National Institute for Health and Care Excellence

Draft for consultation

Intrapartum care for healthy women and babies

[D] Remifentanil patient-controlled analgesia

NICE guideline CG190 (update)

Evidence review underpinning recommendations 1.6.19 to 1.6.22 in the NICE guideline

April 2023

Draft

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Remifentanil patient-controlled analgesia

Review question

What is the effectiveness of remifentanil administered by intravenous patient-controlled analgesia (PCA) compared to other intramuscular opioids?

Introduction

Safe and effective methods of analgesia for use during labour are important for mother and baby outcomes. A commonly used method in the UK is intramuscular (IM) administration of opioids, such as pethidine, diamorphine and meptazinol. However, their use is associated with maternal side effects including nausea, possible effects on the baby such as drowsiness and delay in breastfeeding, and intermittent administration can lead to break-through pain. An alternative is epidural analgesia and while this is an effective method of pain relief, it is associated with an extended second stage of labour and an increased incidence of instrumental births. Furthermore, there may be some women who do not wish to receive an epidural. Patient-controlled infusions of intravenous analgesia may offer a compromise – providing continuous analgesia, avoiding the restrictions and possible complications of an epidural, and being acceptable to women. Remifentanil is an opioid analgesic for IV administration with a short duration of action which is known to be metabolised by neonates and which offers the potential for use in obstetric PCA.

This review aims to identify the evidence for the safety and effectiveness of IV remifentanil PCA compared to other IM opioids.

Summary of the protocol

See Table 1 for a summary of the Population, Intervention, Comparison and Outcome (PICO) characteristics of this review.

Table 1: Summary of the protocol (PICO table)

Population	• Women in labour who are pregnant with a single baby, who go into labour at term (37 to 42 weeks of pregnancy) and who do not have any pre-existing medical conditions or antenatal conditions that predispose to a higher risk birth • Women in labour whose baby has not been identified before labour to be at high risk of adverse outcomes • Singleton babies born at term (37 to 42 weeks of pregnancy) with no previously identified problems (for example, congenital malformations, genetic anomalies, intrauterine growth restriction, placental problems)
Intervention	• Remifentanil administered by intravenous patient controlled analgesia
Comparison	• Opioids administered intramuscularly: ○ Pethidine ○ Diamorphine ○ Meptazinol

Outcome	Critical • Use of rescue epidural analgesia • Respiratory depression in the mother • Neonatal respiratory depression **Important** • Mode of birth (for example spontaneous vaginal, forceps, caesarean birth) • Women's experience of labour and birth, including experience of pain • Neonatal unit admission • Breastfeeding

For further details see the review protocol in appendix A.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document (supplement 1).

During guideline development, the BNF notation for oxytocin dose changed to 'units', so this has been reflected in the evidence report. The evidence tables in appendix D reflect the dose notations as defined by the original study.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

Effectiveness

Included studies

Five studies were included in this review: 4 randomised controlled trials (RCTs) (Gunes 2014, Ng 2011, Thurlow 2002 and Wilson 2018) and 1 retrospective cohort study (Murray 2019).

Four RCTs compared IV remifentanil PCA to IM pethidine (Gunes 2014, Ng 2011, Thurlow 2002 and Wilson 2018). One of these studies included a third arm which compared IV remifentanil PCA with a background infusion of remifentanil to IM pethidine (Gunes 2014). The retrospective cohort study compared IV remifentanil PCA to IM diamorphine (Murray 2019).

The bolus dose of remifentanil administered by the PCA device varied between studies: 2 studies used a 40 microgram bolus of remifentanil (Murray 2019 and Wilson 2002); 1 study used a 20 microgram bolus (Thurlow 2002); and 2 studies used a bolus dose which accounted for the weight of the woman (Gunes 2014 and Ng 2011). The Thurlow 2002 study was a very small pilot study with a low (20 micrograms) dose of remifentanil, and for this reason the results from this study were not meta-analysed with other studies with higher dose of remifentanil. The rate of delivery and lockout period for each bolus varied between studies.

The included studies were conducted in Ireland, Hong Kong, Turkey and the UK

The included studies are summarised in Table 2.

See the literature search strategy in appendix B and study selection flow chart in appendix C.

Excluded studies

Studies not included in this review are listed, and reasons for their exclusion are provided in appendix J.

1 Summary of included studies

2 Summaries of the studies that were included in this review are presented in Table 2.

3 **Table 2: Summary of included studies**

Study	Population	Intervention	Comparison	Outcomes
Gunes 2014 Randomised controlled trial Turkey	N= 90 Gestational age, mean (SD): 39.4 (0.6)	IV remifentanil PCA • 0.25 microgram kg^{-1} bolus of remifentanil (2 mg remifentanil in 100 mL of sodium chloride 0.9%, 20 µg mL^{-1}) via canula and PCA pump IV remifentanil PCA + infusion • 0.25 microgram kg^{-1} bolus of remifentanil (2 mg remifentanil in 100 mL of sodium chloride 0.9%, 20 µg mL^{-1}) via canula and PCA pump and continuous infusion remifentanil (0.025 microgram kg^{-1} hr^{-1}) For both groups: • 2 minute lockout interval (for bolus dose) • Ringer Lactate infusion (started at rate 1-3 mL kg^{-1} h^{-1}) before administration of analgesia	IM pethidine • Intramuscular injection of 1 mg kg^{-1} meperidine • Ringer Lactate infusion (started at rate 1-3 mL kg^{-1} h^{-1}) before administration of analgesia Note: meperidine is an alternative name for pethidine	• Respiratory depression in the mother • Neonatal respiratory depression • Pain in labour
Murray 2019 Retrospective cohort study Ireland	N= 6345 Gestational age: ≥37 weeks	IV remifentanil PCA • 40 microgram remifentanil (1 mL bolus) via dedicated canula and PCA pump • Delivered over 6 seconds, 2 minute lockout interval • No background infusion	IM diamorphine • Intramuscular administration of 5 mg diamorphine by midwives • Up to 2 doses every 4 hours	• Neonatal admission
Ng 2011 Randomised controlled trial Hong Kong	N= 68 Gestational age: 36-40 weeks	IV remifentanil PCA • 25-30 microgram bolus remifentanil via canula and PCA pump (participants weighing < 60 kg received 25 microgram bolus in 1.25 ml; participants weighing ≥60 kg received 30 microgram in 1.5 ml) • 3.75-4.50 minute lockout interval (hourly	IM pethidine • Intramuscular injection of 50 - 75 mg pethidine (participants weighing < 60 kg received 50 mg pethidine in 1.5 ml sodium chloride; participants weighing ≥60 kg received 75 mg	• Mode of birth • Women's experience of labour and birth (satisfaction)

Study	Population	Intervention	Comparison	Outcomes
		limit of 25 ml) • Intramuscular injection of 1.5 ml sodium chloride 0.9% • No background infusion	pethidine in 1.5 ml sodium chloride) • Sodium chloride 0.9% administered intravenously by PCA device, on demand	
Thurlow 2002 Randomised controlled trial UK	N= 36 Gestational age: 38-42 weeks	<u>IV remifentanil PCA</u> • 20 microgram bolus remifentanil via dedicated cannula and PCA pump • Delivered over 20 seconds, 3 minute lockout interval • No background infusion	<u>IM pethidine</u> • Intramuscular injection of 100 mg meperidine • Antiemetic	• Use of rescue epidural analgesia • Mode of birth • Pain 1 hour after analgesia commenced
Wilson 2018 Randomised controlled trial UK	N= 401 Gestational age: 37 weeks	<u>IV remifentanil PCA</u> • 40 microgram bolus remifentanil via dedicated cannula and PCA pump • 2 minute lockout interval • One-to-one midwifery care • No background infusion	<u>IM pethidine</u> • 100 mg dose pethidine administered by intramuscular injection, up to 4 h in frequency, to a maximum dose of 400 mg in 24 h • Delivered by attending midwife • One-to-one midwifery care	• Use of rescue epidural analgesia • Respiratory depression in the mother • Mode of birth • Women's experience of labour and birth (satisfaction) • Pain in labour • Neonatal admission • Breastfeeding

IM: intramuscular; IV: intravenous; PCA: patient-controlled analgesia; SD: standard deviation

See the full evidence tables in appendix D and the forest plots in appendix E.

Summary of the evidence

Overall, across comparisons, IV remifentanil administered by PCA pump (particularly at a dose of 25-40 mcg) had some important benefits compared to pethidine and diamorphine administered intramuscularly and some important harms compared to pethidine administered intramuscularly.

Remifentanil PCA (20 to 40 microgram) versus IM pethidine

Evidence from one RCT suggested that there was an important benefit for the use of rescue analgesia with remifentanil PCA at a dose of 40 micrograms but no evidence of an important difference at a dose of 20 micrograms. For spontaneous vaginal birth there was an important benefit for remifentanil PCA at a dose of 25 to 40 micrograms (2 RCTs) but evidence of an important harm at a dose of 20 micrograms (1 RCT). For instrumental vaginal birth there was an important benefit for remifentanil PCA at 25-40 micrograms (2 RCTs) but no evidence of an important difference at a dose of 20 micrograms (1 RCT). For caesarean birth there was

no evidence of an important difference for remifentanil PCA at 25-40 micrograms (2 RCTs) or 20 micrograms (1 RCT). This evidence was graded as low to very low quality.

Evidence from one large RCT suggested that there was an important harm for remifentanil PCA (40 micrograms) when compared to IM pethidine for the outcome of respiratory depression, measured by the requirement for supplemental oxygen for the mother. There was possible important harm for remifentanil PCA (40 micrograms) when compared to IM pethidine for the outcome respiratory depression measured by oxygen saturation <94%. There was no evidence of important difference in terms of respiratory depression in the mother measured by respiratory rate < 8 breaths per minute, maternal satisfaction, neonatal admission, pain in labour and breastfeeding within first hour of birth for remifentanil PCA (40 micrograms) versus IM pethidine. This evidence was graded as moderate to low quality.

Evidence from one RCT comparing remifentanil PCA (0.25 micrograms/kg) versus IM pethidine, suggested that remifentanil PCA had an important benefit on pain in labour (measured by a verbal rating scale). There was no important difference for remifentanil PCA (0.25 microgram/kg) when compared to IM pethidine for respiratory depression in mother measured by oxygen saturation (threshold undefined) and neonatal respiratory depression. The overall quality of the evidence for these outcomes was considered to be moderate to low quality.

No important benefits of remifentanil PCA (remifentanil 25 microgram bolus if <60kg, 30 micrograms if >60kg) versus IM pethidine were found for the outcome maternal satisfaction. The quality of the evidence contributing to this outcome was considered to be moderate quality.

Remifentanil PCA (0.25 micrograms/kg) plus background infusion versus IM pethidine

For the comparison of remifentanil PCA (0.25 micrograms/kg) with a background infusion versus IM pethidine, one RCT found that remifentanil PCA had an important benefit on pain (measured by a verbal rating scale). The study also reported respiratory depression in the mother and neonatal respiratory depression, however, no important differences were found. Evidence for these outcomes was from a single study with a small sample size and the outcomes were considered moderate to low quality. No other critical or important outcomes were reported for this comparison.

Remifentanil PCA (40 microgram) versus IM diamorphine

For the comparison of remifentanil PCA (40 microgram) versus intramuscular diamorphine, remifentanil PCA had an important benefit on neonatal admission. The quality of the evidence from this observational study was low. No other critical or important outcomes were reported for this comparison.

See appendix F for full GRADE tables.

Economic evidence

Included studies

A systematic review of the economic literature was conducted but no economic studies were identified which were applicable to this review question.

Excluded studies

Economic studies not included in this review are listed and reasons for their exclusion are provided in appendix K.

Summary of included economic evidence

See Table 3 for the economic evidence profile of the economic model developed for this guideline.

Table 3: Economic evidence profile of a systematic review of economic evaluations of the effectiveness of remifentanil administered by intravenous patient-controlled analgesia (PCA) compared to other intramuscular opioids?

				Incremental			
Study	**Limitations**	**Applicability**	**Other comments**	**Costs**	**Effect**	**Cost effectiveness**	**Uncertainty**
NICE guideline model 2022	Minor limitations[1]	Directly applicable	Cost-utility analysis	-£20	0.00051 QALYs	Remifentanil dominates pethidine Incremental NMB = £31	Probabilistic sensitivity analysis suggested there was a 55% probability that remifentanil was cost-effective Mean incremental NMB = £14 (95% CrInt: -£329 to £328)

CrInt = Credible Intervals; NMB = Net monetary benefit; QALY = Quality adjusted life-year
[1] Health state utilities were obtained from published literature, but they were not derived using NICE's preferred method

Economic model

An original economic model was developed to compare remifentanil administered by intravenous PCA with intramuscular pethidine for pain relief in labour. The model is summarised below with full details provided in appendix I.

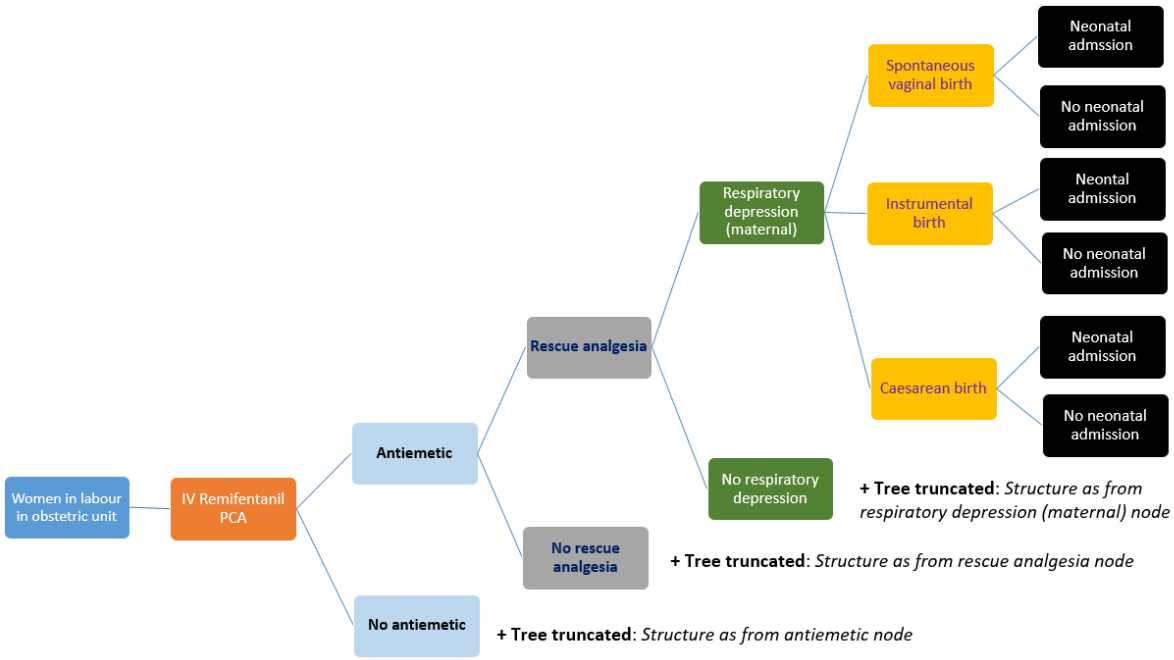
The model took the form of a cost-utility analysis and focused on a population of women with a single baby who go into labour at term and are giving birth in an obstetric unit in an NHS setting. The decision analytic structure of the model is shown in Figure 1. The model was based on a time horizon of 12 weeks reflecting published data on health-related quality of life according to mode of birth.

Clinical outcomes included in the model were the need for rescue analgesia, maternal respiratory depression, mode of birth, use of an antiemetic and pain in labour. Baseline values and relative treatment effects were based on included studies in the systematic review of the evidence. The model included both the costs of the respective treatments along with any costs arising from the clinical outcomes.

A QALY dyad was estimated for each treatment alternative to incorporate any impact on health-related quality of life (HRQoL) on both mother and baby. Health state utilities, estimated from published sources, were assigned to the model's clinical outcomes or "health states". A duration in these "states" was also estimated using published sources in order to

calculate the QALYs over the time horizon of the model for PCA remifentanil and IM pethidine.

Figure 1: Decision model structure



'+' denotes that the tree is truncated at that point

Both deterministic and probabilistic results were calculated. Probabilistic sensitivity analysis involved 10000 repeated Monte Carlo simulations in which model parameters were sampled from a pre-specified probability distribution. In addition to the base case analysis, a number of additional analyses were undertaken to address alternative assumptions with respect to the estimation of health state utilities. Tornado analysis was undertaken to assess the impact of varying different model parameters on the cost-effectiveness of remifentanil and provide insights into the key drivers of model results. It additionally highlighted variables where uncertainty was likely to be more important. This was complemented by several one-way and two-way sensitivity analyses.

The results presented in this analysis provide evidence for the cost-effectiveness of IV remifentanil PCA for pain relief compared to IM pethidine. Deterministic analyses suggested that remifentanil dominated pethidine (cheaper and more effective) and probabilistic sensitivity analyses suggested that, when factoring in parameter uncertainty across those input parameters with a well-defined probability distribution, there was an approximately 57% probability that remifentanil was cost-effective.

Deterministic sensitivity analysis indicated that cost or resource parameters were key drivers of the cost-effectiveness of remifentanil. In the base case analysis reductions in the costs of "downstream" effects just offset the higher cost of remifentanil administration. An "ingredients" based or micro costing approach was used to estimate the costs of PCA remifentanil and IM pethidine. Staffing costs were the most important component of the treatment cost and hence reliable treatment cost estimates depend on accurately estimating the staff grade, tasks and time taken to undertake tasks. Nevertheless, a threshold analysis suggested that remifentanil would remain cost-effective providing its treatment cost was not

more than £191 greater than pethidine, compared with the £146 differential estimated for the base case analysis.

This analysis suggests with that IV remifentanil PCA may be cost-effective relative to an alternative of IM pethidine for pain relief in labour. This finding is driven by the fact that reductions in the costs of rescue analgesia, antiemetic use, and instrumental vaginal births with remifentanil just offset the higher intervention costs associated with remifentanil although it should be recognised that the strength of this finding does depend on accurate estimates of staff time and grade.

Unit costs

Resource	Unit costs	Source
Remifentanil (as Remifentanil hydrochloride) 2 mg	£10.23 per vial	BNF 2021
Pethidine hydrochloride 50 mg per 1 ml	£0.47 per ampoule	BNF 2021
Diamorphine hydrochloride 5 mg	£2.56 per ampoule	BNF 2021
Meptazinol (as Meptazinol hydrochloride) 100 mg per 1 ml	£1.92 per ampoule	BNF 2021

The committee's discussion and interpretation of the evidence

The outcomes that matter most

As the aim of this review was to determine the effectiveness of remifentanil patient-controlled analgesia for pain relief in labour, the committee agreed that use of epidural analgesia was a critical outcome as the need for escalation to regional analgesia is a good measure of the direct effectiveness of the intervention. The committee agreed that respiratory depression in the mother and the baby were critical outcomes for this review as opioids can lead to respiratory depression and so this captures the safety of the intervention. Evidence was available for all of the above 3 critical protocol outcomes.

The committee agreed that mode of birth and women's experience of labour and birth were important outcomes as they wanted to find out whether remifentanil patient-controlled analgesia would reduce the need for interventions during labour and whether this method could improve subjective scores of pain and satisfaction during labour. The committee recognised the great importance of women's experience of labour and birth, including pain, for this review, but they were aware that data on this outcome was likely to be sparse and unlikely to inform decision-making in a meaningful way, so they prioritised other outcomes as critical. The majority of women and babies would have been healthy prior to birth and the committee agreed that neonatal admission should be included as an important outcome to capture any adverse effects on the baby associated with the intervention. The committee agreed that breastfeeding was an important outcome for this review as it may be impacted by the method of pain relief used in labour and it has important consequences for the long-term health of the mother and baby.

The quality of the evidence

The quality of the evidence ranged from low to moderate with most of the evidence being of low quality. The main issues were around the indirectness of the evidence. Most of the studies did not report the risk status of the women or whether the labour was induced. Some of the studies included women who had been induced, and some did not report the proportion of those out of the whole sample who had been induced. There were some concerns with risk of bias in the evidence. This was mainly due to missing data, for example excluding women who were escalated to rescue epidural analgesia. With the exception of one study which included a saline IM injection or saline PCA bolus, there was a risk of bias

across studies due to participants not being blinded to the intervention. Whilst there is no clear evidence of the effectiveness of IV remifentanil PCA over intramuscular opioid on pain relief in labour, it is possible that participants in the PCA arms may have had better perceived control over pain as they could self-administer their analgesic. There were concerns over imprecision of the evidence for several outcomes due to the size of the confidence intervals around the estimate of effect and due to the low number of participants in each arm.

It was not possible to carry out the pre-planned stratification by BMI at booking as no data were available to inform this subgrouping.

Benefits and harms

The committee discussed the evidence around remifentanil PCA and used this alongside their expert opinion and clinical knowledge to make recommendations. The committee noted that the studies used included different doses of remifentanil and that this may impact on the results seen so considered the evidence in terms of doses. They also noted that one study, (Thurlow 2002) was a very small pilot study with a low (20 micrograms) dose of remifentanil and that the results from this study were very different to those seen in other larger studies. The committee therefore considered it was not appropriate to meta-analyse these results (using a random effects model due to the heterogeneity) with the results from the larger studies, and instead considered the results from this study separately.

For the comparison of remifentanil PCA (25 to 40 micrograms) with IM pethidine, there was evidence to suggest that remifentanil reduced the need for rescue epidural analgesia, increased the rate of spontaneous vaginal birth and reduced instrumental vaginal birth. However, there was no important difference in terms of caesarean birth, respiratory depression in the mother measured by respiratory rate < 8 breaths per minute, maternal satisfaction, neonatal unit admission, pain in labour and breastfeeding within first hour of birth for remifentanil compared to IM pethidine. However, remifentanil 25 to 40 micrograms increased the requirement for supplemental oxygen compared to IM pethidine. There was a possible increased respiratory depression measured by oxygen saturation <94% saturation with remifentanil 40 micrograms compared to IM pethidine. Remifentanil PCA (0.25 microgram/kg) was associated with reduction in pain in labour (measured by a verbal rating scale) compared to IM pethidine, but there was no important difference in maternal or neonatal respiratory depression.

Low dose remifentanil PCA (20 micrograms) when compared to IM pethidine was found to be associated with a reduction in the rate of spontaneous vaginal birth but there was no important difference for instrumental vaginal birth. There was no clinically important difference between remifentanil PCA 20 micrograms and IM pethidine for use of rescue epidural analgesia and caesarean birth.

