUSAR status, local assessment will not be over-ruled, but the Chief Investigator may add comments prior to reporting to MHRA.

6.5.3 Birmingham Clinical Trials Unit:

- To report SUSARs to MHRA and main REC within required timelines as detailed above.
- To prepare annual safety reports, blinded to treatment, to MHRA, main REC and TSC.
- To prepare SAE safety reports for the DMEC at approximately 6-monthly intervals.
- To report all fatal SAEs to the DMEC for continuous safety review
- To notify Investigators of SUSARs which compromise patient safety

6.5.4 Trial Steering Committee (TSC):

- To provide independent supervision of the scientific and ethical conduct of the trial on behalf of the Trial Sponsor and funding bodies.
- To review data, patient compliance, completion rates, adverse events.
- To receive and consider any recommendations from the DMEC on protocol modifications.

6.5.5 Data Monitoring & Ethics Committee (DMEC):

- To review (initially at approx 6-monthly intervals) overall safety and morbidity data to identify safety issues which may not be apparent on an individual case basis
To recommend to the TSC whether the trial should continue unchanged, continue with protocol modifications, or stop.

7. FOLLOW-UP AND OUTCOME MEASURES

7.1. Primary endpoints/ outcome measures

The proportion of women who have an epidural placed for pain relief in labour, in each group.

7.2. Secondary endpoints/ outcome measures

- The effectiveness of pain relief provided by each technique, quantified by Visual Analogue Scale taken every 30 minutes after time zero, until delivery or transfer to theatre.
- The incidence of maternal side effects, up to the end of 3rd stage, including:
  - Excessive sedation score
  - Oxygen Saturation <94% whilst breathing room air
  - Nausea requiring anti-emetic administration
  - Requirement for supplemental oxygen
  - Respiratory depression (respiratory rate < 8 breaths/minute)
- Delivery mode (Spontaneous, 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
  - Requirement for neonatal resuscitation
  - Incidence of admission to Special Care Baby Unit
- Rate of initiation of breast feeding prior to hospital discharge
- Length of hospital stay
- Maternal satisfaction with childbirth experience determined by postpartum questionnaire prior to discharge from the delivery ward
- Resources used intra- and post-operatively, including PCA consumables, anaesthetist attendance
- Costs of staff training, service procurement and provision of care will be collected alongside clinical outcomes

7.3. Follow-up and timing of assessments

The study is primarily confined to the time period when a participant is in childbirth. Participants enter the study from the time that they request opioid pain relief in labour and remain in the study for the duration of labour until hospital discharge.

The period is therefore measured in days. Active data collection will only occur up to the point of child birth. There will be a single maternal contact thereafter to administer a brief questionnaire which includes metrics of maternal satisfaction and will establish if breast feeding has been initiated. Mean stay in hospital after spontaneous vaginal delivery is 2-3 days. This period can be extended to 5 days if delivery by Caesarean section has been required.

7.4. Health economic outcomes

If remifentanil PCA is clinically effective it may also reduce the direct costs of care by reducing instrumental vaginal delivery and hospital stay. There is also a wider potential NHS economic benefit implicit to a reduction in epidural requirement in the freeing of a limited anaesthetic
resource to be re-deployed to another point of clinical need. A prospective economic evaluation will be conducted alongside the trial with the aim of estimating the cost-effectiveness of remifentanil PCA, in terms of cost per epidural conversion avoided in the remifentanil PCA arm. The economic evaluation will be conducted from a health-service perspective using recommended methods for base case and probabilistic sensitivity analysis.

7.5. Definition of the End of Trial

No further routine follow up will be required after discharge. The definition of the end of the interventional phase of the trial will be when the last participant has given birth, and for the observation phase, when she and her baby have been discharged from hospital.

8. ACCRUAL AND ANALYSIS

8.1. Sample size

Epidural conversion rates of approximately 10% (range 5% to 19%) are commonly reported after remifentanil. This compares to conversion rates of greater than 30% (range 17% to 39%) being representative in women receiving pethidine. Taking a deliberately conservative estimate of intervention effect using these data, a reduction in epidural conversion from 30% (pethidine) to 15% (remifentanil PCA) is reasonable. To detect such a reduction with 90% power at p=0.05, would require 161 women in each arm of the trial, yielding a sample size of 322 in total. Adjustment must also be made to account for attrition of the population at risk as labour progresses. A small number of participants will require urgent delivery by Caesarean Section for fetal indications before a request for further analgesia can be made. Assuming that this will not represent more than 25% of the sample after randomisation (National Caesarean Section Rate), and a 15% emergency Caesarean rate is more realistic, a further 48 women will be recruited to offset this attrition of participants capable of reaching the primary outcome. Allowing for a modest unavailability of primary outcome data and non-adherence of 6%, a total sample size of 400 is therefore proposed.

8.2. Projected accrual and attrition rates

Over last 3 years, there has been on average 11,000 deliveries each year (6,000 at Heartlands Hospital, 4000 at Good Hope Hospital and 1000 at Solihull Hospital) in HEFT Trust. A conservative estimate of 20% of these patients meeting the inclusion criteria of this trial provides a pool of 2,200 /year (183/month) to be recruited for a target of 15/month.

8.3. Statistical Analysis

A detailed analysis plan will be developed and agreed by the Trial Steering Committee and the Data Monitoring Ethic Committee. Demographic factors and clinical characteristics will be summarised with counts (percentages) for categorical variables, mean (standard deviation) for normally distributed continuous variables, or median (interquartile or entire range) for other continuous variables.

8.3.1 Primary analysis

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 remifentanil PCA group will be compared with the group and tested for significance at the two sided 5% level of significance. Risk ratios and 95% confidence intervals will be estimated. As the remifentanil PCA will generally only be available within the context of the RESPISTE Trial, we do not anticipate many protocol deviations.
8.3.2 Sub-group analysis

Perception of pain during labour may be influenced by previous experiences, in particular previous labours, and this may, in turn, influence the request for epidural. Maternal parity will therefore be pre-specified for sub-group analysis of primary outcome.

8.3.3 Handling missing data

The extent of missing data for the primary outcome should be limited, as it is routinely recorded in maternity records and can be collected retrospectively. Remifentanil dose data should be available from the PCA pump machine, but if not collected immediately, may be lost at the next use of the machine. The Maternal Outcome Satisfaction questionnaire must be completed before discharge and research nurses/midwives should make every effort to collect this. Where these time-critical data are missing, multiple imputation methods may be considered to inform a sensitivity analysis.

9. DATA ACCESS AND QUALITY ASSURANCE

9.1. Data management and confidentiality

Personal data and sensitive information required for the Respite Trial will be collected directly from trial participants and hospital notes on data collection forms, coded with the participant’s unique trial number and initials. Participants will be informed about the transfer of this information to the Respite trial office at the BCTU and asked for their consent. The consent form will also be faxed to the RESPITE Trial Office, as this is the sole document with identifiable details, again with consent from the participant. The data will be entered onto a secure computer database, either directly via the internet using secure socket layer encryption technology or indirectly from paper by BCTU staff.

All personal information received in paper format for the trial will be held securely and treated as strictly confidential according to BCTU policies. All staff involved in the RESPITE Trial (clinical, academic, BCTU) share the same duty of care to prevent unauthorised disclosure of personal information. No data that could be used to identify an individual will be published. Data will be stored on a secure server at Birmingham Clinical Trials Unit (BCTU) under the provisions of the Data Protection Act and/or applicable laws and regulations.

9.2. In-house Data Quality Assurance and Validation

The study will adopt a centralised approach to monitoring data quality and compliance. A computer database will be constructed specifically for the study data and will include range and logic checks to prevent erroneous data entry. Independent checking of data entry of paper questionnaires will be periodically undertaken on small sub-samples. The trial statistician will regularly check the balance of allocations by the stratification variables. Source data verification will only be employed if there is reason to believe data quality has been compromised, and then only in a sub-set of practices.

9.2.1 Monitoring and Audit

Investigators and their host Trusts will be required to permit trial-related monitoring and audits to take place by the RESPITE Trial Coordinator, providing direct access to source data and documents as requested. Trusts may also be subject to inspection by the Medicines and Healthcare Products Regulatory Agency and/ or by the Research and Development Manager of their own Trust and should do everything requested by the Chief Investigator in order to prepare and contribute to any inspection or audit. Trial participants will be made aware of the possibility of external audit of data they provide in the participant information sheet.
9.3. Independent Trial Steering Committee

The TSC provides independent supervision for the trial, providing advice to the Chief and Co-Investigators and the Sponsor on all aspects of the trial and affording protection for patients by ensuring the trial is conducted according to the MRC Guidelines for Good Clinical Practice in Clinical Trials.

If the Chief and Co-Investigators are unable to resolve any concern satisfactorily, Principal Investigators, and all others associated with the study, may write through the Trial Office to the chairman of the TSC, drawing attention to any concerns they may have about the possibility of particular side-effects, or of particular categories of patient requiring special study, or about any other matters thought relevant.

9.4. Data Monitoring and Ethics Committee: determining when clear answers have emerged

If remifentanil for pain relief for childbirth really is substantially better or worse than i.m. pethidine with respect to the primary endpoints, then this may become apparent before the target recruitment has been reached. Alternatively, new evidence might emerge from other sources that remifentanil PCA is definitely more, or less, effective than pethidine. To protect against this, during the period of recruitment to the study, interim analyses of major endpoints will be supplied, in strict confidence, to an independent Data Monitoring and Ethics Committee (DMEC) along with updates on results of other related studies, and any other analyses that the DMEC may request. The DMEC will advise the chair of the Trial Steering Committee if, in their view, any of the randomised comparisons in the trial have provided both (a) “proof beyond reasonable doubt” that for all, or for some, types of patient one particular treatment is definitely indicated or definitely contraindicated in terms of a net difference in the major endpoints, and (b) evidence that might reasonably be expected to influence the patient management of many clinicians who are already aware of the other main trial results. The TSC can then decide whether to close or modify any part of the trial. Unless this happens, however, the TMG, TSC, the investigators and all of the central administrative staff (except the statisticians who supply the confidential analyses) will remain unaware of the interim results.