The committee noted that the evidence for remifentanil 40 micrograms compared to diamorphine showed a reduction in neonatal admission, but the committee noted this was based on low quality evidence from the cohort study. Looking at the raw data reported by the study in detail (Murray 2019, data not reported as part of the evidence review), the committee noted that the rate of neonatal admission for women receiving IM diamorphine was higher than PCA remifentanil in 2011 (3.5% vs 1.1%) but by 2013 and 2014 was very similar (1.7% and 1.8% respectively in 2013 and 2.3% and 1.9% respectively in 2014). Furthermore, there was no important difference in terms of neonatal unit admission for the comparison of remifentanil PCA versus IM pethidine. They therefore agreed that it was difficult to conclude that remifentanil reduced neonatal unit admission, and so did not include this in their summary of the risks and benefits for women.

The committee discussed the inconclusive evidence in terms of women's experience of labour and birth for remifentanil PCA versus IM pethidine: there was evidence of an important benefit of remifentanil PCA on pain in labour (when measured by verbal rating scale) from one small RCT using remifentanil 0.25 micrograms/kg (with and without a

background infusion), and no important difference on pain in labour (when measured by a visual analogue scale) from a larger RCT using remifentanil 40 micrograms.

Due to concerns over the quality of the evidence and the heterogeneity of the evidence, the committee agreed that they could not make a strong recommendation. However, based on the evidence that higher doses of remifentanil PCA had benefits for use of rescue epidural analgesia and spontaneous vaginal birth when compared to other IM opioids and there was no evidence of inferiority on pain outcomes, they agreed that remifentanil PCA should be considered instead of intramuscular opioids for women who want ongoing pain relief during labour but who do not want an epidural.

The committee discussed the dose of remifentanil that should be used. They were aware that remifentanil is currently used at a dose of 40 micrograms in a number of obstetric units, and this was in line with the doses used in the two largest and most recent studies (Murray 2018, Wilson 2018). However, the committee noted that it was at this dose that an increase in maternal respiratory depression had been seen. Hence the committee agreed that it was important the recommendations highlighted the need for all units to have clear guidelines in place in responding to respiratory depression if using remifentanil PCA. The committee discussed appropriate settings for using remifentanil PCA and based on their experience and expertise, they agreed that it should only be offered on obstetric units where the risk of respiratory depression could be appropriately managed. Based on this rationale, the committee agreed that intramuscular opioids remain the most appropriate opioid-based pain analgesia in midwifery-led units or for home births.

The committee discussed the benefits and harms of remifentanil PCA using both the evidence and their own experience, and agreed that it was important for healthcare professionals to explain these to women to inform decision making about pain relief in labour. Based on the evidence, the committee agreed that women should be informed which outcomes are more and less likely for remifentanil PCA compared to IM pethidine.

There was evidence showing no increase in neonatal respiratory depression compared to IM opioids, and the committee agreed that this was expected based on the fact that remifentanil is metabolised by ubiquitous pseudocholinesterase enzymes in the neonate to an inactive compound and so can be given throughout labour and birth. The comparison with diamorphine also showed that remifentanil reduced neonatal unit admission, but the committee noted this was based on low quality evidence from the cohort study. Looking at the raw data reported by the study in detail (Murray 2019, data not reported as part of the evidence review), the committee noted that the rate of neonatal admission for women receiving IM diamorphine was higher than PCA remifentanil in 2011 (3.5% vs 1.1%) but by 2013 and 2014 was very similar (1.7% and 1.8% respectively in 2013 and 2.3% and 1.9% respectively in 2014). Furthermore, there was no important difference in terms of neonatal unit admission for the comparison of remifentanil PCA versus IM pethidine. They therefore agreed that it was difficult to conclude that remifentanil reduced neonatal unit admission, and so did not include this in their summary of the risks and benefits for women.

The committee agreed that the recommendations should be explicit in outlining additional monitoring needed to ensure the woman's safety if using remifentanil PCA. Based on the evidence and their own experience and knowledge, the committee agreed it was important that women using remifentanil PCA had continuous one-to-one midwifery care and their respiratory function was monitored, both via observation of breathing and continuous pulse oximetry. In addition, the committee discussed the importance of having supplemental oxygen readily accessible so women would not have to discontinue their pain relief in response to a drop in oxygen saturation. The committee agreed that units should also ensure access to an anaesthetist for all women using remifentanil PCA in order to manage cases of respiratory depression. Based on the evidence and their experience, the committee also agreed that continuous cardiotocography (CTG) monitoring would be required for women using remifentanil PCA. The committee were aware of a large observational study (Melber

2019) in the public domain which was designed to monitor maternal and neonatal outcomes when using remifentanil PCA and inform standards of care. Although this study was not included in this review because it did not include a comparator arm, the committee highlighted that this was an important source of information relevant to guide decisions on standard procedures.

Cost effectiveness and resource use

Remifentanil PCA is more expensive than IM opioids because of higher drug costs and the more intensive staffing requirements for drug administration and monitoring. However, a health economic model developed for this guideline, which compared remifentanil PCA with IM pethidine, suggested that these additional treatment costs for remifentanil could be more than offset by downstream savings resulting from a reduced need for rescue analgesia and antiemetics, lower costs of birth and lower neonatal admission costs. The committee recognised that this cost saving finding was small and sensitive to assumptions about staff tasks, timings, and grade in the administration of the respective drugs as well as the risk of neonatal admission.

The model also suggested that remifentanil PCA would generate small QALY gains when compared to IM pethidine meaning that remifentanil dominated IM pethidine in the deterministic analysis, albeit the net incremental monetary benefit was small in absolute terms. Probabilistic sensitivity analysis suggested that there was a 55% probability that remifentanil PCA was more cost-effective than IM pethidine.

Therefore, the committee considered there was cost-effectiveness evidence to support a consider recommendation for intravenous remifentanil patient-controlled analgesia (PCA) instead of intramuscular opioids as an option for women who want ongoing pain relief during labour, but who do not want an epidural.

Recommendations supported by this evidence review

This evidence review supports recommendations 1.6.19 to 1.6.22.

References

Effectiveness included studies:

Gunes 2014

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Murray 2019

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Ng 2011

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Thurlow 2002

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Albers 1999

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Turner, C.E., Young, J.M., Solomon, M.J., Ludlow, J., Benness, C., Phipps, H. (2008) Vaginal delivery compared with elective caesarean section: the views of pregnant women and clinicians. British Journal of Obstetrics and Gynaecology 115:1494–1502

Wetherington 2014

Wetherington, S., Delong, D., Kini, S., Veledar, E., Schaufele, M.K., Mckenzie-Brown, A.M., Chen, S.C. (2014) Pain quality of life as measured by utilities. Pain Medicine 15(5):865-870

Other:

Melber 2019

Melber, A. A., Jelting, Y., Huber, M., et al. (2019) Remifentanil patient-controlled analgesia in labour: six-year audit of outcome data of the RemiPCA SAFE Network (2010-2015). International journal of obstetric anesthesia, 39, 12–21.

Appendices

Appendix A Review protocols

Review protocol for review question: What is the effectiveness of remifentanil administered by intravenous patient-controlled analgesia (PCA) compared to other intramuscular opioids?

Table 4: Review protocol

Field	Content
PROSPERO registration number	CRD42021256940
Review title	Effectiveness of remifentanil administered by intravenous patient-controlled analgesia (PCA) compared to other intramuscular opioids
Review question	What is the effectiveness of remifentanil administered by intravenous patient-controlled analgesia (PCA) compared to other intramuscular opioids? **Amendment:** A change to the wording of the review question was made to more accurately describe the route of administration of the comparator. Previous review question: What is the effectiveness of opioids administered by intravenous patient-controlled analgesia (PCA) compared to intramuscular administration?
Objective	To update the recommendations in CG190 (2014) on intravenous and intramuscular opioids. Surveillance has identified that opioids administered by intravenous patient controlled analgesia may be associated with a reduction in progression to epidural analgesia, and a reduction in instrumental births.
Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE

Field	Content
	• International Health Technology Assessment database Searches will be restricted by: • English language only • Human studies only Other searches: • Inclusion lists of systematic reviews The full search strategies for MEDLINE database will be published in the final review. For each search, the principal database search strategy is quality assured by a second information scientist using an adaptation of the PRESS 2015 Guideline Evidence-Based Checklist.
Condition or domain being studied	Opioid analgesia for women who are pregnant with a single baby, and are in labour
Population	• Women in labour who are pregnant with a single baby, who go into labour at term (37 to 42 weeks of pregnancy) and who do not have any pre-existing medical conditions or antenatal conditions that predispose to a higher risk birth • Women in labour whose baby has not been identified before labour to be at high risk of adverse outcomes • Singleton babies born at term (37 to 42 weeks of pregnancy) with no previously identified problems (for example, congenital malformations, genetic anomalies, intrauterine growth restriction, placental problems)
Intervention	• Remifentanil administered by intravenous patient-controlled analgesia
Comparator	• Opioids administered intramuscularly: ○ Pethidine ○ Diamorphine ○ Meptazinol (Meptid)
Types of study to be included	Include published full-text papers: • Systematic reviews of RCTs • Parallel RCTs (individual or cluster) • If insufficient RCTs: cohort studies with > 1000 women in each arm Conference abstracts will not be included because these do not typically have sufficient information to allow full critical appraisal.
Other exclusion	Population:

Field	Content
criteria	• Women in labour who are identified before labour to be at high risk, or whose baby is at high risk, of complications or adverse outcomes • Women with non-cephalic presentation • Women in preterm labour • Women with an intrauterine fetal death • Women with multi-fetal pregnancies • Women who are having their labour induced (until active labour is established) • Women who have had a previous caesarean birth or who are having a planned caesarean birth If any study or systematic review includes <1/3 of women with the above characteristics it will be considered for inclusion but, if included, the evidence will be downgraded for indirectness.
Context	This guideline will partly update the following: Intrapartum care for healthy women and babies (CG190)
Primary outcomes (critical outcomes)	• Use of rescue epidural analgesia • Respiratory depression in the mother • Neonatal respiratory depression
Secondary outcomes (important outcomes)	• Mode of birth (for example spontaneous vaginal, forceps, caesarean birth) • Women's experience of labour and birth, including experience of pain • Neonatal admission (includes neonatal intensive care unit [NICU] and special care baby unit [SCBU]) • Breastfeeding
Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI and de-duplicated. Titles and abstracts of the retrieved citations will be screened to identify studies that potentially meet the inclusion criteria outlined in the review protocol. Duplicate screening will not be undertaken for this question. Full versions of the selected studies will be obtained for assessment. Studies that fail to meet the inclusion criteria once the full version has been checked will be excluded at this stage. Each study excluded after checking the full version will be listed, along with the reason for its exclusion.

Field	Content
	A standardised form will be used to extract data from studies. The following data will be extracted: study details (reference, country where study was carried out, type and dates), participant characteristics, inclusion and exclusion criteria, details of the interventions if relevant, setting and follow-up, relevant outcome data and source of funding. One reviewer will extract relevant data into a standardised form, and this will be quality assessed by a senior reviewer.
Risk of bias (quality) assessment	Quality assessment of individual studies will be performed using the following checklists: • ROBIS tool for systematic reviews • Cochrane RoB tool v.2 for RCTs • Cochrane RoB tool v.2 for cluster-randomized trials • Cochrane ROBINS-I tool for non-randomised (clinical) controlled trials and cohort studies The quality assessment will be performed by one reviewer and this will be quality assessed by a senior reviewer.
Strategy for data synthesis	Quantitative findings will be formally summarised in the review. Where multiple studies report on the same outcome for the same comparison, meta-analyses will be conducted using Cochrane Review Manager software. A fixed effect meta-analysis will be conducted and data will be presented as risk ratios if possible or odds ratios when required (for example, if only available in this form in included studies) for dichotomous outcomes, and mean differences or standardised mean differences for continuous outcomes. Heterogeneity in the effect estimates of the individual studies will be assessed using the I2 statistic. Alongside visual inspection of the point estimates and confidence intervals, I^2 values of greater than 50% and 80% will be considered as significant and very significant heterogeneity, respectively. Heterogeneity will be explored as appropriate using sensitivity analyses and pre-specified subgroup analyses. If heterogeneity cannot be explained through subgroup analysis then a random effects model will be used for meta-analysis, or the data will not be pooled. The confidence in the findings across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group: http://www.gradeworkinggroup.org/ Minimally important differences: • Validated scales/continuous outcomes: published MIDs where available • All other outcomes & where published MIDs are not available: 0.8 and 1.25 for all relative dichotomous outcomes ; +/- 0.5x control group SD for continuous outcomes

Field	Content	
Analysis of subgroups	Evidence will be stratified by: • BMI thresholds on booking: ○ Underweight range: <18.5 kg/m^2 ○ Healthy weight range: 18.5 to 24.9 kg/m^2 ○ Overweight range: 25 to 29.99 kg/m^2 ○ Obesity 1: 30 to 34.99 kg/m^2 ○ Obesity 2: 35 to 39.99 kg/m^2 Evidence will be subgrouped by the following only in the event that there is significant heterogeneity in outcomes: • Age of woman (<35 vs >/= 35) • Ethnicity ○ White ○ Asian/Asian British ○ Black/African/Caribbean/Black British ○ Mixed/Multiple ethnic groups ○ Other ethnic group • Women with disability vs not • Deprived socioeconomic group vs not • Country where the study was conducted: high income countries versus low and middle income countries (as defined by the OECD) Where evidence is stratified or subgrouped the committee will consider on a case by case basis if separate recommendations should be made for distinct groups. Separate recommendations may be made where there is evidence of a differential effect of interventions in distinct groups. If there is a lack of evidence in one group, the committee will consider, based on their experience, whether it is reasonable to extrapolate and assume the interventions will have similar effects in that group compared with others.	
Type and method of review	☒	Intervention
	☐	Diagnostic
	☐	Prognostic
	☐	Qualitative

Field	Content	
	☐	Epidemiologic
	☐	Service Delivery
	☐	Other (please specify)
Language	English	
Country	England	
Anticipated or actual start date	20/05/2021	
Anticipated completion date	22/03/2023	
Named contact	5a. Named contact Guideline Development Team National Guideline Alliance (NGA) 5b. Named contact e-mail IPCupdate@nice.org.uk 5c. Organisational affiliation of the review Guideline Development Team NGA, Centre for Guidelines, National Institute for Health and Care Excellence (NICE)	
Review team members	From the Guideline Development Team NGA: • Senior Systematic Reviewer • Systematic Reviewer	
Funding sources/sponsor	This systematic review is being completed by the Guideline Development Team NGA, Centre for Guidelines, which is part of the National Institute for Health and Care Excellence (NICE).	
Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a	

Field	Content
	senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/cg190.
Other registration details	None
URL for published protocol	https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=256940
Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
Keywords	Labour, pain, patient-controlled analgesia
Details of existing review of same topic by same authors	Not applicable
Additional information	None
Details of final publication	www.nice.org.uk

BMI: Body mass index; CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; GRADE: Grading of Recommendations Assessment, Development and Evaluation; MID: minimally important difference; NGA: National Guideline Alliance; NICE: National Institute for Health and Care Excellence; PRESS: peer review of electronic search strategies; RCT: randomised controlled trial; RoB(IS): risk of bias (in systematic reviews); ROBINS-I: Risk of bias in non-randomized studies of interventions; SD: standard deviation

Appendix B Literature search strategies

Literature search strategies for review question: What is the effectiveness of remifentanil administered by intravenous patient-controlled analgesia (PCA) compared to other intramuscular opioids?

Review question search strategies

Database: Medline - OVID interface

Date of last search: 06/12/2022

#	Searches
1	PREGNANCY/
2	PARTURITION/
3	exp LABOR, OBSTETRIC/
4	exp DELIVERY, OBSTETRIC/
5	OBSTETRIC LABOR, PREMATURE/
6	(pregnan$ or labo?r? or childbirth$ or partu$ or intra?part$ or peri?part$).ab,ti.
7	((during or giving or give) adj5 (birth$ or deliver$)).ti,ab.
8	or/1-7
9	REMIFENTANIL/
10	remifentanil.mp.
11	or/9-10
12	ANALGESIA, PATIENT-CONTROLLED/
13	(patient? adj3 control* adj3 analgesi*).ti,ab.
14	PCA.ti,ab.
15	or/12-14
16	8 and 11 and 15
17	limit 16 to english language
18	LETTER/
19	EDITORIAL/
20	NEWS/
21	exp HISTORICAL ARTICLE/
22	ANECDOTES AS TOPIC/
23	COMMENT/
24	CASE REPORT/
25	(letter or comment*).ti.
26	or/18-25
27	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
28	26 not 27
29	ANIMALS/ not HUMANS/
30	exp ANIMALS, LABORATORY/
31	exp ANIMAL EXPERIMENTATION/
32	exp MODELS, ANIMAL/
33	exp RODENTIA/
34	(rat or rats or mouse or mice).ti.
35	or/28-34
36	17 not 35
37	META-ANALYSIS/
38	META-ANALYSIS AS TOPIC/
39	(meta analy* or metanaly* or metaanaly*).ti,ab.
40	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
41	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
42	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
43	(search* adj4 literature).ab.
44	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
45	cochrane.jw.
46	or/37-45
47	randomized controlled trial.pt.
48	controlled clinical trial.pt.
49	pragmatic clinical trial.pt.
50	randomi#ed.ab.
51	placebo.ab.
52	randomly.ab.
53	CLINICAL TRIALS AS TOPIC/

#	Searches
54	trial.ti.
55	or/47-54
56	COHORT STUDIES/
57	FOLLOW-UP STUDIES/
58	LONGITUDINAL STUDIES/
59	PROSPECTIVE STUDIES/
60	RETROSPECTIVE STUDIES/
61	((cohort* or follow-up or follow?up or longitudinal* or prospective* or retrospective*) adj1 (stud* or research or analys*)).tw.
62	(incidence? adj (stud* or research or analys*)).tw.
63	(longitudinal* adj1 (survey* or evaluat*)).tw.
64	(prospective* adj method*).tw.
65	(retrospective* adj design*).tw.
66	or/56-65
67	36 and 46
68	36 and 55
69	36 and 66
70	or/67-69

Database: Embase – OVID interface

Date of last search: 06/12/2022

#	Searches
1	*PREGNANCY/
2	*PERINATAL PERIOD/
3	exp *BIRTH/
4	exp *LABOR/
5	*PREMATURE LABOR/
6	*INTRAPARTUM CARE/
7	(pregnan$ or labo?r? or childbirth$ or partu$ or intra?part$ or peri?part$).ab,ti.
8	((during or giving or give) adj5 (birth$ or deliver$)).ti,ab.
9	or/1-8
10	REMIFENTANIL/
11	remifentanil.mp.
12	or/10-11
13	PATIENT CONTROLLED ANALGESIA/
14	(patient? adj3 control* adj3 analgesi*).ti,ab.
15	PCA.ti,ab.
16	or/13-15
17	9 and 12 and 16
18	limit 17 to english language
19	letter.pt. or LETTER/
20	note.pt.
21	editorial.pt.
22	CASE REPORT/ or CASE STUDY/
23	(letter or comment*).ti.
24	or/19-23
25	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
26	24 not 25
27	ANIMAL/ not HUMAN/
28	NONHUMAN/
29	exp ANIMAL EXPERIMENT/
30	exp EXPERIMENTAL ANIMAL/
31	ANIMAL MODEL/
32	exp RODENT/
33	(rat or rats or mouse or mice).ti.
34	or/26-33
35	18 not 34
36	SYSTEMATIC REVIEW/
37	META-ANALYSIS/
38	(meta analy* or metanaly* or metaanaly*).ti,ab.
39	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
40	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
41	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
42	(search* adj4 literature).ab.
43	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
44	((pool* or combined) adj2 (data or trials or studies or results)).ab.