9.4.1 Confidentiality of personal data

The details of each participant will be collected from hospital notes by using the Respite data collection forms onto a dedicated, secure, encrypted trial database, specifically constructed for the purpose. This will have the capacity to uniquely identify individuals without integration to the randomization database, which has restricted access.

BCTU is highly experienced in the storage and management of confidential data and utilizes advanced security systems to protect personal details of research records. Trial data provided to the Data Monitoring Committee will be anonymised but study group allocation will be provided, since it is necessary for their deliberations. Investigators will not have access to personal information other than accrual figures detailing study progress at each centre. This will merely report on accrual rate and volume in a generic manner.

9.5. Long-term storage of data

After the end of the trial, the site files from each centre will be collected and incorporated into the trial master file held by the BCTU.

* Appropriate criteria of proof beyond reasonable doubt cannot be specified precisely, but a difference of at least three standard deviations in an interim analysis of a major endpoint may be needed to justify halting, or modifying, the study prematurely. If this criterion were to be adopted, it would have the practical advantage that the exact number of interim analyses would be of little importance, so no fixed schedule is proposed.
In line with the Medicines for Human Use (Clinical Trials) Regulations, once data collection is complete on all participants, all data will be stored for at least 5 years (but ideally not less than 15 years). This will allow adequate time for review and reappraisal, and in particular with the Respite trial, form the basis for further follow-up research. Any queries or concerns about the data, conduct or conclusions of the trial can also be resolved in this time. Limited data on the participants and records of any adverse events may be kept for longer if recommended by an independent advisory board.

Trial data will be stored within the BCTU under controlled conditions for at least 3 years after closure. Long-term offsite data archiving facilities will be considered for storage after this time. The BCTU has standard processes for both hard copy and computer database legacy archiving.

10. ORGANISATION AND RESPONSIBILITIES

To ensure the smooth running of the trial and to minimise the overall procedural workload, it is proposed that each participating centre should designate individuals who would be chiefly responsible for local co-ordination of clinical and administrative aspects of the trial.

All investigators are responsible for ensuring that any research they undertake follows the agreed protocol, for helping care professionals to ensure that participants receive appropriate care while involved in research, for protecting the integrity and confidentiality of clinical and other records and data generated by the research, and for reporting any failures in these respects, adverse drug reactions and other events or suspected misconduct through the appropriate systems.

10.1. Centre eligibility

Participating centres will be hospitals, with “Consultant-led” Care in labour and delivery. Most of these units care for more than 4000 women per year, although the availability of midwifery care and attending anaesthetic and obstetric clinicians is more relevant than an absolute number threshold. Labour wards recruiting to RESPITE will be required to offer minimum standards of maternal monitoring as described in Section 5.1.2, demonstrate that the organisational infrastructure of labour ward care can support PCA opioid administration in a safe manner and have the resource capacity to support 1:1 midwifery care to women in childbirth.

10.2. Local Co-ordinator at each centre

Each Centre should nominate a doctor to act as the local Principal Investigator and bear responsibility for the conduct of research at their centre. Close collaboration between all clinical teams is particularly important in Pethidine in order that patients for whom Remifentanil is an option can be identified sufficiently early for entry. The responsibilities of the local Principal Investigator will be to ensure that all medical and nursing staff involved in the care of Respite are well informed about the study and trained in trial procedures, including obtaining informed consent. The local Principal Investigator should liaise with the Trial Coordinator on logistic and administrative matters connected with the trial.

10.3. Nursing/Widwife Co-ordinator at each centre

Each participating centre should also designate one nurse as local Nursing Coordinator. This person would be responsible for ensuring that all eligible patients are considered for the study, that patients are provided with study information sheets, and have an opportunity to discuss the study if required. The nurse may be responsible for collecting the patient data. Again, this person would be sent updates and newsletters, and would be invited to training and progress meetings.

10.4. The RESPITE Trial Office

The Trial Office at the University of Birmingham Clinical Trials Unit (BCTU) is responsible for providing all trial materials, including the trial folders containing printed materials and the update slides. These will be supplied to each collaborating centre, after relevant ethics committee
approval has been obtained. Additional supplies of any printed material can be obtained on request. The Trial Office also provides the central randomisation service and is responsible for collection and checking of data (including reports of serious adverse events thought to be due to trial treatment), for reporting of serious and unexpected adverse events to the sponsor and/or regulatory authorities and for analyses. The Trial Office will help resolve any local problems that may be encountered in trial participation.

10.5. Research Governance
The conduct of the trial will be according to the Medicines for Human Use (Clinical Trials) Regulations 2004 and any subsequent amendments and the principles of the International Committee on Harmonisation Good Clinical Practice Guidelines.