#	Searches
45	cochrane.jw.
46	or/36-45
47	random*.ti,ab.
48	factorial*.ti,ab.
49	(crossover* or cross over*).ti,ab.
50	((doubl* or singl*) adj blind*).ti,ab.
51	(assign* or allocat* or volunteer* or placebo*).ti,ab.
52	CROSSOVER PROCEDURE/
53	SINGLE BLIND PROCEDURE/
54	RANDOMIZED CONTROLLED TRIAL/
55	DOUBLE BLIND PROCEDURE/
56	or/47-55
57	COHORT ANALYSIS/
58	FOLLOW UP/
59	LONGITUDINAL STUDY/
60	PROSPECTIVE STUDY/
61	RETROSPECTIVE STUDIES/
62	((cohort* or follow-up or follow?up or longitudinal* or prospective* or retrospective*) adj1 (stud* or research or analys*)).tw.
63	(incidence? adj (stud* or research or analys*)).tw.
64	(longitudinal* adj1 (survey* or evaluat*)).tw.
65	(prospective* adj method*).tw.
66	(retrospective* adj design*).tw.
67	or/57-66
68	35 and 46
69	35 and 56
70	35 and 67
71	or/68-70

Databases: Cochrane Central Register of Controlled Trials; and Cochrane Database of Systematic Reviews – Wiley interface

Date of last search: 06/12/2022

#	Searches
#1	MeSH descriptor: [Pregnancy] this term only
#2	MeSH descriptor: [Parturition] this term only
#3	MeSH descriptor: [Labor, Obstetric] explode all trees
#4	MeSH descriptor: [Delivery, Obstetric] explode all trees
#5	MeSH descriptor: [Obstetric Labor, Premature] this term only
#6	(pregnan* or labor* or labour* or childbirth* or partu* or intrapart* or intra-part* or peripart* or peri-part*):ti,ab
#7	((during or giving or give) near/5 (birth* or deliver*)):ti,ab
#8	#1 or #2 or #3 or #4 or #5 or #6 or #7
#9	MeSH descriptor: [Remifentanil] this term only
#10	remifentanil:ti,ab
#11	#9 or #10
#12	MeSH descriptor: [Analgesia, Patient-Controlled] this term only
#13	(patient* near/3 control* near/3 analgesi*):ti,ab
#14	PCA:ti,ab
#15	#12 or #13 or #14
#16	#8 and #11 and #15

Database: International Health Technology Assessment

Date of last search: 06/12/2022

#	Searches
	All: remifentanil

Health economics search strategies

Database: Medline – OVID interface

Date of last search: 06/12/2022

#	Searches
1	PREGNANCY/
2	PARTURITION/
3	exp LABOR, OBSTETRIC/
4	exp DELIVERY, OBSTETRIC/
5	OBSTETRIC LABOR, PREMATURE/
6	(pregnan$ or labo?r? or childbirth$ or partu$ or intra?part$ or peri?part$).ab,ti.
7	((during or giving or give) adj5 (birth$ or deliver$)).ti,ab.
8	or/1-7
9	REMIFENTANIL/
10	remifentanil.mp.
11	or/9-10
12	ANALGESIA, PATIENT-CONTROLLED/
13	(patient? adj3 control* adj3 analgesi*).ti,ab.
14	PCA.ti,ab.
15	or/12-14
16	8 and 11 and 15
17	limit 16 to english language
18	LETTER/
19	EDITORIAL/
20	NEWS/
21	exp HISTORICAL ARTICLE/
22	ANECDOTES AS TOPIC/
23	COMMENT/
24	CASE REPORT/
25	(letter or comment*).ti.
26	or/18-25
27	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
28	26 not 27
29	ANIMALS/ not HUMANS/
30	exp ANIMALS, LABORATORY/
31	exp ANIMAL EXPERIMENTATION/
32	exp MODELS, ANIMAL/
33	exp RODENTIA/
34	(rat or rats or mouse or mice).ti.
35	or/28-34
36	17 not 35
37	ECONOMICS/
38	VALUE OF LIFE/
39	exp "COSTS AND COST ANALYSIS"/
40	exp ECONOMICS, HOSPITAL/
41	exp ECONOMICS, MEDICAL/
42	exp RESOURCE ALLOCATION/
43	ECONOMICS, NURSING/
44	ECONOMICS, PHARMACEUTICAL/
45	exp "FEES AND CHARGES"/
46	exp BUDGETS/
47	budget*.ti,ab.
48	cost*.ti,ab.
49	(economic* or pharmaco?economic*).ti,ab.
50	(price* or pricing*).ti,ab.
51	(financ* or fee or fees or expenditure* or saving*).ti,ab.
52	(value adj2 (money or monetary)).ti,ab.
53	resourc* allocat*.ti,ab.
54	(fund or funds or funding* or funded).ti,ab.
55	(ration or rations or rationing* or rationed).ti,ab.
56	ec.fs.
57	or/37-56
58	36 and 57

Database: Embase – OVID interface

Date of last search: 06/12/2022

#	Searches
1	*PREGNANCY/
2	*PERINATAL PERIOD/
3	exp *BIRTH/
4	exp *LABOR/
5	*PREMATURE LABOR/
6	*INTRAPARTUM CARE/
7	(pregnan$ or labo?r? or childbirth$ or partu$ or intra?part$ or peri?part$).ab,ti.
8	((during or giving or give) adj5 (birth$ or deliver$)).ti,ab.
9	or/1-8
10	REMIFENTANIL/
11	remifentanil.mp.
12	or/10-11
13	PATIENT CONTROLLED ANALGESIA/
14	(patient? adj3 control* adj3 analgesi*).ti,ab.
15	PCA.ti,ab.
16	or/13-15
17	9 and 12 and 16
18	limit 17 to english language
19	letter.pt. or LETTER/
20	note.pt.
21	editorial.pt.
22	CASE REPORT/ or CASE STUDY/
23	(letter or comment*).ti.
24	or/19-23
25	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
26	24 not 25
27	ANIMAL/ not HUMAN/
28	NONHUMAN/
29	exp ANIMAL EXPERIMENT/
30	exp EXPERIMENTAL ANIMAL/
31	ANIMAL MODEL/
32	exp RODENT/
33	(rat or rats or mouse or mice).ti.
34	or/26-33
35	18 not 34
36	HEALTH ECONOMICS/
37	exp ECONOMIC EVALUATION/
38	exp HEALTH CARE COST/
39	exp FEE/
40	BUDGET/
41	FUNDING/
42	RESOURCE ALLOCATION/
43	budget*.ti,ab.
44	cost*.ti,ab.
45	(economic* or pharmaco?economic*).ti,ab.
46	(price* or pricing*).ti,ab.
47	(financ* or fee or fees or expenditure* or saving*).ti,ab.
48	(value adj2 (money or monetary)).ti,ab.
49	resourc* allocat*.ti,ab.
50	(fund or funds or funding* or funded).ti,ab.
51	(ration or rations or rationing* or rationed).ti,ab.
52	or/36-51
53	35 and 52

Database: Cochrane Central Register of Controlled Trials – Wiley interface

Date of last search: 06/12/2022

#	Searches
#1	MeSH descriptor: [Pregnancy] this term only
#2	MeSH descriptor: [Parturition] this term only
#3	MeSH descriptor: [Labor, Obstetric] explode all trees
#4	MeSH descriptor: [Delivery, Obstetric] explode all trees
#5	MeSH descriptor: [Obstetric Labor, Premature] this term only
#6	(pregnan* or labor* or labour* or childbirth* or partu* or intrapart* or intra-part* or peripart* or peri-part*):ti,ab
#7	((during or giving or give) near/5 (birth* or deliver*)):ti,ab
#8	#1 or #2 or #3 or #4 or #5 or #6 or #7

#	Searches
#9	MeSH descriptor: [Remifentanil] this term only
#10	remifentanil:ti,ab
#11	#9 or #10
#12	MeSH descriptor: [Analgesia, Patient-Controlled] this term only
#13	(patient* near/3 control* near/3 analgesi*):ti,ab
#14	PCA:ti,ab
#15	#12 or #13 or #14
#16	#8 and #11 and #15
#17	MeSH descriptor: [Economics] this term only
#18	MeSH descriptor: [Value of Life] this term only
#19	MeSH descriptor: [Costs and Cost Analysis] explode all trees
#20	MeSH descriptor: [Economics, Hospital] explode all trees
#21	MeSH descriptor: [Economics, Medical] explode all trees
#22	MeSH descriptor: [Resource Allocation] explode all trees
#23	MeSH descriptor: [Economics, Nursing] this term only
#24	MeSH descriptor: [Economics, Pharmaceutical] this term only
#25	MeSH descriptor: [Fees and Charges] explode all trees
#26	MeSH descriptor: [Budgets] explode all trees
#27	budget*:ti,ab
#28	cost*:ti,ab
#29	(economic* or pharmaco?economic*):ti,ab
#30	(price* or pricing*):ti,ab
#31	(financ* or fee or fees or expenditure* or saving*):ti,ab
#32	(value near/2 (money or monetary)):ti,ab
#33	resourc* allocat*:ti,ab
#34	(fund or funds or funding* or funded):ti,ab
#35	(ration or rations or rationing* or rationed):ti,ab
#36	#17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35
#37	#16 and #36

Database: International Health Technology Assessment

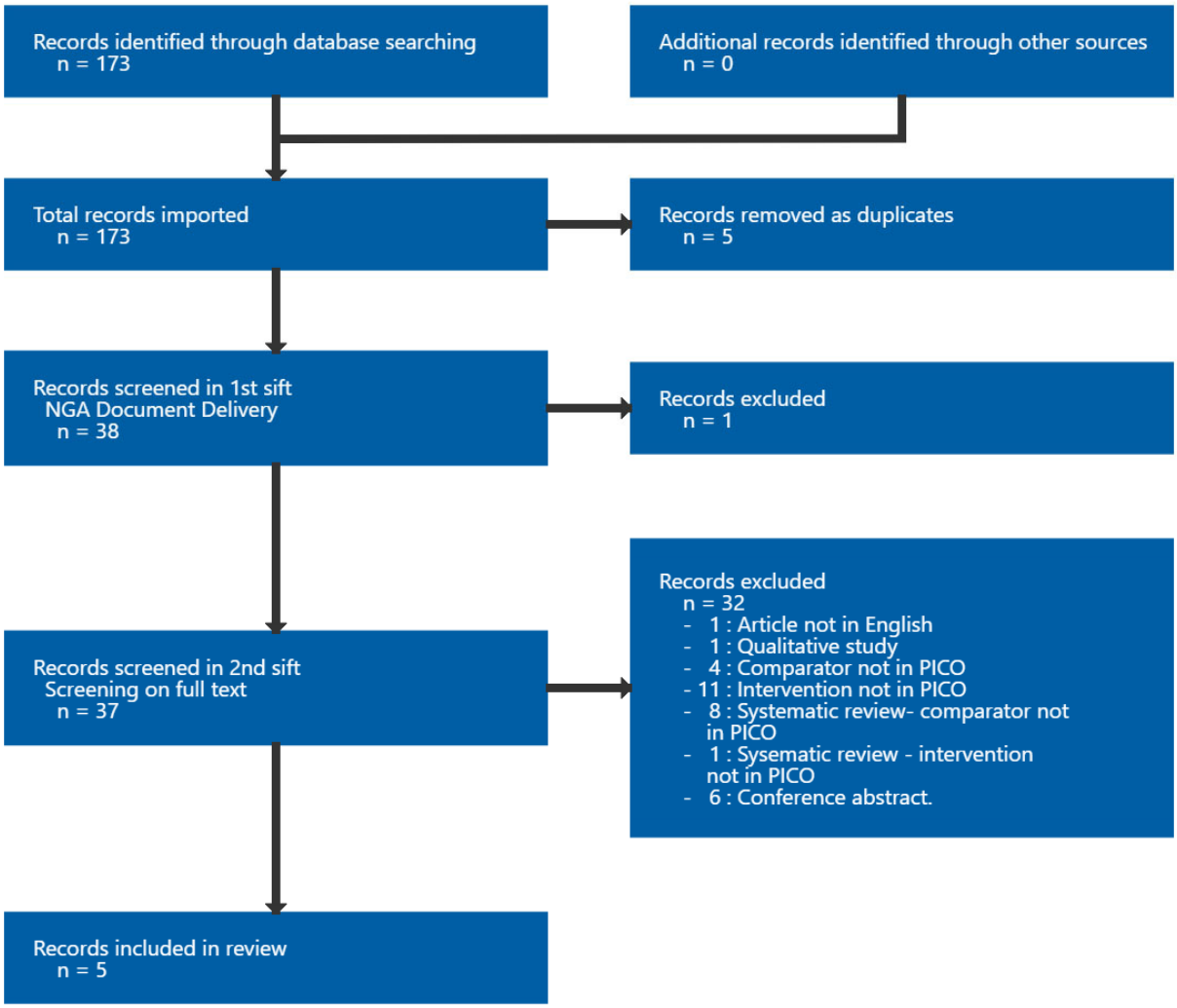
Date of last search: 06/12/2022

#	Searches
	All: remifentanil

Appendix C Effectiveness evidence study selection

Study selection for: What is the effectiveness of remifentanil administered by intravenous patient-controlled analgesia (PCA) compared to other intramuscular opioids?

Figure 2: Study selection flow chart



Note: for this review, de-duplication was done outside of EPPI in EndNote for practical reasons, therefore the study selection flowchart does not accurately reflect the records removed as duplicates.

Appendix D Evidence tables

Evidence tables for review question: What is the effectiveness of remifentanil administered by intravenous patient-controlled analgesia (PCA) compared to other intramuscular opioids?

Gunes, 2014

Bibliographic Reference Gunes, Suleyman; Turktan, Mediha; Gulec, Umran Kucukgoz; Hatipoglu, Zehra; Unlugenc, Hakki; Isik, Geylan; The Comparison of Patient-Controlled Remifentanil Administered by Two Different Protocols (Bolus and Bolus+Infusion) and Intramuscular Meperidine for Labor Analgesia; Turkish journal of anaesthesiology and reanimation; 2014; vol. 42 (no. 5); 264-9

Study details

Country/ies where study was carried out	Turkey
Study type	Randomised controlled trial (RCT)
Study dates	Not reported
Inclusion criteria	• Planned vaginal delivery
Exclusion criteria	• Any obstetric or gestational risk factors • BMI > 40 • History of opioid allergy, long-term opioid use or chronic pain
Patient characteristics	Age, mean (SD) • IV remifentanil PCA group: 25.4 (4.6) • IV remifentanil PCA + infusion group: 25.6 (4.6) • IM meperidine group: 26.6 (4.6) Gestation, mean (SD)

	• IV remifentanil PCA group: 39.7 (0.5) • IV remifentanil PCA + infusion group: 39.3 (0.5) • IM meperidine group: 39.1 (0.8) Weight, mean (SD) • IV remifentanil PCA group: 73.9 (7.6) • IV remifentanil PCA + infusion group: 74.1 (7.0) • IM meperidine group: 72.8 (9.5)
Intervention(s)/control	IV remifentanil PCA group • 0.25 µg kg-1 bolus of remifentanil (2 mg remifentanil in 100 mL of sodium chloride 0.9%, 20 µg mL-1) via canula and PCA pump • Lockout interval of 2 minutes • Ringer Lactate infusion (started at rate 1-3 mL kg-1 h-1) before administration of analgesia IV remifentanil PCA + infusion group • 0.25 µg kg-1 bolus of remifentanil (2 mg remifentanil in 100 mL of sodium chloride 0.9%, 20 µg mL-1) and continuous infusion remifentanil (0.025 µg kg-1 hr-1) via canula and PCA pump • Lockout interval of 2 minutes (for bolus dose) • Ringer Lactate infusion (started at rate 1-3 mL kg-1 h-1) before administration of analgesia IM meperidine group • Intramuscular injection of 1 mg kg-1 meperidine • Ringer Lactate infusion (started at rate 1-3 mL kg-1 h-1) before administration of analgesia
Sources of funding	No funding
Sample size	N = 90
Other information	

Outcomes

Respiratory depression

Outcome	Intravenous remifentanil patient-controlled analgesia (PCA) group, , N = 30	Intravenous remifentanil patient-controlled analgesia (PCA) + infusion group, , N = 30	Intramuscular meperidine group, , N = 30
Respiratory depression in the mother measured by oxygen saturation (threshold undefined by study authors) No of events	n = 0	n = 0	n = 0
Neonatal respiratory depression No of events	n = 0	n = 0	n = 0

Pain

Outcome	Intravenous remifentanil patient-controlled analgesia (PCA) group, , N = 30	Intravenous remifentanil patient-controlled analgesia (PCA) + infusion group, , N = 30	Intramuscular meperidine group, , N = 30
VRS pain score (0= no pain, 10= the worst possible pain imaginable) in labour Mean (SD)	5.2 (1.2)	5.4 (1)	7 (1.3)

Critical appraisal

Section	Question	Answer

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Participant allocation randomised and concealed)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(Unclear if intention-to-treat protocol followed)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Some concerns *(Denominator data not reported for outcomes so not possible to determine adherence)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(Unable to ascertain if any data is missing as study does not report denominators for each outcome. Likely that any missingness in the outcomes depended on their true values)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(No clear evidence that remifentanil PCA is more effective than meperidine for pain relief, or vice versa. However, participants in remifentanil PCA group may have better perceived control over pain compared to meperidine group and this may have introduced bias in measurement of pain)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(Standard outcomes reported, but not pre-specified)*
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Partially applicable *(onset of spontaneous labour not specified in participant eligibility criteria, and proportion of participants with induced labour not reported)*

Section	Question	Answer
Overall bias and Directness	Risk of bias variation across outcomes	None detected

Murray, 2019

Bibliographic Reference	Murray, H.; Hodgkinson, P.; Hughes, D.; Remifentanil patient-controlled intravenous analgesia during labour: a retrospective observational study of 10years' experience; International Journal of Obstetric Anesthesia; 2019; vol. 39; 29-34

Study details

Country/ies where study was carried out	Ireland
Study type	Retrospective cohort study
Study dates	January 2005 to December 2014
Inclusion criteria	• gestation ≥37 weeks • women in established labour • women delivering in the unit who had received the study drugs and regimens of interest for labour analgesia
Exclusion criteria	• women undergoing elective caesarean birth • women receiving Entonox only or oral analgesics only
Patient characteristics	Not reported
Intervention(s)/control	IV remifentanil PCA group • Single 1 mL bolus of 40 ug reminfentanil via dedicated canula and PCA pump • Delivered over 6 seconds, with 2 minute lockout interval

	• No background infusion <u>IM diamorphine group</u> • Intramuscular administration of 5 mg diamorphine by midwives • Up to 2 doses every 4 hours
Sources of funding	No funding
Sample size	N= 14684 (N= 6345 for outcome of interest)
Other information	Gestational age not reported

Outcomes

Neonatal admission

Outcome	**Intravenous remifentanil patient-controlled analgesia (PCA) group, , N = 3938**	**Intramuscular diamorphine, , N = 2407**
Admission to NICU No of events	n = 63	n = 65

Critical appraisal

Section	**Question**	**Answer**
1. Bias due to confounding	Risk of bias judgement for confounding	Serious *(Participants were not randomised to treatment groups, but chose treatment regimen. Participant characteristics not recorded and likely that baseline differences in characteristics between groups may be associated with intervention and outcomes)*
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low *(Low risk of bias as all women delivering in study unit were included if they had received the drug regimens of interest)*

Section	Question	Answer
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low *(Interventions clearly defined and unlikely to have been affected by knowledge of outcome)*
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Low *(Discrete interventions delivered specified time period)*
5. Bias due to missing data	Risk of bias judgement for missing data	No information *(Denominator for neonatal admission taken as only the births included in the analysis for neonatal admission (2011-2014). Total number of women receiving remifentanil and diamorphine during this time differs; likely due to exclusions based on pre-specified exclusion criteria)*
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Low *(Neonatal admission is an objective measure)*
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low *(Standard outcome)*
Overall bias	Risk of bias judgement	Serious
Overall bias	Risk of bias variation across outcomes	Not applicable
Overall bias	Directness	Partially applicable *(onset of spontaneous labour not specified in participant eligibility criteria, and proportion of participants with induced labour not reported)*

Ng, 2011

Bibliographic Reference	Ng, T. K.; Cheng, B. C.; Chan, W. S.; Lam, K. K.; Chan, M. T.; A double-blind randomised comparison of intravenous patient-controlled remifentanil with intramuscular pethidine for labour analgesia; Anaesthesia; 2011; vol. 66 (no. 9); 796-801

Study details

Country/ies where study was carried out	Hong Kong
Study type	Randomised controlled trial (RCT)
Study dates	Not reported
Inclusion criteria	• 36–40 weeks' gestation • cephalic presentation • in first stage of spontaneous labour • requested parenteral opioid for labour analgesia
Exclusion criteria	• obstetric risk factors (including, gestational diabetes, pregnancy induced hypertension or antepartum haemorrhage)
Patient characteristics	<u>Age, mean (SD)</u> • IV remifentanil PCA group: 28 (5) • IM pethidine group: 29 (5) <u>Gestation, median (IQR)</u> • IV remifentanil PCA group: 39 (38-40) • IM pethidine group: 39 (39-40) <u>Parity = 0, number (%)</u>

	• IV remifentanil PCA group: 30 (88) • IM pethidine group: 28 (82) Weight, mean (SD) • IV remifentanil PCA group: 68.2 kg (11.1) • IM pethidine group: 69.0 kg (8.9) Syntocinon augmentation, n (%) • IV remifentanil PCA group: 27 (79) • IM pethidine group: 30 (88)
Intervention(s)/control	IV remifentanil PCA • 25- 30 ug bolus remifentanil via canula and PCA pump (participants weighing < 60 kg: 25 µg bolus in 1.25 ml; participants weighing ≥60 kg: 30 µg in 1.5 ml) • Lockout interval of 3.75-4.50 min (hourly limit of 25 ml) • Intramuscular injection of 1.5 ml sodium chloride 0.9% • No background infusion IM pethidine • Intramuscular injection of 50 - 75 mg pethidine • Participants weighing < 60 kg: 50 mg pethidine in 1.5 ml sodium chloride; participants weighing ≥60 kg: 75 mg pethidine in 1.5 ml sodium chloride • Sodium chloride 0.9% administered intravenously by PCA device, on demand
Sources of funding	No external funding received
Sample size	N = 68

Outcomes

Mode of birth

Outcome	Intravenous remifentanil patient-controlled analgesia (PCA) group, , N = 34	Intramuscular pethidine group, , N = 34
Spontaneous vaginal No of events	n = 24	n = 19
Instrumental (forceps or suction) No of events	n = 3	n = 5
Caesarean birth No of events	n = 7	n = 10

Satisfaction

Outcome	Intravenous remifentanil patient-controlled analgesia (PCA) group, , N = 34	Intramuscular pethidine group, , N = 34
VAS satisfaction score 0 = totally dissatisfied; 10 = totally satisfied Median (IQR)	8 (6 to 9)	6 (5 to 7)

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Participant allocation randomised and concealed)*

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Intervention assignment blinded to participants, all healthcare workers and outcome assessors)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low *(No evidence of non-adherence. Intention-to-treat analysis followed)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(Number of participants with VAS pain scores not reported. Graphical representation of data only. Unable to determine if data is complete.)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(Blinding of outcome assessors and participants minimises risk of bias in this domain)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(Standard outcomes reported and pre-specified in protocol)*
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	None detected

Thurlow, 2002

Bibliographic Reference Thurlow, J. A.; Laxton, C. H.; Dick, A.; Waterhouse, P.; Sherman, L.; Goodman, N. W.; Remifentanil by patient-controlled analgesia compared with intramuscular meperidine for pain relief in labour; British journal of anaesthesia; 2002; vol. 88 (no. 3); 374-378

Study details

Country/ies where study was carried out	UK
Study type	Randomised controlled trial (RCT)
Study dates	Not reported
Inclusion criteria	• 18- 40 years of age • 38- 42 weeks' gestation • in early labour
Exclusion criteria	• weight < 50 kg or > 100 kg
Patient characteristics	Age, median (IQR) • IV remifentanil PCA group: 29 (25-30) • IM meperidine group: 28 (22-32) Gestation • IV remifentanil PCA group: 39.6 (39-40) • IM meperidine group: 40.1 (39.25-41) Parity =1, number (%) • IV remifentanil PCA group: 13 (72) • IM meperidine group: 13 (72) Weight, median (IQR) • IV remifentanil PCA group: 64 kg (58-76)

	• IM meperidine group: 66.5 kg (58-78) Spontaneous onset of labour, n (%) • IV remifentanil PCA group: 15 (88) • IM meperidine group: 16 (89)
Intervention(s)/control	IV remifentanil PCA group • 20 ug bolus remifentanil via dedicated cannula and PCA pump • Delivered over 20 seconds, with 3 minute lockout interval • No background infusion IM meperidine group • intramuscular injection of 100 mg meperidine • antiemetic
Sources of funding	Not reported
Sample size	N= 36

Outcomes

Rescue epidural

Outcome	**Intravenous remifentanil patient-controlled analgesia (PCA) group, , N = 18**	**Intramuscular meperidine, , N = 18**
Use of rescue epidural analgesia	n = 7	n = 3

Outcome	Intravenous remifentanil patient-controlled analgesia (PCA) group, , N = 18	Intramuscular meperidine, , N = 18
No of events		

Mode of birth

Outcome	Intravenous remifentanil patient-controlled analgesia (PCA) group, , N = 18	Intramuscular meperidine, , N = 17
Spontaneous vaginal No of events	n = 11	n = 16
Instrumental (forceps or suction) No of events	n = 4	n = 1
Caesarean birth No of events	n = 3	n = 0

Pain

Outcome	Intravenous remifentanil patient-controlled analgesia (PCA) group, , N = 18	Intramuscular meperidine, , N = 18
VAS pain score at 1 hour after analgesia commenced Median (IQR)	48 (22 to 50.5)	72 (62 to 90)

Critical appraisal

Section	Question	Answer

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(Participant allocation randomised and concealed, however, small sample size (n= 36) makes baseline differences more likely. Differences in fetal position and baseline anxiety levels may be a source of bias.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(participants and outcome assessors were not blinded, study was an open randomised trial)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Some concerns *(Deviations from assigned intervention regimen in both arms due to participants choosing epidural analgesia, but intention to treat analysis followed. Study authors report that antiemetic was not given to women in the remifentanil group, suggesting it was available to women in the meperidine group.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(Data available for nearly all participants for outcomes of interest)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(No clear evidence that remifentanil PCA is more effective than meperidine for pain relief, or vice versa. However, participants in remifentanil PCA group may have better perceived control over pain compared to meperidine group and this may have introduced bias in measurement of pain)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(Standard outcomes reported, but not pre-specified)*
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	Low overall, however, study authors report that sedative effect of meperidine may have influenced womens' choice to request epidural analgesia

Wilson, 2018

Bibliographic Reference	Wilson, M. J. A.; MacArthur, C.; Hewitt, C. A.; Handley, K.; Gao, F.; Beeson, L.; Daniels, J.; Intravenous remifentanil patient-controlled analgesia versus intramuscular pethidine for pain relief in labour (RESPITE): an open-label, multicentre, randomised controlled trial; Lancet (london, england); 2018; vol. 392 (no. 10148); 662-672

Study details

Country/ies where study was carried out	UK
Study type	Randomised controlled trial (RCT)
Study dates	May 2014 - September 2016
Inclusion criteria	• ≥16 years of age • 37 weeks gestation • singleton live baby • cephalic presentation • in established labour (defined by study authors as regular painful contractions irrespective of cervical dilatation) • intending vaginal birth
Exclusion criteria	• no opioid analgesia in the preceding 4 h • no contraindications to remifentanil, pethidine, or epidural analgesia • not participating in any other drug trial
Patient characteristics	Age, mean (SD) • IV remifentanil PCA group: 29.4 (6.1) • IM pethidine group: 29.3 (6.1)

	Parity, median (IQR) • IV remifentanil PCA group: 0 (0-1) • IM pethidine group: 0 (0-1) Weight, mean (SD) • IV remifentanil PCA group: 73.1 (18.4) • IM pethidine group: 75.0 (17.2) Ethnicity, n (%) • IV remifentanil PCA group: White 146 (73), Black or Black British 8 (4), Asian 31 (14), Mixed/ multiple groups 3 (1), Other 9 (4) • IM pethidine group: White 157 (79), Black or Black British 7 (4), Asian 30 (16), Mixed/ multiple groups 3 (1), Other 5 (3) Induction of labour, n (%) • IV remifentanil PCA group: 137 (68) • IM pethidine group: 136 (68)
Intervention(s)/control	IV remifentanil PCA group • 40 µg bolus remifentanil via dedicated cannula and PCA pump • Lockout interval of 2 min • One-to-one midwifery care • No background infusion IM pethidine group • 100 mg dose pethidine administered by intramuscular injection, up to 4 h in frequency, to a maximum dose of 400 mg in 24 h • Delivered by attending midwife

	• One-to-one midwifery care
Sources of funding	National Institute for Health Research Clinician Scientist Award
Sample size	N= 401

Outcomes

Epidural analgesia

Outcome	**Intravenous remifentanil patient-controlled analgesia (PCA) group, , N = 201**	**Intramuscular pethidine group, , N = 199**
Use of rescue epidural analgesia No of events	n = 39	n = 81

Respiratory depression in the mother

Outcome	**Intravenous remifentanil patient-controlled analgesia (PCA) group, , N = 189**	**Intramuscular pethidine group, , N = 154**
Respiratory depression measured by oxygen saturation (< 94% while breathing room air) No of events	n = 26	n = 8
Outcome	**Intravenous remifentanil patient-controlled analgesia (PCA) group, , N = 76**	**Intramuscular pethidine group, , N = 76**
Respiratory depression measured by requirement for supplemental oxygen No of events	n = 35	n = 1

Outcome	Intravenous remifentanil patient-controlled analgesia (PCA) group, , N = 189	Intramuscular pethidine group, , N = 154
Outcome	**Intravenous remifentanil patient-controlled analgesia (PCA) group, , N = 189**	**Intramuscular pethidine group, , N = 152**
Respiratory depression measured by respiratory rate < 8 breaths per minute No of events	n = 1	n = 0

Mode of birth

Outcome	Intravenous remifentanil patient-controlled analgesia (PCA) group, , N = 201	Intramuscular pethidine group, , N = 199
Spontaneous vaginal No of events	n = 128	n = 106
Instrumental (forceps or suction) No of events	n = 31	n = 52
Caesarean birth No of events	n = 42	n = 41

Pain

Outcome	Intravenous remifentanil patient-controlled analgesia (PCA) group, , N = 150	Intramuscular pethidine group, , N = 117
VAS pain score Mean (SD)	75.9 (27.09)	80.34 (26.24)

Satisfaction

Outcome	Intravenous remifentanil patient-controlled analgesia (PCA) group, , N = 184	Intramuscular pethidine group, , N = 176
Satisfied with overall childbirth experience Strongly agree and agree Sample size	n = 153	n = 156

Neonatal admission

Outcome	Intravenous remifentanil patient-controlled analgesia (PCA) group, , N = 201	Intramuscular pethidine group, , N = 199
Admission to higher level care No of events	n = 8	n = 9

Breastfeeding

Outcome	Intravenous remifentanil patient-controlled analgesia (PCA) group, , N = 195	Intramuscular pethidine group, , N = 195
Breastfeeding within first hour of birth Sample size	n = 90	n = 91

Critical appraisal

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low *(Participant allocation randomised and concealed)*

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Study follows intention to treat analysis)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Some concerns *(Difference in adherence between groups explored through sensitivity analysis and found not to effect outcomes. Some concerns over imbalance of anti-emetic administration between groups (79% in IV remifentanil PCA group vs 32% in IM pethidine group) which could affect VAS satisfaction outcome)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(VAS pain scores: Slight imbalance in denominator between groups (17 in IV remifentanil PCA group vs 23 in IM pethidine group). Outcome not routinely recorded and discontinued for women requesting epidural, resulting in missing data for outcome likely to be associated with its true value. Respiratory depression: Imbalance in denominator between groups (14 in IV remifentanil PCA group vs 47 in IM pethidine group). Missing data not explained and unclear if associated with true value of outcome. Low number of events recorded for this outcome reduce risk of bias.)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(Unblinded, but mostly objective outcomes. For pain relief, no clear evidence that remifentanil PCA is more effective than pethidine, or vice versa. However, concerns of bias introduced in measurement of pain outcome arising from differences in participants' perceived control over pain)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low *(Standard outcomes reported and pre-specified in protocol)*
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Partially applicable *(> 1/3 participants in both arms had their labour induced, before the onset of*

Section	Question	Answer
		spontaneous labour)
Overall bias and Directness	Risk of bias variation across outcomes	Imbalance in missing data between groups for respiratory depression addressed in domain 3.

Appendix E Forest plots

Forest plots for review question: What is the effectiveness of remifentanil administered by intravenous patient-controlled analgesia (PCA) compared to other intramuscular opioids?

This section includes forest plots only for outcomes that are meta-analysed. Outcomes from single studies are not presented here; the quality assessment for such outcomes is provided in the GRADE profiles in appendix F.

Comparison 1. Intravenous remifentanil PCA versus intramuscular pethidine

Figure 3: Spontaneous vaginal birth (remifentanil 25-40 micrograms)

Figure 4: Instrumental vaginal birth (remifentanil 25-40 micrograms)

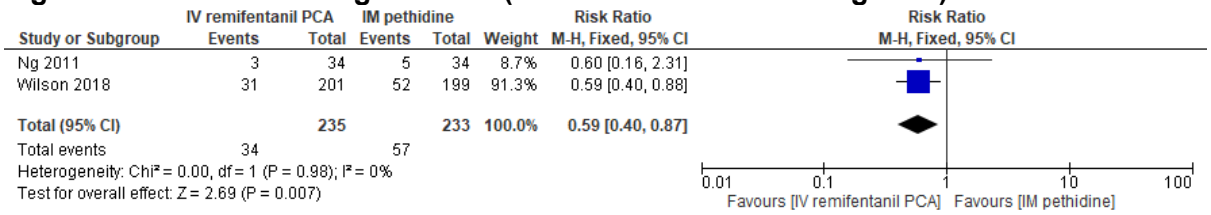
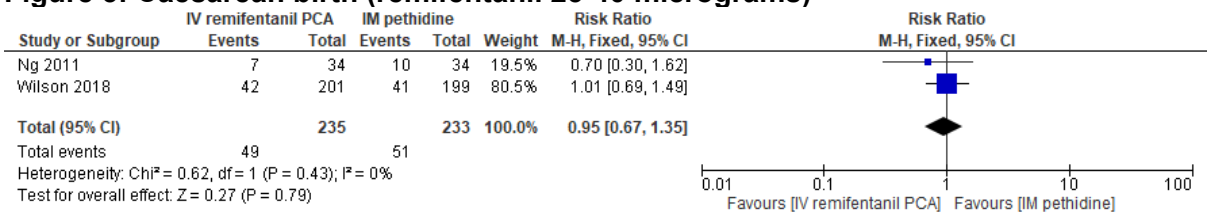


Figure 5: Caesarean birth (remifentanil 25-40 micrograms)



Appendix F GRADE tables

GRADE tables for review question: What is the effectiveness of remifentanil administered by intravenous patient-controlled analgesia (PCA) compared to other intramuscular opioids?

Table 5: Evidence profile for comparison 1. Intravenous remifentanil PCA versus intramuscular pethidine

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IV remifentanil PCA	IM pethidine	Relative (95% CI)	Absolute	Quality	Importance
Use of rescue epidural analgesia (remifentanil 40 micrograms) (Better indicated by lower values)												
1 (Wilson 2018)	randomised trial	serious[1]	No serious inconsistency	serious[3]	no serious imprecision	none	39/201 (19.4%)	81/199 (40.7%)	RR 0.48 (0.34 to 0.66)	212 fewer per 1000 (from 138 fewer to 269 fewer)	LOW	CRITICAL
Use of rescue epidural analgesia (remifentanil 20 micrograms) (Better indicated by lower values)												
1 (Thurlow 2002)[a]	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	very serious imprecision[8]	None	7/18 (38.9%)	3/18 (16.17%)	RR 2.33 (0.71 to 7.63)	222 more per 1000 (from 48 fewer to 1000 more)	VERY LOW	CRITICAL
Respiratory depression in the mother measured by oxygen saturation (remifentanil 0.25 micrograms/kg) (threshold undefined) (Better indicated by lower values)												
1 (Gunes 2014)	randomised trial	serious[1]	no serious inconsistency	serious[3]	very serious imprecision[5]	None	0/30 (0%)	0/30 (0%)	RD 0.00 (-0.06 to 0.06)	0 fewer per 1000 (from 60 fewer to 60 more)	VERY LOW	CRITICAL
Respiratory depression in the mother measured by oxygen saturation <94% (remifentanil 40 micrograms) (Better indicated by lower values)												
1 (Wilson 2018)	randomised trial	serious[1]	no serious inconsistency	serious[3]	serious imprecision[7]	None	26/189 (13.8%)	8/154 (5.2%)	RR 2.65 (1.23 to 5.68)	86 more per 1000 (from 12 more to 243 more)	VERY LOW	CRITICAL
Respiratory depression in the mother measured by requirement for supplemental oxygen (remifentanil 40 micrograms) (Better indicated by lower values)												
1 (Wilson 2018)	randomised trial	serious[1]	no serious inconsistency	serious[3]	no serious imprecision	none	35/76 (46.1%)	1/76 (1.3%)	RR 35(4.92 to 249.02)	447 more per 1000 (from 52 more to 1000	LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IV remifentanil PCA	IM pethidine	Relative (95% CI)	Absolute	Quality	Importance
										more)		
Respiratory depression in the mother measured by respiratory rate < 8 breaths per minute (remifentanil 40 micrograms) (Better indicated by lower values)												
1 (Wilson 2018)	randomised trial	serious[1]	no serious inconsistency	serious[3]	very serious imprecision[8]	none	1/187 (0.5%)	0/152 (0%)	POR 6.13 (0.12 to 315.39)	0 more per 1000 (from 0 fewer to 0 more)	VERY LOW	CRITICAL
Neonatal respiratory depression (remifentanil 0.25 micrograms/kg)												
1 (Gunes 2014)	randomised trial	serious[1]	no serious inconsistency	serious[4]	very serious[5]	none	0/30 (0%)	0/30 (0%)	RD 0.00 (-0.06 to 0.06)	0 fewer per 1000 (from 60 fewer to 60 more)	LOW	CRITICAL
Mode of birth (remifentanil 25-40 micrograms) - Spontaneous vaginal												
2 (Ng 2011, Wilson 2018)	randomised trials	serious[1]	serious[6]	serious[3]	serious[7]	none	152/235 (64.7%)	125/233 (53.6%)	RR 1.21 (1.04 to 1.4)	113 more per 1000 (from 21 more to 115 more)	VERY LOW	IMPORTANT
Mode of birth (remifentanil 20 micrograms) - Spontaneous vaginal												
1 (Thurlow 2002)[a]	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[7]	none	11/18 (61.1%)	16/17 (94.1%)	RR 0.65 (0.44 to 0.96)	329 fewer per 1000 (from 38 fewer to 527 fewer)	LOW	IMPORTANT
Mode of birth (remifentanil 25-40 micrograms) - Instrumental (forceps or suction)												
2 (Ng 2011, Wilson 2018)	randomised trials	serious[1]	no serious inconsistency	serious[3]	serious[7]	none	34/235 (14.5%)	57/233 (24.5%)	RR 0.59 (0.4 to 0.87)	100 fewer per 1000 (from 32 fewer to 147 fewer)	LOW	IMPORTANT
Mode of birth (remifentanil 20 micrograms) - Instrumental (forceps or suction)												
1 (Thurlow 2002)[a]	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	very serious[8]	none	1/18 (22.2%)	1/17 (5.9%)	RR 3.78 (0.47 to 30.5)	164 more per 1000 (from 31 fewer to 1000 more)	VERY LOW	IMPORTANT
Mode of birth (remifentanil 25-40 micrograms) - Caesarean birth												
2 (Ng 2011,	randomised trials	serious[1]	no serious inconsistency	serious[3]	very serious[8]	none	49/235	51/233	RR 0.95	11 fewer	LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IV remifentanil PCA	IM pethidine	Relative (95% CI)	Absolute		
Wilson 2018)							(20.9%)	(21.9%)	(0.67 to 1.35)	per 1000 (from 72 fewer to 77 more)		
Mode of birth (remifentanil 20 micrograms) - Caesarean birth												
1 (Thurlow 2002)[a]	Randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[8]	none	3/18 (16.7%)	0/17 (0%)	RR 6.63 (0.37 to 119.59)	0 fewer per 1,000 (0 fewer to 0 fewer)	VERY LOW	IMPORTANT
Maternal satisfaction (remifentanil 25 to 30 micrograms) (assessed with: VAS satisfaction score; Better indicated by lower values)												
1 (Ng 2011)	randomised trials	no serious concerns	no serious inconsistency	no serious indirectness	very serious[5]	none	34 Median (IQR): 8 (6-9)	34 Median (IQR): 6 (5-7)	-	-	MODERATE	IMPORTANT
Maternal satisfaction (remifentanil 40 micrograms) (assessed with: women who agree or strongly agree with 'I was satisfied with my overall childbirth experience'; Better indicated by lower values)												
1 (Wilson 2018)	randomised trials	serious[1]	no serious inconsistency	serious[3]	no serious imprecision	none	153/184 (83.2%)	156/176 (88.6%)	RR 0.94 (0.86 to 1.02)	53 fewer per 1000 (from 124 fewer to 18 more)	MODERATE	IMPORTANT
Pain in labour (remifentanil 0.25 micrograms/kg) (measured with: Verbal rating scale; range of scores: 0- 10; Better indicated by lower values)												
1 (Gunes 2014)	randomised trials	serious[1]	no serious inconsistency	serious[4]	no serious imprecision	none	30 Mean (SD): 5.2 (1.2)	30 Mean (SD): 7 (1.3)	MD -1.80 (-2.43 to -1.17)	1.8 lower (from 2.43 lower to 1.17 lower)	MODERATE	IMPORTANT
Pain 2 hours after analgesia commenced (remifentanil 20 micrograms) (measured with: Visual analogue scale; range of scores: 0-100; Better indicated by lower values)												
1 (Thurlow 2002)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[5]	none	18 Median (IQR): 66.5 (57-78)	18 Median (IQR): 82.5 (75-90)	-	-	LOW	IMPORTANT
Pain in labour (remifentanil 40 micrograms) (measured with: Visual analogue scale; range of scores: 0-100; Better indicated by lower values)												
1 (Wilson 2018)	randomised trials	serious[1]	no serious inconsistency	serious[3]	no serious imprecision	none	150 Mean (SD): 75.9 (27.1)	117 Mean (SD): 80.34 (26.2)	MD -4.44 (-10.87 to 1.99)	4.44 lower (10.87 lower to 1.99 higher)	MODERATE	IMPORTANT
Neonatal admission (remifentanil 40 micrograms) (Better indicated by lower values)												
1	randomise	serious[1]	no serious	serious[3]	very serious[8]	none	8/201	9/199	RR 0.88	5 fewer per	LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IV remifentanil PCA	IM pethidine	Relative (95% CI)	Absolute		
(Wilson 2018)	d trials		inconsistency				(4%)	(4.5%)	(0.35 to 2.23)	1000 (from 29 fewer to 56 more)		
Breastfeeding within first hour of birth (remifentanil 40 micrograms)												
1 (Wilson 2018)	randomised trials	serious[1]	no serious inconsistency	serious[3]	no serious imprecision	none	90/195 (46.2%)	91/195 (46.7%)	RR 0.99 (0.8 to 1.22)	5 fewer per 1000 (from 93 fewer to 103 more)	LOW	IMPORTANT

RR: risk ratio; RD: risk difference; POR: peto odds ratio; MD: mean difference;
[a] Thurlow was analysed separately as it used a lower dose of remifentanil
[1] Serious risk of bias in the evidence contributing to the outcomes as per RoB 2
[2] Very serious heterogeneity
[3] Population is indirect due to > 1/3 participants having their labour induced
[4] Population is indirect due to whether labour was induced is not reported and spontaneous onset of labour is not specified in the eligibility criteria
[5] Sample size <200
[6] Serious heterogeneity
[7] 95% CI crosses 1 MID
[8] 95% CI crosses 2 MIDs

Table 6: Evidence profile for comparison 2. Intravenous remifentanil PCA + background infusion versus intramuscular pethidine

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IV remifentanil PCA + background infusion	IM meperidine	Relative (95% CI)	Absolute		
Respiratory depression in the mother measured by oxygen saturation (threshold undefined) (remifentanil 0.25 micrograms/kg+ background infusion) (Better indicated by lower values)												
1 (Gunes 2014)	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	0/30 (0%)	0/30 (0%)	RD 0.00 (-0.06 to 0.06)	0 fewer per 1000 (from 60 fewer to 60 more)	LOW	CRITICAL
Neonatal respiratory depression (remifentanil 0.25 micrograms/kg+ background infusion) (Better indicated by lower values)												
1 (Gunes 2014)	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	0/30 (0%)	0/30 (0%)	RD 0.00 (-0.06 to 0.06)	0 fewer per 1000 (from 60 fewer to 60 more)	LOW	CRITICAL
Pain in labour (remifentanil 0.25 micrograms/kg + background infusion) measured with: Verbal rating scale; range of score: 0- 10; Better indicated by lower values)												
1	randomised	serious[1]	no serious	serious[2]	no serious	none	30	30	MD -1.6 (-	1.6 lower	MODER	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IV remifentanil PCA + background infusion	IM meperidine	Relative (95% CI)	Absolute		
(Gunes 2014)	trials		inconsistency		imprecision		Mean (SD): 5.4 (1.0)	Mean (SD): 7.0 (1.3)	2.19 to -1.01)	(2.19 to 1.01 lower)	ATE	

RD: risk difference; MD: mean difference
[1] Serious risk of bias in the evidence contributing to the outcomes as per RoB 2
[2] Population is indirect due to whether labour was induced or not is not reported

Table 7: Evidence profile for comparison 3. Intravenous remifentanil PCA versus intramuscular diamorphine

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IV remifentanil PCA	IM diamorphine	Relative (95% CI)	Absolute		
Neonatal admission (remifentanil 40 micrograms) (Better indicated by lower values)												
1 (Murray 2019)	observational studies	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	63/3938 (1.6%)	65/2407 (2.7%)	RR 0.59 (0.42 to 0.83)	11 fewer per 1000 (from 5 fewer to 16 fewer)	LOW	IMPORTANT

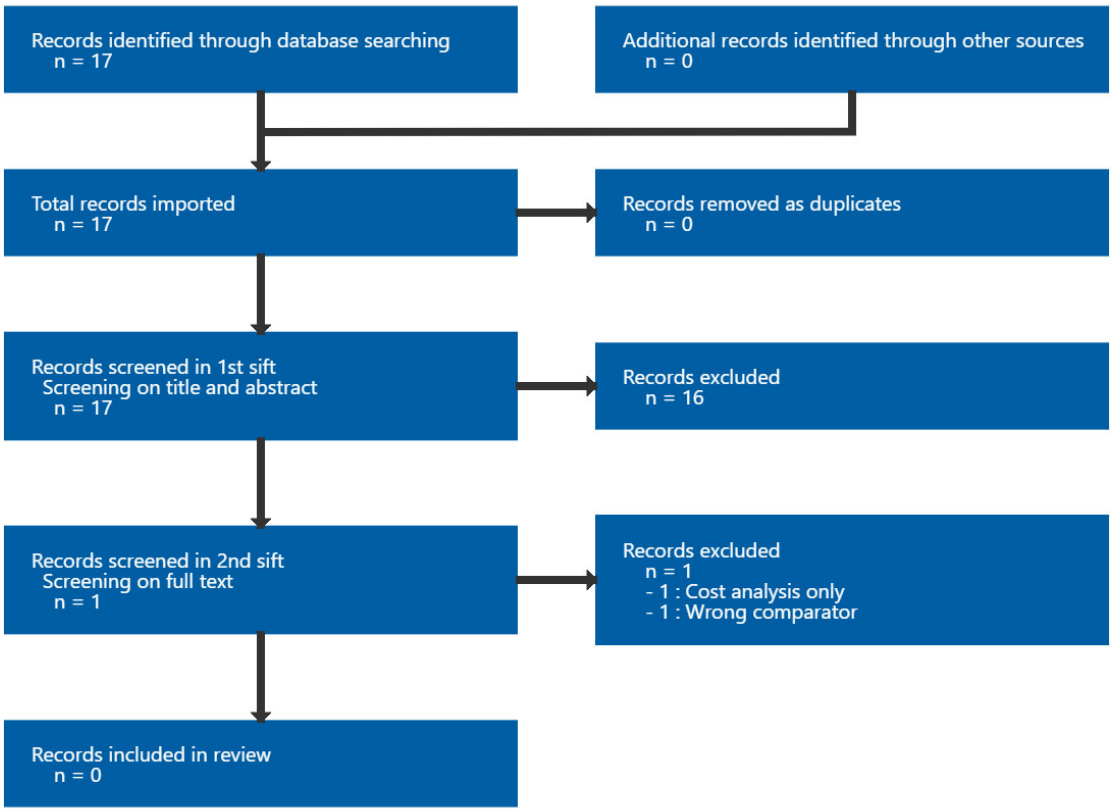
RR: risk ratio
[1]Serious risk of bias in the evidence contributing to the outcomes as per ROBINS-I
[2] Population is indirect due to whether labour was induced is not reported and spontaneous onset of labour is not specified in the eligibility criteria
[3] 95% CI crosses 1 MID

Appendix G Economic evidence study selection

Study selection for: What is the effectiveness of remifentanil administered by intravenous patient-controlled analgesia (PCA) compared to other intramuscular opioids?