All centres will be required to sign an Investigator's Agreement, detailing their commitment to accrual, compliance, Good Clinical Practice, confidentiality and publication. Deviations from the agreement will be monitored and the TSC will decide whether any action needs to be taken, e.g. withdrawal of funding, suspension of centre.

The Trial Office will ensure researchers not employed by an NHS organisation hold an NHS honorary contract for that organisation.

10.5.1 Ethical and Trust Management Approval
The Trial has a favourable ethical opinion from NRES Committee East Midlands - Nottingham 2 Multi-centre Research Ethics Committee (MREC) approval, determining that the trial design respects the rights, safety and wellbeing of the participants.

The Local Comprehensive Research Network will conduct governance checks and assess the facilities and resources needed to run the trial, in order to give host site permission. The Trial Office is able to help the local Principal Investigator in the process of the site specific assessment by completing much of Site Specific Information section of the standard IRAS form as possible. The local Principal Investigator will be responsible for liaison with the Trust management with respect to locality issues and obtaining the necessary signatures at their Trust.

As soon as Trust approval has been obtained, the Trial Office will send a folder containing all trial materials to the local Principal Investigator. Potential trial participants can then start to be approached

10.5.2 Clinical Trial Authorisation
The Trial Office has obtained Clinical Trials Authorisation from the Medicines and Healthcare Regulatory Authority and has obtained a unique EudraCT number for the trial.

10.6. Funding and Cost implications
The research costs of the trial are funded by a grant from the NIHR awarded to the University of Birmingham.

The trial has been designed to minimise extra ‘service support’ costs for participating hospitals, with no extra visits to hospital and no extra tests. Additional costs associated with the trial, e.g. gaining consent, are estimated in the Site Specific Information section of the standard IRAS form. These costs should be met by accessing the Trust’s Support for Science budget via the Local Comprehensive Research Network.

10.7. Indemnity
There are no special arrangements for compensation for non-negligent harm suffered by patients as a result of participating in the study. The study is not an industry-sponsored trial and so
ABPI/ABHI guidelines on indemnity do not apply. The normal NHS indemnity liability arrangements for research detailed in HSG96(48) will operate in this case.

However, it should be stressed that in terms of negligent liability, NHS Trust hospitals have a duty of care to a patient being treated within their hospital, whether or not that patient is participating in a clinical trial. Apart from defective products, legal liability does not arise where there is non-negligent harm. NHS Trusts may not offer advance indemnities or take out commercial insurance for non-negligent harm.

10.8. Publication

A meeting will be held after the end of the study to allow discussion of the main results among the collaborators prior to publication. The success of the study depends entirely on the wholehearted collaboration of a large number of doctors, nurses, midwives and others. For this reason, chief credit for the main results will be given not to the committees or central organisers but to all those who have collaborated in the study. Centres will be permitted to publish data obtained from participants in the RESPITE Trial that use trial outcome measures but do not relate to the trial randomised evaluation and hypothesis.

10.9. Ancillary studies

It is requested that any proposals for formal additional studies of the effects of the trial treatments on some patients (e.g. special investigations in selected hospitals) be referred to the Trial Management Committee for consideration. In general, it would be preferable for the trial to be kept as simple as possible, and add-on studies will need to be fully justified.
11. REFERENCE LIST


APPENDIX A PATIENT INFORMATION SHEET

Thank you for taking time to read this information.

RESPITE Trial Co-ordinator:
Dr Victoria Brookes
Birmingham Clinical Trials Unit (BCTU)
Robert Aitken Institute
University of Birmingham
Birmingham
B15 2TT
Tel: 0121 415 9108
Fax: 0121 415 9136
Email: v.l.brookes@bham.ac.uk

This study is being funded by the National Institute of Health Research (NIHR) and conducted by the University of Birmingham. The Clinical Trials Unit (BCTU) is dedicated to improving the care provided to women and their families during pregnancy and childbirth (www.birmingham.ac.uk/BCTU)

Participant Information Leaflet

Remifentanil intravenous patient controlled analgesia (PCA) versus intramuscular Pethidine for pain relief in labour

CI - Dr Matthew J A Wilson

LOCAL HOSPITAL RESPITE STUDY RESEARCH STAFF CONTACT DETAILS:

LEAD RESPITE STUDY DR’s NAME:

LEAD RESPITE STUDY DR’s TEL:

RESPITE STUDY RESEARCH MIDWIFE NAME:

RESPITE STUDY RESEARCH MIDWIFE TEL:

ISRCTN: tbc    REC:13/EM/0259    EudraCT:2012-005257-22

Respite Participant Information Leaflet version 1.1 date 03/7/13
Invitation to join the “RESPITE” study
You are being invited to take part in research study called the RESPIE study. The study is for women in childbirth who request strong pain relief during labour. It will find out which form of pain relief is the most effective in reducing the need for other forms of pain relief, such as an epidural.

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

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

What is the purpose of the study?
Childbirth can be a painful experience. Providing women with prompt pain relief is a priority for the midwives and doctors who care for them in labour. There are several forms of pain relief available to women, including Entonox (“Gas-and-air”), strong pain relieving drugs, such as Pethidine and epidurals.

Pethidine is the standard drug given in the UK, usually by injection into the thigh or arm. It is effective, but can cause side effects such as drowsiness and sickness.

What if there is a problem?
If you are worried about any aspect of this study, you should first speak to the lead doctor or Midwife for the RESPIE study at your hospital. If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. Details can be obtained from the hospital Patient Advice and Information Liaison Service (PALS): ENTER LOCAL PALS LOCATION/CONTACT DETAILS HERE!

Will participation in the study affect my legal rights?
If you are harmed as a result of negligence then you may have grounds for legal action against the NHS (in respect of any harm which has resulted from any clinical procedure) or Birmingham University (in respect of any harm solely arising out of participation in the study).

Where can I find the results of the study?
The results of the study will be published in a scientific journal and on the study website (www.respite.bham.ac.uk) A summary of the study findings will also be published by the NIHR. You will not be identified in any report or publication.
Is it possible to choose PCA without taking part in the study?
The hospitals taking part in this research study do not routinely offer Remifentanil PCA. Therefore, it will be only available as part of the study unless there are specific medical reasons for its use.

Who is organising and funding the research?
The University of Birmingham Clinical Trials Unit is organising this research.
The National Institute of Health Research (NIHR) is funding the research. The NIHR is part of the UK Government, Department of Health.

Who has approved the study?
This study has been reviewed by NHS Research and Ethics Committee East Midlands – Nottingham 2 (REC). The REC looks after the rights, well-being and dignity of patients. The REC reference number is given on the front page of this document. This study was also reviewed by the NIHR to ensure it met the necessary scientific standards.

Can seek independent advice about participation?
If you would like more information about the study itself you can ask to speak to the lead doctor or midwife for the RESPITE at this hospital. These contact details are on the last page of this leaflet. The hospital Trust's Research and Development (R&D) Office can also be contacted. They will give you advice about how to contact someone for independent advice.

In recent years, some labour wards have begun to offer a different drug called Remifentanil for pain relief to some women. Remifentanil is given by “Patient Controlled Analgesia” through a drip. By pressing a hand-held button, women give themselves a small dose of drug whilst having a contraction. Research done so far shows that Remifentanil is safe for women, and their babies, and provides effective pain relief. However, it is not yet offered as standard care. As with Pethidine, women can experience drowsiness and sickness.

Epidurals provide excellent pain relief but can increase the chance of forceps or suction delivery. We do not know yet which of Remifentanil or Pethidine is better at helping women avoid the need for an episiotomy and experience a more straightforward birth. The RESPITE study will find this out.

Why am I being asked to consider the study?
You are being asked to consider taking part in this study because the midwives and doctors caring for you are expecting you to have a vaginal birth. We hope that 400 women will agree to take part, half of whom will receive Pethidine and half Remifentanil for pain relief in labour.

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

What would happen to me if I take part?
If you are happy to take part in the study, you will be asked to sign a consent form. The person who takes consent will then enter your details into a computer. This will allocate you to either the Pethidine or Remifentanil group. The decision about which group you would go into will be made by chance, rather like the toss of a coin. This is important because it ensures that the two forms of pain relief can be tested fairly against each other.
What does being in the study involve?
Information about your labour will be collected by the midwife until you give birth and be kept confidentially. During your labour, you will be asked how effective your pain relief is. We will record details of when you and your baby are discharged from hospital, and details of any treatments you and your baby receive whilst in hospital. You will also be asked to fill in a short questionnaire to find out what you thought of the care you received during your labour and the birth of your baby. There are no further tests or hospital visits connected with this study. No payments are available for taking part in this study.

What are the possible benefits of taking part?
You will be offered pain relief in labour whether you participate in the study or not. We cannot promise the study will help you as an individual, but the answers we get from this study will help improve the care provided to women in labour in the future.

Are there any side effects or risks involved?
Both Pethidine and Remifentanil are strong drugs related to morphine. Women can experience side effects such as drowsiness, dizziness or sickness with both. All women taking part will be monitored constantly by their midwife for drowsiness and anti-sickness medication given promptly if required. There are no known differences in risks to mother and baby for either type of pain relief.
There are no restrictions on having an epidural if you need one.

Will my taking part in this study be kept confidential?
Yes, all information collected in the study will remain strictly confidential, similar to your medical records. If you take part, the study team will record information on a secure database. No named information will be published in any report of the study. Information transferred out of the hospital will not have your name or any contact details attached to it. If you withdrew from the study, we would only use the data already collected up to that point.

This completes the introduction. If, after reading this, the study sounds like something you may be interested in and you would consider taking part, please read the following additional information before making any decision.

Additional Information about RESPITE; more about pain relief in labour:
There are many options for pain relief in labour ranging from breathing and relaxation exercises, TENS devices, inhaled Entonox (gas-and-air), strong pain relieving drugs and epidurals. It is important that women discuss all these methods with their midwife in order to make an informed choice.