No economic evidence was identified which was applicable to this review question.

Figure 6: Study selection flow chart



Appendix H Economic evidence tables

Economic evidence tables for review question: What is the effectiveness of remifentanil administered by intravenous patient-controlled analgesia (PCA) compared to other intramuscular opioids?

No evidence was identified which was applicable to this review question.

Appendix I Economic model

Economic model for review question: What is the effectiveness of remifentanil administered by intravenous patient-controlled analgesia (PCA) compared to other intramuscular opioids?

Cost-utility analysis of remifentanil administered by intravenous PCA compared to intramuscular pethidine for pain relief in labour

Introduction

Epidural analgesia is considered the most effective pain relief in labour, but it is known to increase the risk of instrumental vaginal birth. Although, it is associated with high levels of maternal satisfaction, it is not acceptable to all women. Intramuscular (IM) pethidine is a common alternative form of pain relief in labour but is also associated with a number of maternal side effects and many women still go to require an epidural for acceptable pain relief. Remifentanil administered by intravenous (IV) PCA is an alternative to IM pethidine which may confer a number of advantages, although uptake has thought to have been hindered by concerns about maternal respiratory depression. Furthermore, remifentanil is more expensive than pethidine and intravenous administration is more resource intensive in terms of both equipment and staffing. Therefore, the guideline committee prioritised this topic for economic analysis especially as recommendations had the potential to change current NHS practice.

Methods

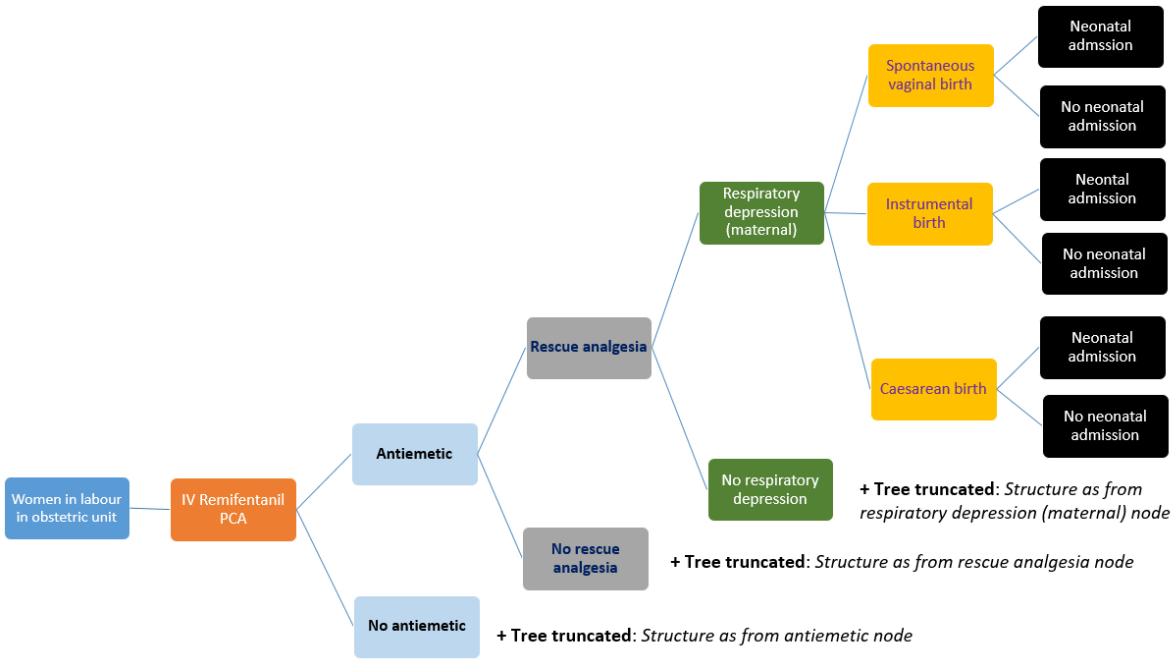
Setting and population

The model population was women with a single baby who go into labour at term and giving birth in an obstetric unit in an NHS hospital setting. The population is limited to women who do not have any pre-existing medical conditions or antenatal conditions that predispose to a higher risk birth and to babies with no previously identified problems (for example, congenital malformations, genetic anomalies, intrauterine growth restriction, placental problems).

Model structure

A decision analytic model was developed in Microsoft Excel® to assess the cost-utility of remifentanil administered by IV PCA compared to IM pethidine for pain relief in labour. A schematic of the model is shown in Figure 7 which illustrates the decision analytic framework for the IV remifentanil PCA comparator. The IM pethidine decision structure is identical. Probabilities attached to decision tree branches are mostly derived from the systematic review of the clinical evidence undertaken for this guideline. The time horizon of the analysis was 12 weeks which was based on Tan 2010.

Figure 7: Schematic of the decision model



'+' denotes that the tree is truncated at that point

Model outcomes

Table 8 indicates the outcomes for which comparative clinical evidence was found in this evidence review for IV remifentanil PCA relative to IM pethidine. Table 8 also indicates whether this outcome was used in the economic model as well as a rationale for inclusion or exclusion.

Table 8: Assessment of outcomes in clinical review for inclusion in the economic model

Outcome	Included in economic analysis	Rationale for inclusion or exclusion
Use of rescue analgesia	Yes, base case analysis	Indicates "downstream" resource use and impact on health-related quality of life
Maternal respiratory depression measured by oxygen saturation	No	It was thought an alternative measure of maternal respiratory depression gave a better indication of "downstream" resource use and health-related quality of life
Maternal respiratory depression measured by requirement for supplementary oxygen	Yes	Indicates "downstream" resource use and impact on health-related quality of life
Maternal respiratory depression measured by oxygen saturation	No	It was thought an alternative measure of maternal respiratory depression gave a better indication of "downstream" resource use and health-related quality of life
Neonatal respiratory intervention	No	Zero events in both the intervention and control arm

Outcome	Included in economic analysis	Rationale for inclusion or exclusion
Mode of birth	Yes	Indicates "downstream" resource use and impact on health-related quality of life
Maternal satisfaction	No	Not related to resource use or health-related quality of life
Pain in labour	Sensitivity analysis (for pain outcome measured on visual analogue scale)	Not directly related to "downstream" resource use and likely to be related to need for rescue analgesia and therefore a risk of double counting with respect to health-related quality of life
Neonatal admission	Yes	Indicates "downstream" resource use and impact on health-related quality of life
Breastfeeding	No	Complex to model longer terms of this and evidence in the review indicated almost identical event rates consistent with a null hypothesis of no difference

In addition, the use of an antiemetic was included as an outcome as, although this was not a prioritised outcome in the clinical review protocol, it was reported in the Respite trial (Wilson 2018) and potentially has a "downstream" resource implication which may vary according to the intervention.

Effectiveness

Baseline

The baseline model parameters were taken from the event rates for IM pethidine (the comparator) obtained from the results of included studies in the systematic review of the clinical evidence (see Table 5). These are summarised in Table 9.

Table 9: Model parameter values for IM pethidine

Variable	Value	Probability distribution	Distribution parameters
Rescue analgesia	40.7%	Beta	$\alpha = 81, \beta = 118$
Maternal respiratory depression	1.3%	Beta	$\alpha = 1, \beta = 75$
Neonatal admission	4.5%	Beta	$\alpha = 9, \beta = 190$
Antiemetic	67.7%	Beta	$\alpha = 134, \beta = 64$
Spontaneous vaginal birth	56.4%	Dirichlet	$\gamma_1 = 141, \gamma_2 = 58, \gamma_3 = 51$
Instrumental vaginal birth	23.2%	Dirichlet	$\gamma_1 = 141, \gamma_2 = 58, \gamma_3 = 51$
Caesarean birth	20.4%	Dirichlet	$\gamma_1 = 141, \gamma_2 = 58, \gamma_3 = 51$
Pain in labour – health state utility [a]	0.1966	Normal	$\mu = 0.1966, \sigma = 0.0242$

(a) This is used as alternative to rescue analgesia for QALY estimation in a sensitivity analysis.

Relative treatment effects

With the exception of antiemetic use, relative treatment effect parameters for the model were taken from the included studies in the systematic review of the clinical evidence, see Table 5. The relative treatment effect for antiemetic use was taken from Wilson (2018). The relative

treatment effects for IV remifentanil PCA (the intervention) relative to IM pethidine are summarised in Table 10.

Table 10: Relative treatment effects of IV remifentanil PCA compared to IM pethidine

Variable	Value	Probability distribution	Distribution parameters
Rescue analgesia RR	0.48	Log-normal	$\mu = -0.73$, $\sigma = 0.17$
Maternal respiratory depression LOR	4.16	Normal	$\mu = 4.16$, $\sigma = 1.03$
Neonatal admission RR	0.88	Log-normal	$\mu = -0.13$, $\sigma = 0.47$
Antiemetic RR	0.31	Log-normal	$\mu = -1.17$, $\sigma = 0.15$
Spontaneous vaginal birth	64.4%	Dirichlet	$\gamma_1 = 163$, $\gamma_2 = 38$, $\gamma_3 = 52$
Instrumental vaginal birth	15.0%	Dirichlet	$\gamma_1 = 163$, $\gamma_2 = 38$, $\gamma_3 = 52$
Caesarean birth	20.6%	Dirichlet	$\gamma_1 = 163$, $\gamma_2 = 38$, $\gamma_3 = 52$
Pain health state disutility MD [a]	-0.04	Normal	$\mu = -0.04$, $\sigma = 0.03$

LOR = log odds ratio; MD = mean difference; RR = relative risk

(a) This is used as alternative to rescue analgesia for QALY estimation in a sensitivity analysis.

Costs and resource use

In accordance with NICE methodology a NHS and Personal Social Services (PSS) perspective was adopted for this analysis (https://www.nice.org.uk/Media/Default/About/what-we-do/our-programmes/developing-NICE-guidelines-the-manual.pdf). Costs were based on a 2021-22 price year. The model input cost parameters are given in Table 11. Any costs occurring after 1-year were discounted at an annual rate of 3.5% in line with NICE methods.

Table 11: Model cost input parameters

Variable	Value	Probability Distribution	Distribution parameters	Source
IV Remifentanil PCA	£183	Deterministic	N/A	Ingredient's based costing see below
IM pethidine	£37	Deterministic	N/A	Ingredient's based costing see below
Rescue analgesia [a]	£582	Normal	μ= £582, σ = £89	National Schedule of NHS Costs 2019-20 [b]
Maternal respiratory depression	£19	Deterministic	N/A	Ingredient's based costing see below
Antiemetic	£37	Deterministic	N/A	Ingredient's based costing see below
Spontaneous vaginal birth	£2,007	Normal	μ= £2,007, σ = £39	National Schedule of NHS Costs 2019-20 [c]
Instrumental vaginal birth	£2,518	Normal	μ= £2,518, σ = £46	National Schedule of NHS Costs 2019-20 [d]
Emergency caesarean birth	£5,379	Normal	μ= £5,379, σ = £68	National Schedule of

Variable	Value	Probability Distribution	Distribution parameters	Source
				NHS Costs [e]
Neonatal admission	£2,328	Normal	μ= £2,328, σ = £51	National Schedule of NHS Costs

(a) In the RESPITE study (Wilson 2018) rescue analgesia implied epidural. The epidural cost is estimated from the difference in costs between "Normal Delivery, with Epidural or Induction, with CC Score 0" and "Normal Delivery with CC Score 0"
(b) Currency code NZ31C and NZ30C for non-elective short stay procedures
(c) A weighted average of currency code NZ30
(d) A weighted average of currency code NZ40
(e) A weighted average of currency code NZ51
(f) A weighted average of currency code XA01Z, XA02Z, XA03Z, XA04Z, XA05Z

For a number of model cost inputs there was no nationally published source and therefore an "ingredient's" based or micro-costing was undertaken to estimate these costs.

a. IV remifentanil PCA

The consumable resources in providing IV remifentanil PCA are listed in Table 12 along with their unit cost. Based on a private communication from an obstetric unit in Northern Ireland where remifentanil has been widely used (Ulster Hospital, South Eastern Health and Social Care Trust) it was estimated that 80% of women would require 1-bag of remifentanil solution and that 20% of patients would require 2-bags.

Table 12: Consumable unit costs for remifentanil PCA

Resource	Unit cost	Source
Consumables (single use equipment) for preparation of a PCA remifentanil system		
100ml 0.9% saline [a]	£2.23	https://openprescribing.net/national/england/09020 21S0AACJCJ/price-per-unit/ (accessed 31/05/2022)
2 x 2mg remifentanil [a]	£20.45	https://bnf.nice.org.uk/medicinal-forms/remifentanil.html (accessed 31/05/2022)
5ml syringe [a]	£0.05	https://www.medisave.co.uk/bd-discardit-5ml-2-piece-eccentric-tip-syringe-box-of-100.html (accessed 31/05/2022)
Blunt needle for drawing up [a]	£0.11	https://www.medisave.co.uk/bd-blunt-fill-safety-draw-up-needle-18-g-red-40-mm-1-45-degr-qty100.html?gclid=Cj0KCQiAjc2QBhDgARIsAMc3SqRwZqK-ke3ULYIprmDFAt_Dc9aR0oMuZrNws704GeECKKs7fGV8K2gaAqUGEALw_wcB (accessed 31/05/2022)
Label for the bag of remifentanil solution [a]	£0.02	https://www.celfix.co.uk/product/10-drugs-added-infusion/ (communication with company stated that cost is around £24.00 per roll of 1500 labels)
Remifentanil PCA sticker [a]	£0.02	https://www.amazon.co.uk/Labels-Sheet-Sheets-Label-Labels4u/dp/B00IJUWDX0 (accessed 31/05/2022)
Giving set	£10.92	Administration set for Bodyguard 575 PCA Pump (NHS Supply Chain 2021)
Dedicated cannula for PCA remifentanil		
Pair of gloves	£0.07	https://www.medisave.co.uk/nitrile-gloves-medical-grade-cat-iii-ppe-medium.html (accessed

Resource	Unit cost	Source
		31/05/2022)
Chloraprep wipe	£0.30	https://bnf.nice.org.uk/medicinal-forms/chlorhexidine-gluconate-with-isopropyl-alcohol.html (accessed 31/05/2022)
20G cannula	£0.54	Safety Cannula Straight With Wings - Pink 20G x 32mm PUR (NHS Supply Chain 2021)
Sterile dressing	£1.77	https://www.drugtariff.nhsbsa.nhs.uk/#/00726198-DD/DD00726009/Part%20IXA-Dressings (accessed 31/05/2022)

(a) Per bag of remifentanil solution

The staffing resources required to provide IV remifentanil PCA are described in Table 13 and the unit costs of staffing per working hour are shown in Table 14.

Table 13: Staff tasks in providing IV remifentanil PCA

Task	Time (minutes)	Staff responsible	Source
Drawing up/checking drug	10	1 x midwife, 1 x anaesthetic registrar	Guideline committee
Setting up infusion	30	1 x midwife, 1 x anaesthetic registrar	Guideline committee
Cannula placement	10	1 x midwife	Guideline committee
Patient monitoring	30	1 x midwife, 1 x anaesthetic registrar	Guideline committee

Table 14: Staff unit costs

Staff	Unit cost per working hour	Source
Midwife [a]	£51	PSSRU (2021)
Registrar anaesthetist	£52	PSSRU (2021)
Consultant anaesthetist	£123	PSSRU (2021)

(a) Based on Band 6 nurse

Costs associated with the infusion pump equipment are given in Table 15.

Table 15: Equipment related costs in providing IV remifentanil PCA

Item	Cost	Source
Infusion pump [a]	£3,000	Guideline committee
Accessories	£1,000	Guideline committee
Maintenance and servicing [b]	£347	Guideline committee
Total equipment cost	**£4,347**	

(a) This is based on 30 epidural pumps costing £90,000 including VAT
(b) This is based on point-of-sale maintenance costs of £10,400 over 5 years, including the warranty for 30 epidural pumps

It was assumed that the equipment has a 10-year lifespan and no resale value and that all expenditures related to equipment occur at the time of purchase. It was then possible to derive an equivalent annual cost of the equipment needed to provide IV remifentanil PCA using the following formula:

$$E = (K - [S \div \{1 + r\}^{n}]) \div A(n,r)$$

where:

E = annual equivalent cost

K = Purchase price of equipment = £4,347

S = resale value = £0

r = discount (interest rate) = 3.5%

n = equipment lifespan = 10-years

A(n,r) = annuity factor (n years at interest rate r) = 8.317 (see Table 16 below)

Table 16: Table of Annuity Factors

	Interest rate									
Time Years	**0.5%**	**1.0%**	**1.5%**	**2.0%**	**2.5%**	**3.0%**	**3.5%**	**4.0%**	**4.5%**	**5.0%**
1	0.995	0.990	0.985	0.980	0.976	0.971	0.966	0.962	0.957	0.952
2	1.985	1.970	1.956	1.942	1.927	1.913	1.900	1.886	1.873	1.859
3	2.970	2.941	2.912	2.884	2.856	2.829	2.802	2.775	2.749	2.723
4	3.950	3.902	3.854	3.808	3.762	3.717	3.673	3.630	3.588	3.546
5	4.926	4.853	4.783	4.713	4.646	4.580	4.515	4.452	4.390	4.329
6	5.896	5.795	5.697	5.601	5.508	5.417	5.329	5.242	5.158	5.076
7	6.862	6.728	6.598	6.472	6.349	6.230	6.115	6.002	5.893	5.786
8	7.823	7.652	7.486	7.325	7.170	7.020	6.874	6.733	6.596	6.463
9	8.779	8.566	8.361	8.162	7.971	7.786	7.608	7.435	7.269	7.108
10	9.730	9.471	9.222	8.983	8.752	8.530	**8.317**	8.111	7.913	7.722

E = £4,347 ÷ 8.317

Equivalent annual cost of equipment = £522.65

Having estimated an equivalent cost, a cost per labour using IV remifentanil PCA was estimated as follows using information supplied by a committee member:

Births in NHS Trust: 11,500

Births using IV remifentanil PCA: 115 (1%)

Number of infusion pumps across NHS Trust: 3

Number of labours using pump per annum: 38

Equipment cost per labour = £522.65 ÷ 38 = **£13.75**

The resource elements of the IV remifentanil PCA costing are summarised in Table 17.

Table 17: Summary of IV remifentanil PCA micro costing

Category	Cost
Consumables	£41.05
Staffing	£128.67
Equipment	£13.75
Total	**£183.47**

b. IM pethidine

The consumable resources in providing IM pethidine are listed in Table 18 along with their unit cost. It was assumed that 90% of women would require 1 dose of pethidine and that 10% of women would need a second dose (Fairlie 1999).

Table 18: Consumable unit costs for IM pethidine

Resource	Unit cost	Source
Consumables (single use equipment) for IM pethidine		
Pethidine 100mg/2ml solution for injection ampoules [a, b]	£0.47	https://bnf.nice.org.uk/medicinal-forms/pethidine-hydrochloride.html (accessed 31/05/2022)
2ml syringe [b]	£0.03	https://www.medisave.co.uk/bd-discardit-2ml-concentric-tip-syringe-2-piece-box-of-100.html (accessed 31/05/2022)
Blunt needle for drawing up [b]	£0.11	https://www.medisave.co.uk/bd-blunt-fill-safety-draw-up-needle-18-g-red-40-mm-1-45-degr-qty100.html?gclid=Cj0KCQiAjc2QBhDgARIsAMc3SqRwZqK-ke3ULYIprmDFAt_Dc9aR0oMuZrNws704GeECKKs7fGV8K2gaAqUGEALw_wcB (accessed 31/05/2022)
Label/marker [b]	£0.03	https://www.medical-world.co.uk/p/needles-syringes-cannulas/syringe-labels/miscellaneous-drugs/labels-syringe-medilabel-dexamethasone-mg/ml-15-x-1/2-x-400-dispenser/8424 (accessed 3/05/2022)
Pair of gloves [b]	£0.07	https://www.medisave.co.uk/nitrile-gloves-medical-grade-cat-iii-ppe-medium.html (accessed 31/05/2022)
Chloraprep wipe [b]	£0.30	https://bnf.nice.org.uk/medicinal-forms/chlorhexidine-gluconate-with-isopropyl-alcohol.html (accessed 31/05/2022)
Injection needle 22G [b]	£0.04	https://www.medisave.co.uk/terumo-agani-needle-22g-black-x-1-25-x-100.html (accessed 31/05/2022)
Sterile dressing [b]	£1.77	https://www.drugtariff.nhsbsa.nhs.uk/#/00726198-DD/DD00726009/Part%20IXA-Dressings (accessed 31/05/2022)

(a) For obstetric analgesia BNF states: 50–100 mg, then 50–100 mg after 1–3 hours if required; maximum 400 mg per day.
(b) Per dose

The staffing resources required to provide IM pethidine are outlined in Table 19 with staffing costs as per Table 14.

Table 19: Staff tasks in providing IM pethidine

Task	Time (minutes)	Staff responsible	Source
Drawing up/checking drug	10	2 x midwife	Guideline committee

Task	Time (minutes)	Staff responsible	Source
Giving IM drug	10	2 x midwife	Guideline committee

Table 20 summarises the components of the IM pethidine micro costing.

Table 20: Summary of IM pethidine micro costing

Category	Cost
Consumables	£3.09
Staffing	£34.00
Total	**£37.09**

c. Maternal respiratory depression

The costs of treating maternal respiratory depression were based on the consumable costs detailed in Table 21.

Table 21: Consumable unit costs for treating maternal respiratory depression

Resource	Unit cost	Source
Oxygen mask and tubing	£1.55	https://www.medisave.co.uk/adult-oxygen-mask-with-tubing.html?gclid=CjwKCAiAsNKQBhAPEiwAB-I5zYOMai_G4vnM7oBlS1DdQ2rdrDlMJoaElJjKyq3nw51vb2Oitc6czxoCLyMQAvD_BwE (accessed 31/05/2022)
Oxygen [a]	£17.77	https://www.boconline.co.uk/shop/en/uk/gas-a-z/oxygen/oxygen-cylinder-medical-grade-compressed-gas (accessed 31/05/2022)

(a) Based on a 300-litre oxygen cylinder of medical grade compressed Gas

d. Antiemetic

The micro costing of antiemetic treatment was based on the consumables listed in Table 22, the assumptions about staffing itemised in Table 23 and the staff unit costs outlined in Table 14.

Table 22: Consumable unit costs for antiemetic

Resource	Unit cost	Source
Prochlorperazine mesilate 12.5 mg per 1 ml	£0.52	https://bnf.nice.org.uk/drugs/prochlorperazine/medicinal-forms/#solution-for-injection (accessed 31/05/2022)
1ml syringe	£0.11	https://www.medisave.co.uk/b-d-1ml-plastipak-syringes-per-box-of-100-p-4267.html (accessed 31/05/2022)
Blunt needle for drawing up	£0.11	https://www.medisave.co.uk/bd-blunt-fill-safety-draw-up-needle-18-g-red-40-mm-1-45-degr-qty100.html?gclid=Cj0KCQiAjc2QBhDgARIsAMc3SqRwZqK-ke3ULYIprmDFAt_Dc9aR0oMuZrNws704GeECKKs7fGV8K2gaAqUGEALw_wcB

Resource	Unit cost	Source
		(accessed 31/05/2022)
Label/marker	£0.03	https://www.medical-world.co.uk/p/needles-syringes-cannulas/syringe-labels/miscellaneous-drugs/labels-syringe-medilabel-dexamethasone-mg/ml-15-x-1/2-x-400-dispenser/8424 (accessed 31/05/2022)
Pair of gloves	£0.07	https://www.medisave.co.uk/nitrile-gloves-medical-grade-cat-iii-ppe-medium.html (accessed 31/05/2022)
Chloraprep wipe	£0.30	https://bnf.nice.org.uk/medicinal-forms/chlorhexidine-gluconate-with-isopropyl-alcohol.html (accessed 31/05/2022)
Injection needle 22G	£0.04	https://www.medisave.co.uk/terumo-agani-needle-22g-black-x-1-25-x-100.html (accessed 31/05/2022)
Sterile dressing	£1.77	https://www.drugtariff.nhsbsa.nhs.uk/#/00726198-DD/DD00726009/Part%20IXA-Dressings (accessed 31/05/2022)

Table 23: Staff tasks in providing antiemetic

Task	Time (minutes)	Staff responsible	Source
Drawing up/checking drug	10	2 x midwife	Guideline committee
Giving IM drug	10	2 x midwife	Guideline committee

The summary of the micro costing of antiemetic treatment is shown in Table 24.

Table 24: Summary of antiemetic micro costing

Category	Cost
Consumables	£2.94
Staffing	£34.00
Total	**£36.94**

Health state utilities and QALYs

Evidence indicated that there were differences in outcomes when using IV remifentanil PCA compared to IM pethidine which would be expected to effect health-related quality of life (HRQoL). Therefore, the model attempted to estimate the incremental QALY gains (or losses) of IV remifentanil PCA relative to IM pethidine by assigning health state utilities (HSU) and durations to the following outcomes.

- Spontaneous vaginal birth
- Instrumental vaginal birth
- Caesarean birth
- Caesarean birth with a neonatal admission
- Neonatal admission
- Need for rescue analgesia
- Maternal respiratory depression

The model used a QALY dyad approach to include both mothers and baby in the calculation of QALYs. The base case HSU and their durations are summarised in Table 25 below. The difference between the health state utility in perfect health and the health state utility associated with a particular outcome was used to estimate the health state utility loss from a particular outcome. The use of a "perfect" health state utility reflected the baseline in Tan (2010) and whilst such an assumption will likely overstate the loss in QALYs from other health states, it does not effect the difference in incremental QALYs between treatment alternatives presented in this report. This is because the baseline health state utility only impacts on the incremental QALYs if a different duration is assumed for different health states relating to mode of birth or if a duration of reduced health state utility from neonatal admission is assumed to be shorter than the model time horizon. No discounting of QALYs was required as it was assumed that the duration for all health states was less than 1-year.

Table 25: Health state utility values and duration

Outcome	Health state utility	Duration	Source
Perfect health maternal [a]	1.00	N/A	
Perfect health neonatal [a]	1.00	N/A	
Spontaneous vaginal birth [a]	0.86	12 weeks	https://bmcpregnancychildbirth.biomedcentral.com/articles/10.1186/1471-2393-10-3/tables/2
Instrumental vaginal birth [a]	0.86	12 weeks	https://bmcpregnancychildbirth.biomedcentral.com/articles/10.1186/1471-2393-10-3/tables/2
Caesarean birth [a]	0.78	12 weeks	https://bmcpregnancychildbirth.biomedcentral.com/articles/10.1186/1471-2393-10-3/tables/2
Caesarean birth with neonatal admission (maternal QALY) [a]	0.76	12 weeks	https://bmcpregnancychildbirth.biomedcentral.com/articles/10.1186/1471-2393-10-3/tables/2
Neonatal admission [a]	0.58	12 weeks	https://bmcpregnancychildbirth.biomedcentral.com/articles/10.1186/1471-2393-10-3/tables/2
Need for rescue analgesia [b, c]	0.59	1 hour	https://academic.oup.com/painmedicine/article/15/5/865/1812216
Maternal respiratory depression [a, d]	1.00	N/A	

(a) These variables were treated deterministically in probabilistic sensitivity analysis as no measure of dispersion was included alongside the reporting of point estimate
(b) This was based on the mean EQ-5D health state utility for pain overall, across patients experiencing mild, moderate and severe pain
(c) In probabilistic sensitivity analysis this was sampled using a normal distribution and a standard deviation = 0.0179
(d) In the base case analysis, it was assumed there was no loss in health state utility due to maternal respiratory depression

Sensitivity analysis

A wide range of sensitivity analyses were undertaken to explore and quantify the extent to which conclusions about the cost-effectiveness of the IV remifentanil PCA were robust with respect to uncertainty in the model inputs.

i. Probabilistic sensitivity analysis (PSA)

Probabilistic sensitivity analysis was undertaken to assess parameter uncertainty simultaneously across a number of model inputs. This involved running 10000 Monte Carlo simulations of the model, with many model inputs sampled from a specified probability distribution for each iteration. Probabilistic sensitivity analysis was undertaken for the base case analysis but also for the following departures from the base case:

a. *Estimating the health state utility loss from pain scores rather than the need for rescue analgesia using the mean of maximum pain score*

   The systematic review presented data on scores for pain in labour (see Table 5). This was not included in the base case analysis because it was thought that this was likely to be strongly correlated with the need for rescue analgesia. In other words, it was thought that women who needed rescue analgesia were likely to report higher pain scores on average than women who did not need rescue analgesia. Utilising both outcomes was therefore considered to carry a risk of double counting.

   In this analysis the heath state utility was estimated from the outcome of pain in labour using the mean of the maximum pain score measured on a visual analogue scale as indicated by Table 9 for the baseline and Table 10 for the treatment effect. When using change in pain score as a sensitivity analysis, rather than assigning a health state utility to rescue analgesia, it was assumed that pain duration was 8 hours based on the mean duration of labour for nulliparous women (Albers 1999). It should be noted that as a mechanism for estimating health state utility this is a departure from the NICE reference case as, although the pain scores are measured on a 0-1 scale, they are not a preference-based measure.

   Whilst a health state utility was not assigned to rescue analgesia for this analysis the outcome was still used to estimate differences between IM pethidine and IV remifentanil PCA in costs.

b. *Estimating the health state utility loss from pain scores rather than the need for rescue analgesia using the median scores*

   This is similar to the analysis ‘a’ above but used the reported median pain scores rather than the mean of the maximum pain score (Wilson 2018). The changes to model inputs for this analysis are indicated in Table 26.

Table 26: Model inputs for health state utility using scores for pain in labour based on median values

	Health state utility	Standard error	Distribution
Baseline	0.3542	0.030	Normal
Treatment effect size [a]	-0.1391	0.038	Normal

(a) Mean difference health state disutility

c. *Using health state utilities for forceps and vacuum extraction birth to estimate a health state utility for instrumental vaginal birth that is different from spontaneous vaginal birth*

This analysis assumed that the health state utility of all vaginal birth was that reported in Table 25 but that this reflected a weighted average of different health state utilities for spontaneous and instrumental vaginal birth calculated using data in Table 27 as outlined below.

Table 27: Data used to estimate the health state utilities of instrumental and spontaneous vaginal birth based on reported health state utility values for forceps and vacuum extraction births

Item	Value	Source
Health state utility forceps birth	0.73	https://elearning.rcog.org.uk/sites/default/files/Caesarean%20section/Turner_BJOG_2008.pdf
Heath state utility vacuum extraction birth	0.79	https://elearning.rcog.org.uk/sites/default/files/Caesarean%20section/Turner_BJOG_2008.pdf
Proportion of instrumental births forceps	0.598	https://digital.nhs.uk/data-and-information/publications/statistical/nhs-maternity-statistics/2020-21
Proportion of instrumental births vacuum extraction	0.402	https://digital.nhs.uk/data-and-information/publications/statistical/nhs-maternity-statistics/2020-21
Proportion of vaginal births spontaneous	0.806	https://digital.nhs.uk/data-and-information/publications/statistical/nhs-maternity-statistics/2020-21/deliveries---2021-hes
Proportion of vaginal birth instrumental	0.194	https://digital.nhs.uk/data-and-information/publications/statistical/nhs-maternity-statistics/2020-21/deliveries---2021-hes

Weighted average health state utility for instrumental vaginal birth:

(0.73 x 0.598) + (0.79 x 0.402) = 0.75

Weighted average health state utility for spontaneous vaginal birth:

(0.86 – (0.194 x 0.75)) ÷ 0.806 = 0.89

d. Using health state utilities for 3rd and 4th degree perineal tears to estimate a health state utility for instrumental vaginal birth that is different from spontaneous vaginal birth

Again, this analysis assumed that the health state utility of all vaginal birth was that reported in Table 25. In this case health state utility data for 3rd and 4th degree perineal tears was used to estimate a separate health state utility for spontaneous and instrumental vaginal birth. Data in Table 27 and Table 28 was used to calculate these utilities, with the calculation shown below.

Table 28: Data used to estimate the health state utilities of instrumental and spontaneous vaginal birth based on reported health state utility values for 3rd and 4th degree perineal tears

Item	Value	Source
Proportion OASI spontaneous vaginal birth	0.06	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6429882/#!po=75.0000

Item	Value	Source
Proportion OASI instrumental (vacuum extraction) birth	0.13	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6429882/#!po=75.0000
Health state utility 3rd/4th degree perineal tears	0.72	https://elearning.rcog.org.uk/sites/default/files/Caesarean%20section/Turner_BJOG_2008.pdf

OASI = Obstetric anal sphincter injury

Weights for average births with no 3rd/4th degree tears:

(0.806 x (1-0.06) + (0.194 x (1-0.13)) = 0.926

Weights for average births with 3rd/4th degree tears:

1 – 0.926 = 0.074

Weighted average health state utility of births with no 3rd/4th degree tears:

(0.86 – (0.074 x 0.72)) ÷ 0.926 = 0.87

Weighted average health state utility for spontaneous vaginal births:

(0.87 x 0.94) + (0.72 x 0.06) = 0.862

Weighted average health state utility for instrumental vaginal births:

(0.87 x 0.87) + (0.72 x 0.13) = 0.851

ii.Tornado diagram

A Tornado diagram is used to depict multiple one-way sensitivity analysis where inputs for model variables are varied one at a time between an upper and lower value, holding all other model inputs constant in order to demonstrate the sensitivity of the results to changes in selected variables. These analyses are then incorporated into a single Tornado diagram which gives a visual indication as to the relative importance of uncertainty to the cost-effectiveness results in these selected variables.

The variable covered in the Tornado analysis, their upper and lower values and rationale for the range are given in Table 29.

Table 29: Variables and parameter values used in Tornado diagram

Variable	Lower value	Higher value
Remifentanil costs [a]	£158	£309
Pethidine costs [b]	£17	£44
Antiemetic costs [c]	£17	£43
Rescue analgesia costs [d]	£184	£1,130
Maternal respiratory	£2	£100

Variable	Lower value	Higher value
depression costs [e]		
Rescue analgesia relative risk [f]	0.40	0.74
Neonatal admission relative risks [f]	0.35	2.23
Antiemetic use relative risk [f]	0.23	0.41
Maternal respiratory depression log odds ratio [f]	2.14	6.18
Instrumental vaginal birth rate (remifentanil) [f]	0.106	0.194
Instrumental vaginal birth health state utility [g]	0.50	0.86
Rescue analgesia health state utility [h]	0.48	0.74
Maternal respiratory depression health state utility [i]	0.50	1.00
Pump use per annum (number of labours) [j]	1	140

(a) Lower value based on a 20% reduction in the time taken to undertake the tasks outlined in Table 13; Upper value based on substitution of anaesthetic registrar for a consultant for the tasks outlined in Table 13 and a 20% increase in the time taken to undertake those tasks

(b) Lower value based on requiring only 1 midwife to undertake the tasks outlined in Table 19 and assuming a 20% reduction in the time taken to undertake those tasks; Upper value is based on a 20% increase in the time taken to undertake the tasks outlined in Table 19

(c) Lower value based on requiring only 1 midwife to undertake the tasks outlined in Table 23 and assuming a 20% reduction in the time taken to undertake those tasks; Upper value is based on a 20% increase in the time taken to undertake the tasks outlined in Table 23

(d) Lower value is based on the difference in NHS Reference Costs between "Normal delivery, with epidural or induction, with CC score 0" and "Normal delivery with CC score 0" for the category Community Health Services; Upper value is based on the difference in NHS Reference Costs between "Normal delivery, with epidural or induction, with CC score 0" and "Normal delivery with CC score 0" for the category Elective Inpatients

(e) Lower value assumes a trivial cost for oxygen; Upper value is a convenient round number – it is much larger than the default value to demonstrate the degree of model sensitivity to a change which would make remifentanil relatively less cost-effective

(f) The range of values is based on the lower and upper 95% confidence intervals

(g) Lower value is based on the lowest value used for the health state utility of instrumental vaginal birth; the upper value is the default value as it was deemed clinically implausible to have a higher health state utility for an instrumental vaginal birth than a spontaneous vaginal birth

(h) Lower value is based on a health state utility for severe pain (https://academic.oup.com/painmedicine/article/15/5/865/1812216); Upper value is based on health state utility for mild pain (https://academic.oup.com/painmedicine/article/15/5/865/1812216)

(i) Lower value is based on a convenient round number which is much lower than the default value to demonstrate the degree of model sensitivity to a change which would make remifentanil less cost-effective, Upper value is the same as the default value as this is already at the maximum value for this parameter

(j) Lower value is based on "worst case" scenario for remifentanil cost; Upper value based on personal communication from Belfast Health and Social Care Trust indicating that 5 remifentanil pumps were used for 700 births in 2014

iii. One-way sensitivity analysis

One-way sensitivity analysis involves varying one model parameter whilst holding all other model inputs constant to assess how sensitive the model is to changes in this parameter. It can also be used to identify a threshold value for that parameter (if there is one) at which the cost-effectiveness decision would change. Sensitivity analysis is presented for the following variables, all of which were treated deterministically in the probabilistic analysis.

- Remifentanil costs
- Pethidine costs

- Antiemetic costs
- Rescue analgesia costs
- Maternal respiratory depression costs
- Instrumental vaginal births health state utility
- Rescue analgesia health state utility
- Maternal respiratory depression health state utility
- Pump use per annum (number of labours)

One-way sensitivity analysis was undertaken using the same upper and lower values used in the sensitivity analysis unless a wider range was necessary to illustrate the threshold value for cost-effectiveness.

iv. Two-way sensitivity analysis

Similar to one-way sensitivity analysis, this involves changing the input parameters for 2 variables whilst holding all other model inputs constant. It can highlight the relationship between the 2 variables in determining cost-effectiveness and the extent of any trade-offs between them.

Results

Base case analysis

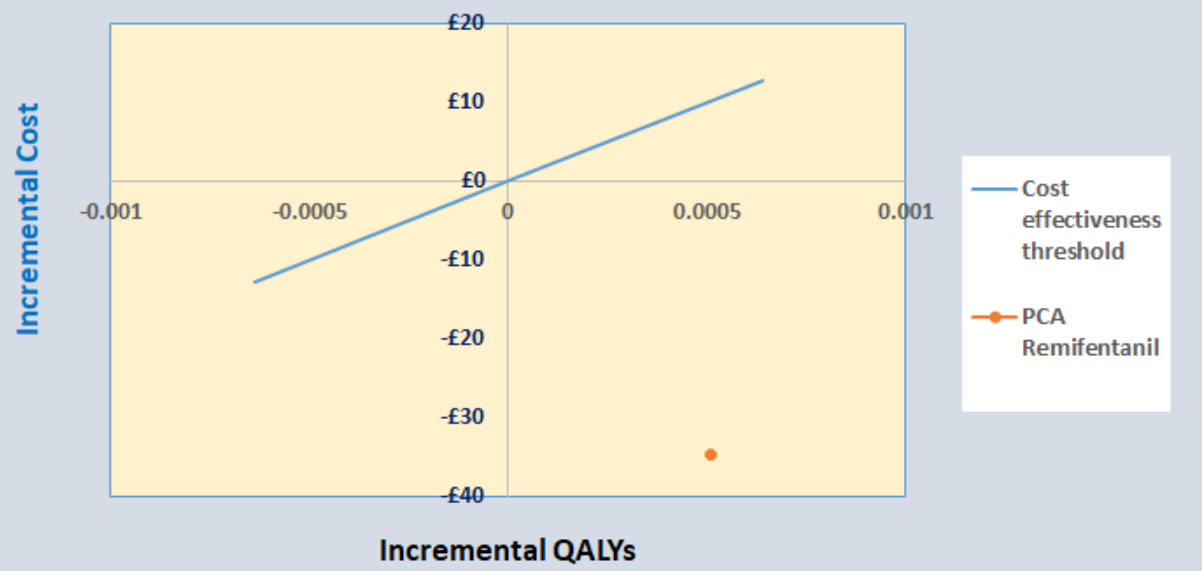
The deterministic result for the model in the base case analysis is shown in Table 30 and Figure 8. It indicates that IV remifentanil PCA dominates IM pethidine, being cheaper and generating more QALYs. The cost-effectiveness of remifentanil is also indicated by it having a positive incremental net monetary benefit of £31.

Table 30: Base case deterministic analysis

Outcome	IM pethidine	IV remifentanil PCA
Intervention cost	£37	£183
Respiratory depression cost	£0	£9
Rescue analgesia cost	£237	£114
Antiemetic cost	£25	£8
Birth cost	£2,813	£2,777
Neonatal admission cost	£105	£93
Total Cost	**£3,218**	**£3,198**
Incremental cost		-£35
QALYs	**0.41987**	**0.42038**
Incremental QALYs		0.00051
ICER	**Dominated**	**Dominant**
Net monetary benefit	£5,179	£5,224
Incremental net monetary benefit		**£45**

ICER = Incremental cost-effectiveness ratio; QALYs = Quality adjusted life years

Figure 8: Deterministic analysis of base case analysis represented on a cost-effectiveness plane



The results of the probabilistic sensitivity analysis are shown in Table 31 and in the scatterplot diagram of 10000 Monte Carlo simulations in Figure 9. The PSA estimates a 57% probability that IV remifentanil PCA is cost-effective relative to IM pethidine with remifentanil having a mean incremental net monetary benefit of £21.