Pethidine has a long track record of safety and has been used for many years in childbirth. It is usually given by injection into the arm or thigh, as the picture below shows.

“Patient Controlled Analgesia” (PCA) is a method of pain relief routinely used after surgery, but rarely in childbirth. The pictures below show a PCA device in use. The use of Remifentanil PCA for pain relief in labour is currently restricted in most labour wards, to women who cannot receive other forms of pain relief for medical reasons, but this is changing. Therefore, it is important that we do this research now. The “Pump” is programmed to give a safe amount of drug, so that the button can be pressed as often as necessary.
APPENDIX B: PATIENT CONSENT FORM

To be printed on Local Trust Headed Paper

A Randomised Controlled Trial of Remifentanil
intravenous patient Controlled analgesia (PCA) versus
intramuscular pethidine for pain relief in labour

Consent Form

I confirm that I have read and understand the information sheet dated 03/07/2013 version 1.1 for the
above study. I have had the opportunity to consider the information, ask questions and these have been
answered satisfactorily.

I understand that my participation is voluntary and that if I take part, I am free to withdraw at any time,
without giving a reason, and without my medical care or legal rights being affected.

I understand that my doctors will provide a copy of my consent form and personal information about my
progress, in confidence, to the central organisers at Birmingham Clinical Trials Unit (BCTU) for use in the
Respite trial. I understand that the information held by the NHS may be used to keep in touch with me and
follow up my health status.

I understand that the information collected will be used for medical research only and that I will not be
identified in any way in the analysis and reporting of the results. I understand that relevant sections of my
medical notes and data collected during the study may be looked at by individuals from the University of
Birmingham, regulatory authorities or the NHS Trust, where it is relevant to my taking part in this research.
I give permission for these individuals to have access to my records.

I understand what is involved in the Respite Trial and agree to participate.

Respite Trial Number: Initial each box to confirm consent

Name of Participant Date Signature

Name of Person taking consent Date Signature

I have interpreted the information above to the best of my ability and in a way in which the patient can
understand (if applicable).

Name of Interpreter Date Signature

Copies of Respite Consent Forms: Original copy for Respite site file, 1 copy for patient, 1 copy to be kept in patient’s hospital notes and 1
copy to be faxed to Respite Trial Office on 0121 415 9136:
Respite Trial Office, Birmingham Clinical Trials Unit, School of Cancer Sciences, University of Birmingham, Birmingham, B15 2TT
Version 1.1 03/07/2013
APPENDIX C: RANDOMISATION FORM

Eligibility and Randomisation

Study Number  Completed by...............................(print)...............................(sign)
Patient Initials Completed date D D M M Y Y Y Y

PLEASE COMPLETE BEFORE RANDOMISATION

SECTION 1: IDENTIFICATION DETAILS- please complete or attach patient sticker

Hospital: ..........................................................................................................................
Randomising clinician: ..............................................................................................
First name: ....................................................................................................................
Family name: ..............................................................................................................
Hospital ID number: ..................................................................................................
Date of Birth D D M M Y Y Y Y
NHS number: ............................................................................................................
Ethnic group: White ☐ Black/Black British ☐ Chinese/East Asian ☐ Other ☐
Asian (Indian) ☐ Asian (Pakistan) ☐ Asian (Bangladesh) ☐ Mixed ☐

SECTION 2: ELIGIBILITY CHECKLIST

Please complete this section before logging on to the RESPITE website to obtain a study number.
Confirm the woman has the following characteristics:

1.1 Age 16 years or older? ☐ ☐
1.2 Beyond 37+0 weeks gestation? ☐ ☐
1.3 Live, singleton, cephalic presentation? ☐ ☐
1.4 In established labour with vaginal birth intended? ☐ ☐
1.5 Able to receive trial drugs? ☐ ☐
1.6 Any contraindication to epidural? ☐ ☐
1.7 Able to understand English or translator available? ☐ ☐
1.8 Receiving long term opioid therapy (inc. methadone)? ☐ ☐
1.9 Systemic opioid pain relief in last 4 hours? ☐ ☐
If all the criteria are fulfilled, the woman in your care is eligible to participate in the RESPITE study.

Please ensure that the consent form for participation in the study has been signed prior to randomisation.

2.0 Has the woman given written consent for participation in RESPITE? ☐ ☐
2.1 Nulliparous? ☐ ☐
2.2 Induced labour ☐ OR Spontaneous labour ☐ (please tick one)

SECTION 3: RANDOMISATION TO GROUP ALLOCATION – please complete at the time of randomisation

NOW Randomise!
www.trials.bham.ac.uk/respite

Log on to the RESPITE website and follow the instructions on screen OR telephone 0800 953 0274. The randomisation system
operator will provide you with a unique study number and group allocation for the woman in your care. Please enter these below:

Group allocation: Pethidine injection ☐ OR Remifentanil PCA ☐ (please tick one)
RESPITE study number: ☐☐☐☐☐☐ Date of randomisation: D D M M Y Y Y Y

ISRCTN 29654603

File this form in the Trial Folder
Randomisation Form V1.1 dated 04.12.13

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APPENDIX D: SERIOUS ADVERSE EVENT FORM

Please report immediately any SERIOUS ADVERSE EVENTS (see protocol section 6.0 for definition), occurring at any time during treatment, by completing all of the details below and faxing this form to the Respite Trial Office on 0121 415 9136.

Part A: Identification details
Respite Trial Number
Consultant
Patient’s Initials
Patient’s NHS No:
Hospital
Patient’s date of birth: _____/_____/_____
Patient’s Hospital No:

Part B: SAE Type
Is this an initial or follow-up report? Initial Report [ ] Follow-up report [ ]
Is this the final report? Yes [ ] No [ ]

Reason for Reporting
Maternal death? [ ] Yes [ ] No [ ] Date of death: _____/_____/_____.
Neonatal death? [ ] Yes [ ] No [ ] Date of death: _____/_____/_____.
Life-threatening event? [ ] Yes [ ] No [ ]
In-patient hospitalisation or prolongation of existing hospitalisation? [ ] Yes [ ] No [ ] If yes, no of days? ……………………………
Persistent or significant disability/incapacity? [ ] Yes [ ] No [ ]
Excessive sedation with respiratory depression? [ ] Yes [ ] No [ ] with Pethidine [ ] or Remifentanil [ ] (tick)
Other pertinent medical reason for reporting? [ ] Yes [ ] No [ ]
If other, please specify: …………………………………………………

Part C: SAE Description
Date Event Started: _____/_____/_____ Date Event Ceased: _____/_____/_____.
Details of Adverse Event (please attach copies of relevant reports):
…………………………………………………………………………………………………………………………
…………………………………………………………………………………………………………………………
…………………………………………………………………………………………………………………………

Part D: Trial Treatment
Total dose administered (enter below):
…………………………………………………………………………………………………………………………
This section must be completed by a clinician
Causality Assessment (please tick)
1 Probably unrelated to treatment [ ]
2 Possibly related to treatment [ ]
3 Probably related to treatment [ ]
4 Definitely related to treatment [ ]
Action taken due to SAE (please tick)
1 None [ ]
2 Treatment stopped [ ]
3 Treatment delayed [ ]
Please give reasons if you consider the event to be treatment related:
…………………………………………………………………………………………………………………………
…………………………………………………………………………………………………………………………
…………………………………………………………………………………………………………………………

Was the SAE unexpected, i.e. of a type or severity which is NOT consistent with the up-to-date SPC for Remifentanil or Pethidine
(available at http://www.medicines.org.uk/)
This section must be completed by a clinician
Unexpected [ ] Expected [ ]
Please give reasons if you consider the event to be unexpected:
…………………………………………………………………………………………………………………………
…………………………………………………………………………………………………………………………

Once faxed, please return this form (with copies of relevant reports) to:
Respite Trial Office, Birmingham Clinical Trials Unit, School of Cancer Sciences, University of Birmingham, Birmingham, B15 2TT
Tel: 0121 415 9108; Fax 0121 415 9136; Email: HC007ETrials@bham.ac.uk; Website: www.birmingham.ac.uk/emc
ISRCTN: To be confirmed
Version 1.1 03.07.13
Part E: Concomitant Medication

Has the patient taken any other medication within the last week? Yes ☐ No ☐ If yes, please complete below:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Start date</th>
<th>Tick if continuing or specify stop date</th>
<th>Dose (mg)</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

Part F: Outcome of SAE

Outcome: Fatal ☐ Recovered ☐ Continuing ☐

Please describe the final outcome if the event is continuing at the time of faxing initial report:

___________________________________________________________________________
___________________________________________________________________________
___________________________________________________________________________
___________________________________________________________________________

Signature of Person Reporting: __________________________ Date: DD/MMM/YYYY

You must have signed the Site Delegation Log

Name: __________________________ Position: __________________________ Tel No: __________________________

Signature of Investigator: __________________________ Date: DD/MMM/YYYY

If not completed by Investigator

SUSAR Reporting – BCTU USE ONLY

SAE reference number: __________________________

Date reported to BCTU? DD/MMM/YYYY

Date reported to CI? DD/MMM/YYYY Date reply received from CI? DD/MMM/YYYY

Is this event a SUSAR? Yes ☐ No ☐ If yes: 7 day report OR 15 day report

If NO, is this an SAE? Yes ☐ No ☐

CI comments:

___________________________________________________________________________
___________________________________________________________________________

Signature: __________________________ PRINT Name: __________________________

Date due to be reported to MHRA and MREC: DD/MMM/YYYY

Once filled, please return this form (with copies of relevant reports) to:
Respite Trial Office, Birmingham Clinical Trials Unit, School of Cancer Sciences, University of Birmingham, Birmingham, B15 2TT
Tel: 0121 415 9108; Fax 0121 415 9136; Email: RESPIRE@brcs.bham.ac.uk Website: www.birmingham.ac.uk/respite

ISRCTN To be confirmed

Version 1.1 03/07/13

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### APPENDIX E

**PETHIDINE & REMIFENTANIL - TOXICITY AND KNOWN SIDE EFFECTS**

Toxicities/side-effects that have previously occurred and are listed in the SMPC do not have to be reported to the MHRA. If the outcome of the side-effect is serious, the SAE form should be completed. Any SAE not described below, i.e. a serious toxicity that is unexpected, and believed to be related to study treatment, will be reported as a SUSAR (see section 6 of the protocol).