Table 31: Base case probabilistic sensitivity analysis

Outcome	IM pethidine (95% CrInt)	IV remifentanil PCA (95% CrInt)
Mean cost	£3,217 (£3,022 to £3,422)	£3,196 (£2,995 to £3,437)
Mean QALY	0.4198 (0.4165 to 0.4224)	0.4198 (0.4127 to 0.4233)
Incremental cost		-£22 (-£279 to £247)
Incremental QALY		0.00001 (-0.00591 to 0.00357)
ICER	Dominated	Dominant
Mean NMB		£21 (-£331 to £332)
Probability cost-effective	43.2%	56.8%

ICER = incremental cost-effectiveness ratio; NMB = net monetary benefit; QALY = quality adjusted life-years

Figure 9: Scatterplot of base case PSA on cost-effectiveness plane

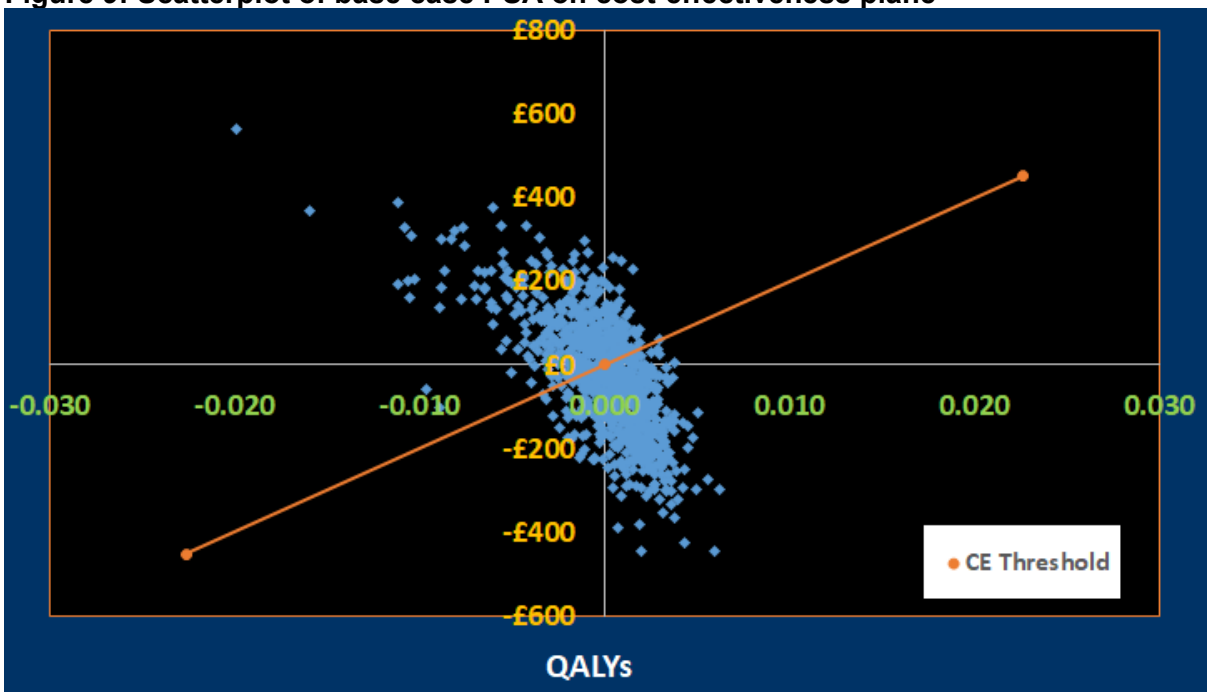
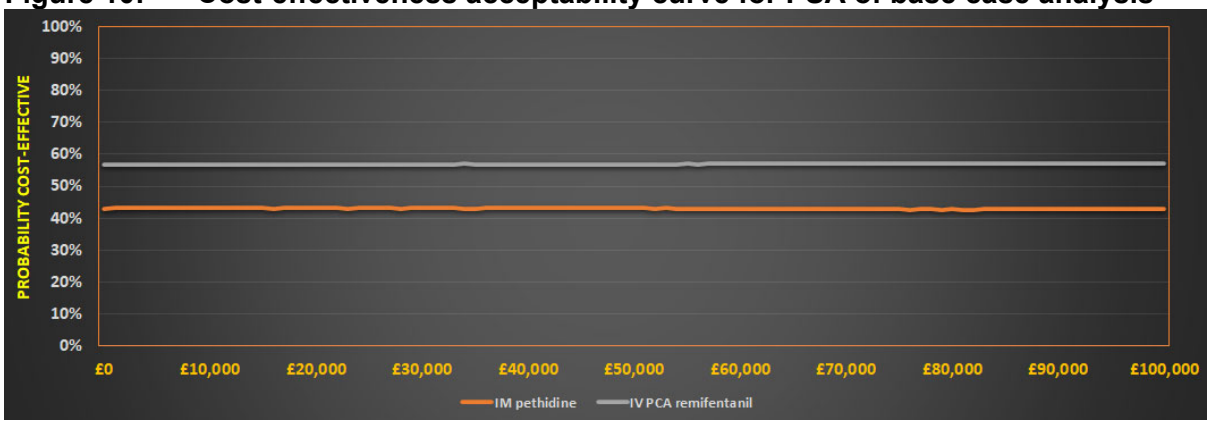


Figure 10 show the cost-effectiveness acceptability curve (CEAC) for the PSA of the base case analysis and suggests that the probability that IV remifentanil PCA is not very sensitive to changes in the cost-effectiveness threshold, with the probability that IV remifentanil PCA is cost-effective only increasing very gradually with an increasing cost-effectiveness threshold.

Figure 10: Cost-effectiveness acceptability curve for PSA of base case analysis



Analysis using pain in labour scores (mean of maximum) to estimate health state utility losses instead of assigning a health state utility to rescue analgesia

The deterministic results of this analysis are tabulated in Table 32 and shown graphically in Figure 11. They show an almost identical result to the base case analysis with IV remifentanil PCA again dominating IM pethidine.

Table 32: Deterministic analysis using pain in labour scores (mean of maximum) to estimate health state utility losses

Outcome	IM pethidine	IV remifentanil PCA

Outcome	IM pethidine	IV remifentanil PCA
Intervention cost	£37	£183
Respiratory depression cost	£0	£9
Rescue analgesia cost	£237	£114
Antiemetic cost	£25	£8
Birth cost	£2,813	£2,777
Neonatal admission cost	£105	£93
Total Cost	**£3,218**	**£3,183**
Incremental cost		-£35
QALYs	**0.41915**	**0.41969**
Incremental QALYs		0.00054
ICER	**Dominated**	**Dominant**
Net monetary benefit	£5,165	£5,211
Incremental net monetary benefit		**£46**

ICER = Incremental cost-effectiveness ratio; QALYs = Quality adjusted life years

Figure 11: Deterministic analysis using pain in labour scores (mean of maximum) to estimate health state utility losses represented on a cost-effectiveness plane

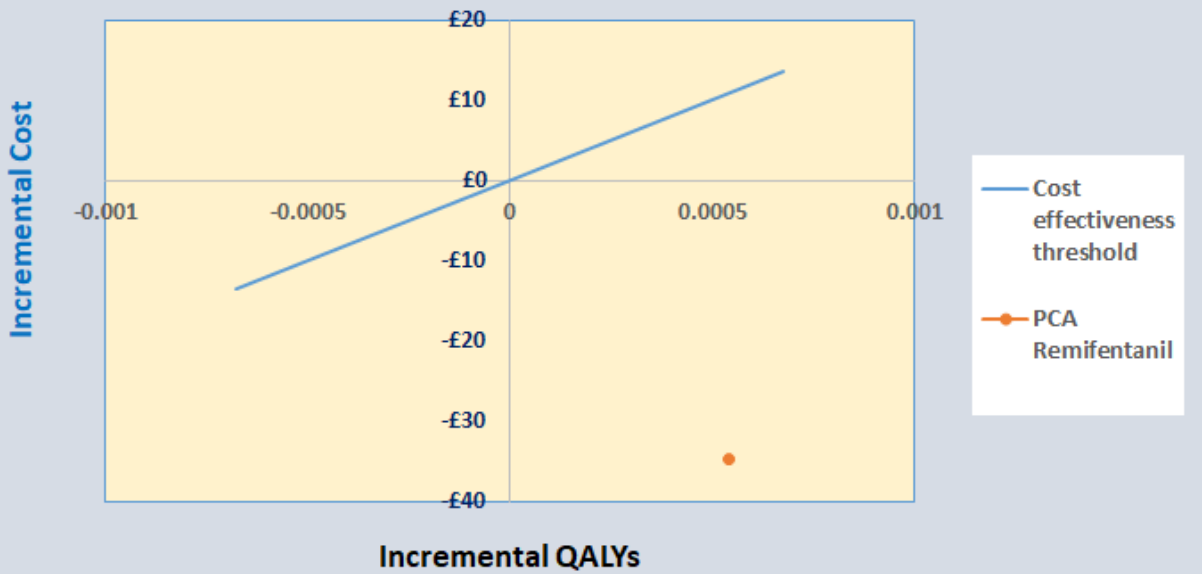


Table 33 and Figure 12 show the results of the PSA when pain in labour scores (mean of maximum) evidence taken from the clinical review are used to estimate the health state utility loss instead of assigning a health state utility loss to rescue analgesia. They indicate that the probability of IV remifentanil being cost-effective relative to IM pethidine is 58%.

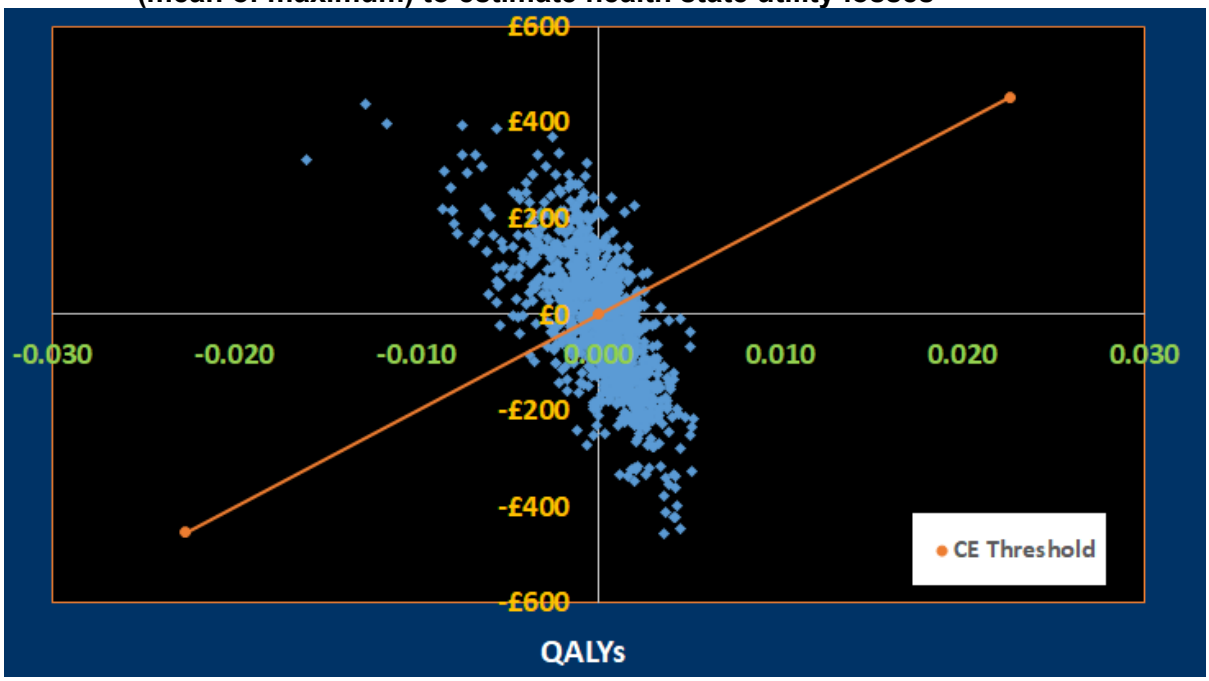
Table 33: Probabilistic sensitivity analysis using pain in labour scores (mean of maximum) to estimate health state utility losses

Outcome	IM pethidine (95% CrInt)	IV remifentanil PCA (95% CrInt)
Mean cost	£3,217 (£3,022 to £3,429)	£3,195 (£2,990 to £3,440)
Mean QALY	0.4191 (0.4158 to 0.4216)	0.4192 (0.4122 to 0.4226)
Incremental cost		-£23 (-£281 to £248)
Incremental QALY		0.00006 (-0.00576 to 0.00369)
ICER	Dominated	Dominant

Outcome	IM pethidine (95% CrInt)	IV remifentanil PCA (95% CrInt)
Mean NMB		£23 (-£327 to £334)
Probability cost-effective	42.2%	57.8%

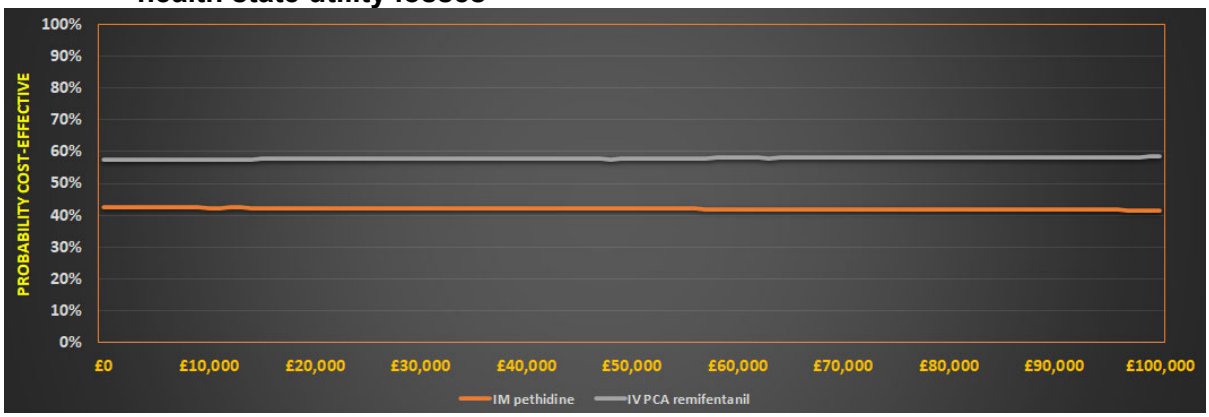
ICER = incremental cost-effectiveness ratio; NMB = net monetary benefit; QALY = quality adjusted life-years

Figure 12: Scatterplot of PSA on cost-effectiveness plane using labour pain scores (mean of maximum) to estimate health state utility losses



The CEAC for this PSA is shown in Figure 13, showing that IV remifentanil is most likely to be cost-effective relative to IM pethidine across a cost-effectiveness threshold ranging from £0 to £100,000 per QALY, which rises slightly with an increasing threshold.

Figure 13: CEAC for PSA using labour pain scores (mean of maximum) to estimate health state utility losses



Analysis using pain in labour scores (median) to estimate health state utility losses instead of assigning a health state utility to rescue analgesia

Table 34 shows the deterministic results for an analysis using the median of pain in labour scores (Wilson 2018) to estimate health state utility losses. This resulted is illustrated

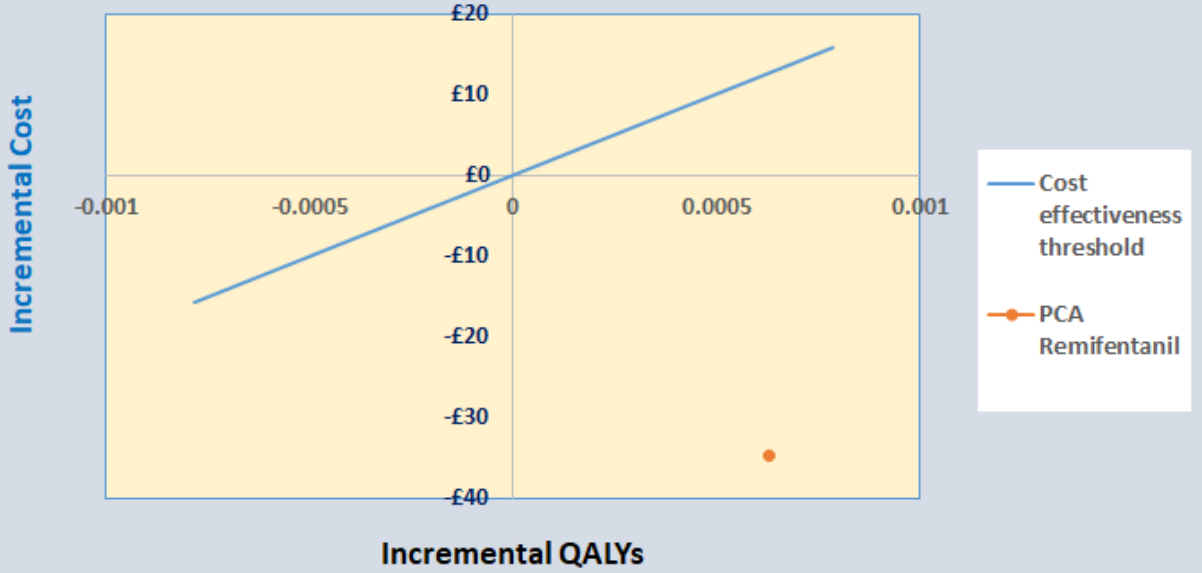
graphically in Figure 14. It continues to show that IV remifentanil PCA dominates IM pethidine, albeit only with a small incremental net monetary benefit.

Table 34: Deterministic analysis using pain in labour scores (median) to estimate health state utility losses

Outcome	IM pethidine	IV remifentanil PCA
Intervention cost	£37	£183
Respiratory depression cost	£0	£9
Rescue analgesia cost	£237	£114
Antiemetic cost	£25	£8
Birth cost	£2,813	£2,777
Neonatal admission cost	£105	£93
Total Cost	**£3,218**	**£3,198**
Incremental cost		-£35
QALYs	**0.41929**	**0.41992**
Incremental QALYs		0.00063
ICER	**Dominated**	**Dominant**
Net monetary benefit	£5,168	£5,215
Incremental net monetary benefit		**£47**

ICER = Incremental cost-effectiveness ratio; QALYs = Quality adjusted life years

Figure 14: Deterministic analysis using pain in labour scores (median) to estimate health state utility losses represented on a cost-effectiveness plane



The results of the PSA using pain in labour scores (median) to estimate health state utility losses are given in Table 35 and Figure 15. The probability that IV remifentanil is cost effective is estimated at 59%, with a mean incremental NMB of £30.

Table 35: Probabilistic sensitivity analysis using pain in labour scores (median) to estimate health state utility losses

Outcome	IM pethidine (95% CrInt)	IV remifentanil PCA (95% CrInt)
Mean cost	£3,218 (£3,021 to £3,426)	£3,192 (£2,988 to £3,425)
Mean QALY	0.4192 (0.4159 to 0.4218)	0.4194 (0.4126 to 0.4228)
Incremental cost		-£27 (-£284 to £240)

Outcome	IM pethidine (95% CrInt)	IV remifentanil PCA (95% CrInt)
Incremental QALY		0.00021 (-0.00541 to 0.00383)
ICER	Dominated	Dominant
Mean NMB		£30 (-£313 to £342)
Probability cost-effective	41.2%	58.8%

ICER = incremental cost-effectiveness ratio; NMB = net monetary benefit; QALY = quality adjusted life-years

Figure 15: Scatterplot of PSA on cost-effectiveness plane using labour pain scores (median) to estimate health state utility losses

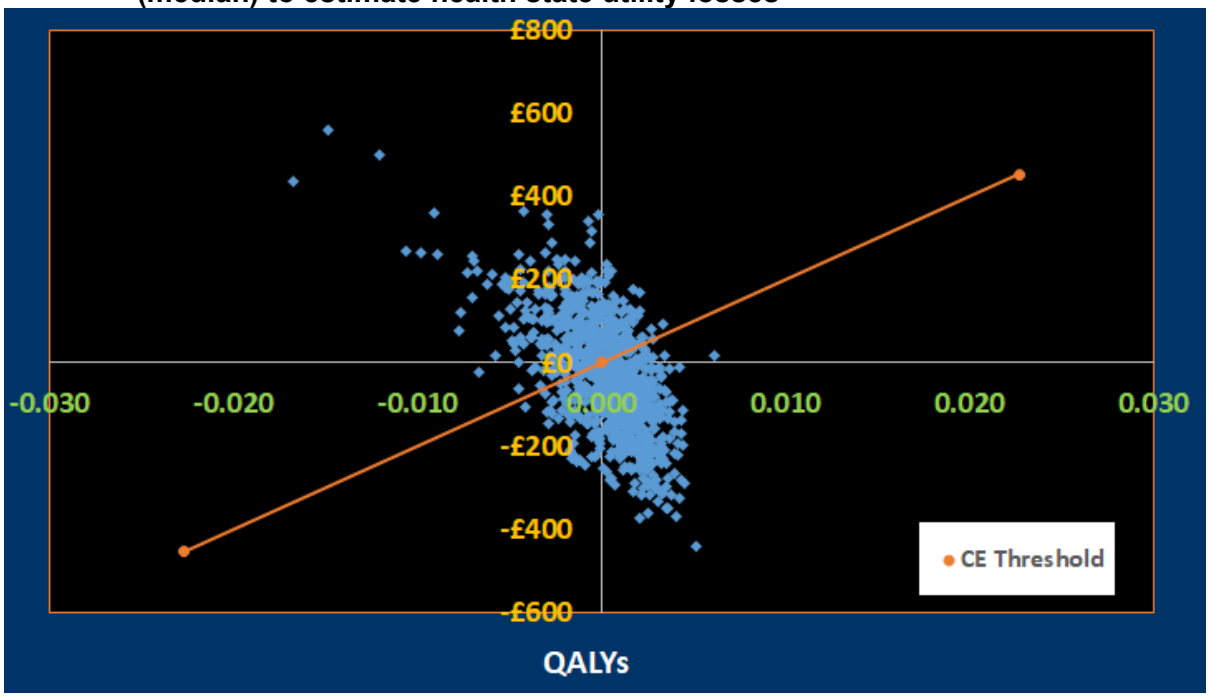
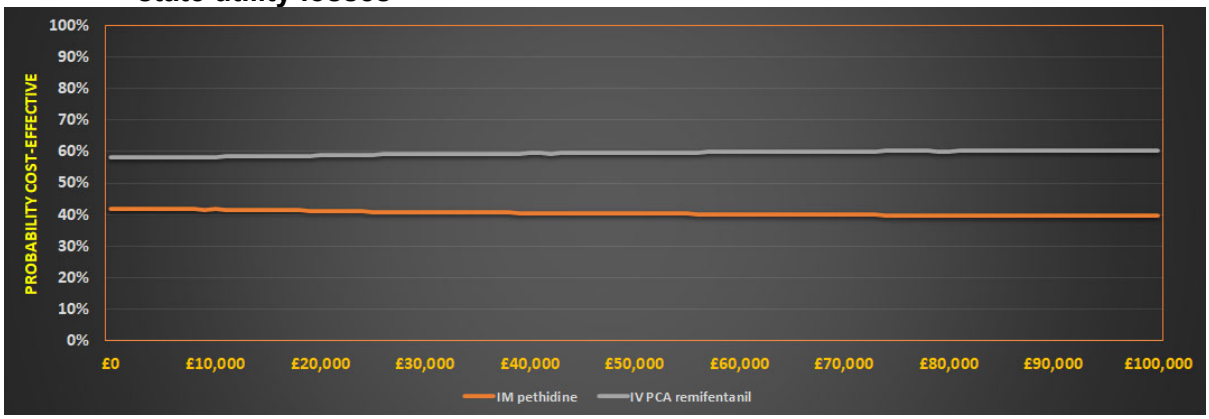


Figure 16 gives the CEAC for the PSA using labour pain scored (median) to estimate health state utility losses with IV remifentanil having a probability of being cost-effective ranging from 58.0% to 60.4% across the cost-effectiveness thresholds graphed.