<table>
<thead>
<tr>
<th>DISORDER GROUP</th>
<th>PETHIDINE</th>
<th>REMIFENTANIL</th>
</tr>
</thead>
</table>
| **Most frequent/common effects** | - Light-headedness  
- Dizziness  
- Hypothermia  
- Sedation  
- Nausea  
- Vomiting  
- Sweating | - Direct extensions of μ-opioid agonist activities | |
| **Respiratory, thoracic & mediastinal** | - Respiratory depression | Common: - Acute respiratory depression  
- Apnoea  
Uncommon: - Hypoxia | |
| **Psychiatric** | - Euphoria  
- Dysphoria  
- Hallucinations | Not known: - Dependence | |
| **Nervous System** | - Weakness  
- Headache  
- Agitation  
- Tremors  
- Uncoordinated muscle movements  
- Convulsions  
- Confusion  
- Mood changes  
- Nervousness  
- Vertigo  
- Anxiety  
- Delirium (in elderly) | Very common: - Skeletal muscle rigidity  
Rare: - Sedation (during awakening after general anaesthesia) | |
| **Eye** | - Visual disturbances  
- Pupil Constriction | | |
| **Cardiac** | - Tachycardia  
- Bradycardia  
- Palpitation | Common: - Bradycardia  
Rare: - Asystole/cardiac arrest (when treated with other anaesthetics) | |
| **Vascular** | - Flushing of the face  
- Hypotension  
- Syncope | Very common: - Hypotension  
Common: - Hypertension | |
| **Gastrointestinal** | - Dry mouth  
- Constipation | Very common: - Nausea and Vomiting  
Uncommon: - Constipation | |
| **Hepatobiliary** | - Biliary tract spasm | | |
| **Skin & Subcutaneous tissue** | - Pruritis  
- Urticaria  
- Other skin rashes | Common: - Pruritis | |
| **Renal & Urinary** | - Urinary retention  
- Difficulty with micturation | | |

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<table>
<thead>
<tr>
<th>Immune System</th>
<th>Rare: Hypersensitivity (inc. Anaphylaxis) (when treated with other anaesthetics)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General/administration site conditions</strong></td>
<td></td>
</tr>
<tr>
<td>Pain at site of injection</td>
<td></td>
</tr>
<tr>
<td>Local tissue irritation</td>
<td></td>
</tr>
<tr>
<td>Wheal and flare over the vein with intravenous injection</td>
<td></td>
</tr>
<tr>
<td>Decreased libido or potency</td>
<td></td>
</tr>
<tr>
<td>Dependence with continued use</td>
<td></td>
</tr>
<tr>
<td>Common: Shivering</td>
<td></td>
</tr>
<tr>
<td>Uncommon: Pain</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Very common</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
<th>Very rare</th>
<th>Not known</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1/10</td>
<td>≥ 1/100</td>
<td>≥ 1/1,000 to &lt; 1/100</td>
<td>≥ 1/10,000 to &lt; 1/1,000</td>
<td>&lt; 1/10,000</td>
<td>(can’t be estimated from available data)</td>
</tr>
</tbody>
</table>
APPENDIX F: TRIAL SCHEMA

RESPITE TRIAL SCHEMA
(Version 1.2: 4/12/13)

ELIGIBILITY
Inclusion criteria
- Requesting systemic opioid analgesia
- 16 years of age or older
- Beyond 37+0 weeks’ gestation
- In established labour 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.

Exclusion criteria
- Contraindication to epidural analgesia
- Contraindication to intramuscular injection
- History of drug sensitivity to Pethidine or Remifentanil
- Long term opioid drug therapy including Methadone
- Systemic opioid pain relief in the last 4 hours.

FLOW DIAGRAM

CONTACT DETAILS
- Matthew Wilson (Chief Investigator)
  University of Birmingham, Experimental Medicine, Edgbaston, Birmingham, B15 2TT
  E-mail: m.la.wilson@bham.ac.uk
- Victoria Brookes (Senior Trial Co-ordinator) RESPITE Study Office
  Tel: 0121 415 9108 (24hr answer phone) E-mail: v.l.brookes@bham.ac.uk

RESPITE Study Office General Enquiries:
Address: Women’s Health Team (rm 365)
University of Birmingham Clinical Trials Unit
Robert Aitken Institute
Edgbaston
Birmingham B15 2TT
Fax: 0121 415 9136
General email: RESPITE@trials.bham.ac.uk
Website: www.birmingham.ac.uk/respite