Figure 16: CEAC for PSA using labour pain scores (median) to estimate health state utility losses



Using health state utilities for forceps and vacuum extraction birth to estimate a health state utility for instrumental vaginal birth that is different from spontaneous vaginal birth

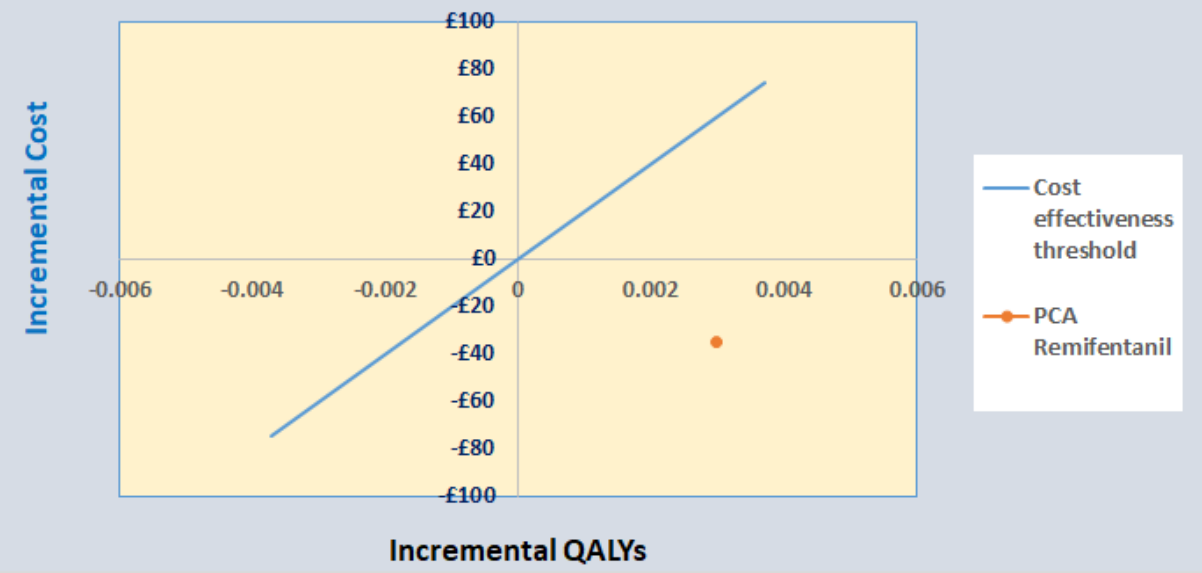
The deterministic results of this analysis where the health state utility of instrumental vaginal birth and spontaneous vaginal birth is estimated from health state utilities for forceps and vacuum extraction birth are provided in Table 36 and illustrated on the cost-effectiveness plane in Figure 17. They show that IV remifentanil is dominant with an incremental NMB of £94.

Table 36: Deterministic analysis using health state utilities for forceps and vacuum births to estimate health state utilities for instrumental and spontaneous vaginal birth

Outcome	IM pethidine	IV remifentanil PCA
Intervention cost	£37	£183
Respiratory depression cost	£0	£9
Rescue analgesia cost	£237	£114
Antiemetic cost	£25	£8
Birth cost	£2,813	£2,777
Neonatal admission cost	£105	£93
Total Cost	**£3,218**	**£3,183**
Incremental cost		-£35
QALYs	**0.41752**	**0.42050**
Incremental QALYs		0.00297
ICER	**Dominated**	**Dominant**
Net monetary benefit	£5,132	£5,227
Incremental net monetary benefit		**£94**

ICER = Incremental cost-effectiveness ratio; QALYs = Quality adjusted life years

Figure 17: Deterministic analysis using health state utilities for forceps and vacuum births to estimate health state utilities for instrumental and spontaneous vaginal birth represented on a cost-effectiveness plane



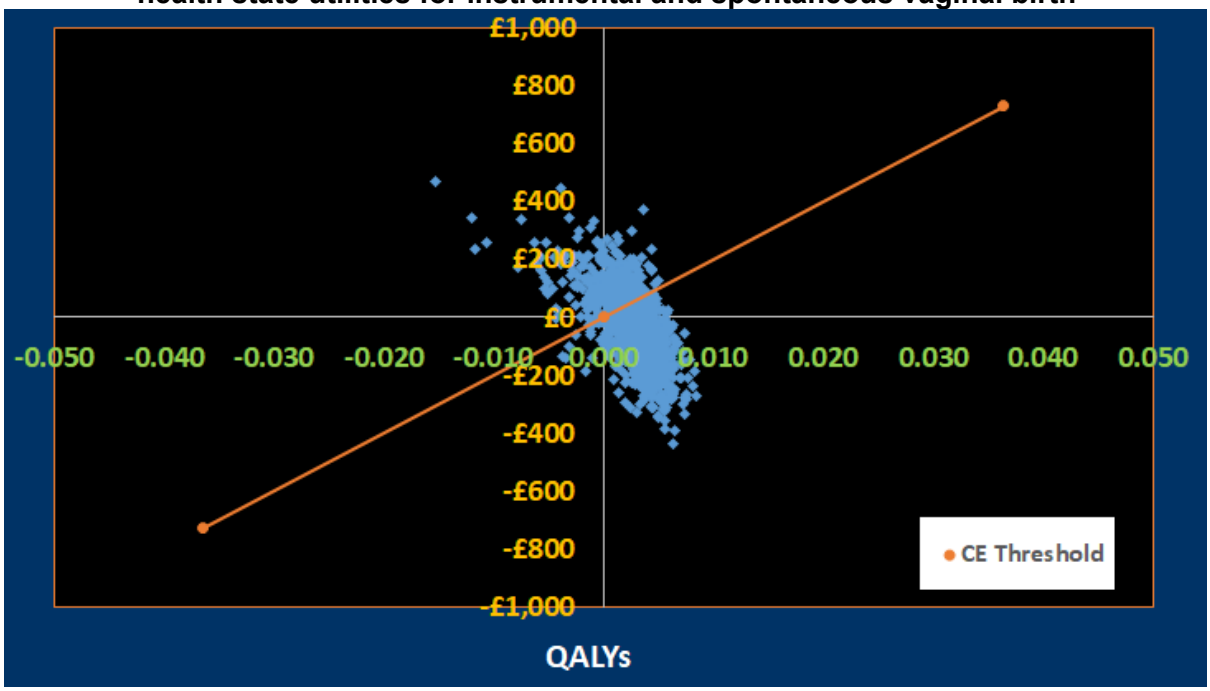
The results of the PSA using health state utilities for forceps and vacuum births to estimate health state utilities for instrumental and spontaneous vaginal birth are given in Table 37 with the induvial Monte Carlo simulations plotted on the scatterplot cost-effectiveness plane in Figure 18. They show that IV remifentanil had a 69% of being cost-effective and a mean incremental NMB of £74. Remifentanil has a higher probability of being cost-effective in this analysis because of a greater health state utility loss attributed to instrumental vaginal birth than in other analyses, with the evidence indicating that remifentanil leads to lower rates of instrumental vaginal birth than pethidine.

Table 37: Probabilistic sensitivity analysis using health state utilities for forceps and vacuum births to estimate health state utilities for instrumental and spontaneous vaginal birth

Outcome	IM pethidine (95% CrInt)	IV remifentanil PCA (95% CrInt)
Mean cost	£3,218 (£3,024 to £3,424)	£3,194 (£2,991 to £3,430)
Mean QALY	0.4175 (0.4138 to 0.4204)	0.4200 (0.4127 to 0.4237)
Incremental cost		-£24 (-£284 to £244)
Incremental QALY		0.00253 (-0.00370 to 0.00665)
ICER	Dominated	Dominant
Mean NMB		£74 (-£277 to £395)
Probability cost-effective	31.2%	68.8%

ICER = incremental cost-effectiveness ratio; NMB = net monetary benefit; QALY = quality adjusted life-years

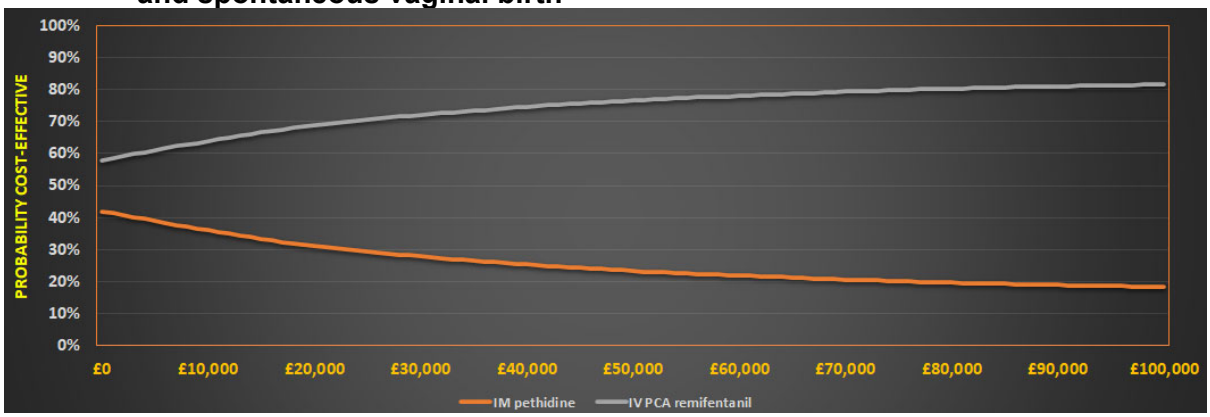
Figure 18: Scatterplot of probabilistic sensitivity analysis on cost-effectiveness plane using health state utilities for forceps and vacuum births to estimate health state utilities for instrumental and spontaneous vaginal birth



The CEAC in Figure 19 shows that remifentanil has a 58% chance of being cheaper than pethidine (probability cost-effective at a threshold of £0 per QALY) and that this probability rises to a maximum of 82% at a cost-effectiveness threshold of £100,000 per QALY. In this case the rise in the probability of remifentanil being cost-effective, with an increasing threshold, is more marked than in the previous analyses. This is because at higher cost-

effectiveness thresholds more simulations involving a higher remifentanil cost are likely to become cost-effective because of the higher mean QALYs.

Figure 19: CEAC for probabilistic sensitivity analysis using health state utilities for forceps and vacuum births to estimate health state utilities for instrumental and spontaneous vaginal birth



Using health state utilities for 3rd and 4th degree perineal tears to estimate a health state utility for instrumental vaginal birth that is different from spontaneous vaginal birth

Table 38 and Figure 20 show the deterministic results for the analysis where health state utility data for 3rd and 4th degree perineal tears is used to estimate the health state utility for instrumental and spontaneous vaginal birth. As with other analyses, remifentanil dominates pethidine and, in this case, the incremental NMB is £49.

Table 38: Deterministic analysis using health state utilities for 3rd and 4th degree perineal tears to estimate health state utilities for instrumental and spontaneous vaginal birth

Outcome	IM pethidine	IV remifentanil PCA
Intervention cost	£37	£183
Respiratory depression cost	£0	£9
Rescue analgesia cost	£237	£114
Antiemetic cost	£25	£8
Birth cost	£2,813	£2,777
Neonatal admission cost	£105	£93
Total Cost	**£3,218**	**£3,198**
Incremental cost		-£35
QALYs	**0.41968**	**0.42039**
Incremental QALYs		0.00071
ICER	**Dominated**	**Dominant**
Net monetary benefit	£5,176	£5,224
Incremental net monetary benefit		**£49**

ICER = Incremental cost-effectiveness ratio; QALYs = Quality adjusted life years

Figure 20: Deterministic analysis using health state utilities for 3rd and 4th degree perineal tears to estimate health state utilities for instrumental and spontaneous vaginal birth represented on a cost-effectiveness plane

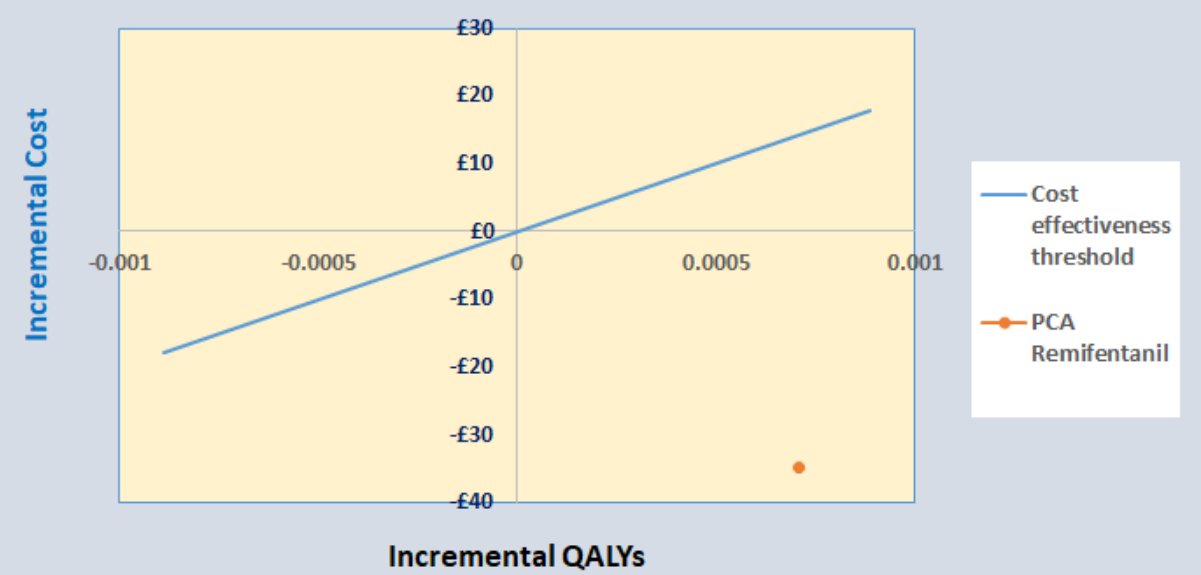


Table 39 tabulates the results of the PSA where health state utilities for 3rd and 4th degree perineal tears are used to estimate health state utilities for instrumental and spontaneous vaginal births. The results of individual simulations are depicted on a scatterplot cost-effectiveness plane in Figure 21.

Table 39: Probabilistic sensitivity analysis using health state utilities for 3rd and 4th degree perineal tears to estimate health state utilities for instrumental and spontaneous vaginal birth

Outcome	IM pethidine (95% CrInt)	IV remifentanil PCA (95% CrInt)
Mean cost	£3,217 (£3,021 to £3,421)	£3,195 (£2,987 to £3,436)
Mean QALY	0.4196 (0.4163 to 0.4222)	0.4199 (0.4127 to 0.4233)
Incremental cost		-£24 (-£276 to £245)
Incremental QALY		0.00025 (-0.00557 to 0.00386)
ICER	Dominated	Dominant
Mean NMB		£28 (-£320 to £336)
Probability cost-effective	41.5%	58.5%

ICER = incremental cost-effectiveness ratio; NMB = net monetary benefit; QALY = quality adjusted life-years

Figure 21: Scatterplot of probabilistic sensitivity analysis on cost-effectiveness plane using health state utilities for 3rd and 4th degree perineal tears to estimate health state utilities for instrumental and spontaneous vaginal birth

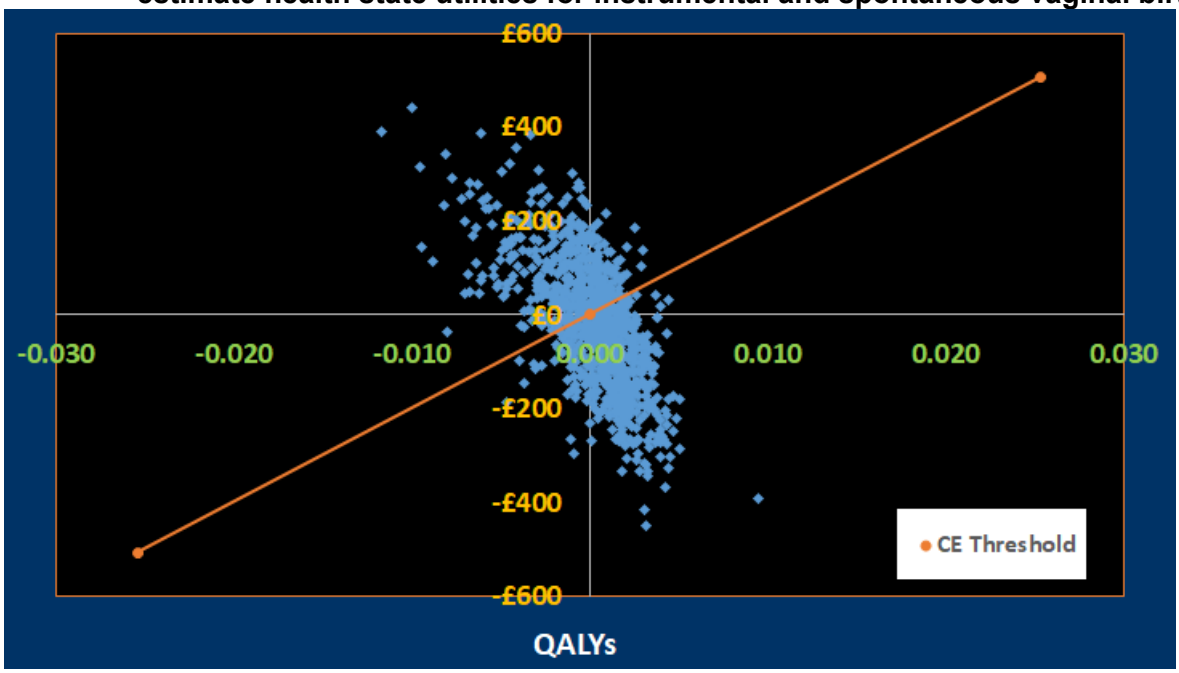
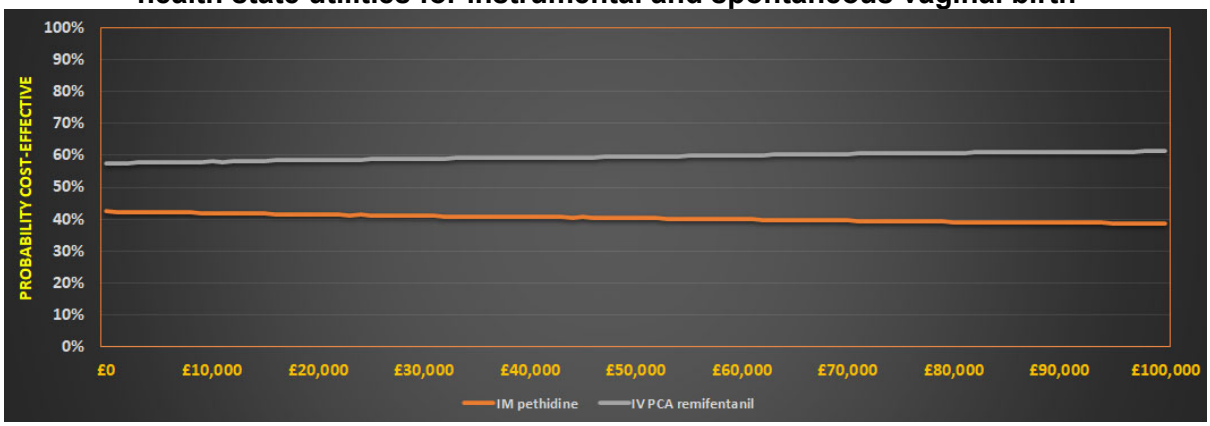


Figure 22 shows the CEAC for this PSA using health state utilities for 3rd and 4th degree perineal tears to estimate health state utilities for instrumental vaginal births. Remifentanil is cost-effective across the range of cost-effectiveness thresholds. The small QALY gains from reducing instrumental vaginal birth leads to a slowly rising probability that remifentanil is cost-effectiveness at higher thresholds.

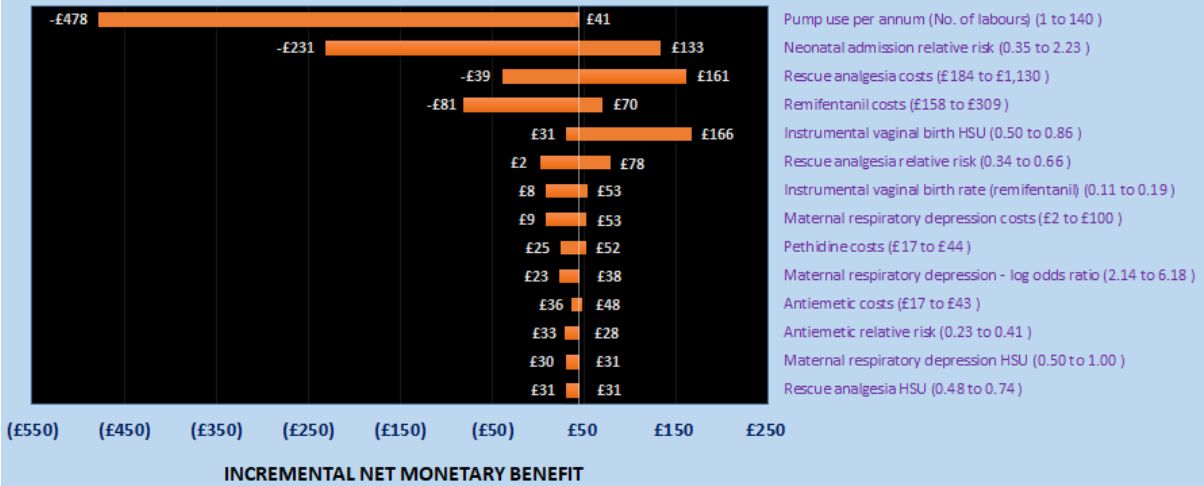
Figure 22: CEAC for probabilistic sensitivity analysis using health state utilities using health state utilities for 3rd and 4th degree perineal tears to estimate health state utilities for instrumental and spontaneous vaginal birth



Tornado diagram

A Tornado diagram, which shows the impact of varying different model parameters on the cost-effectiveness of remifentanil is shown in Figure 23. The NMB of the base case is shown by the vertical yellow line and NMB values of greater than £0 indicate that remifentanil is cost effective.

Figure 23: Tornado diagram



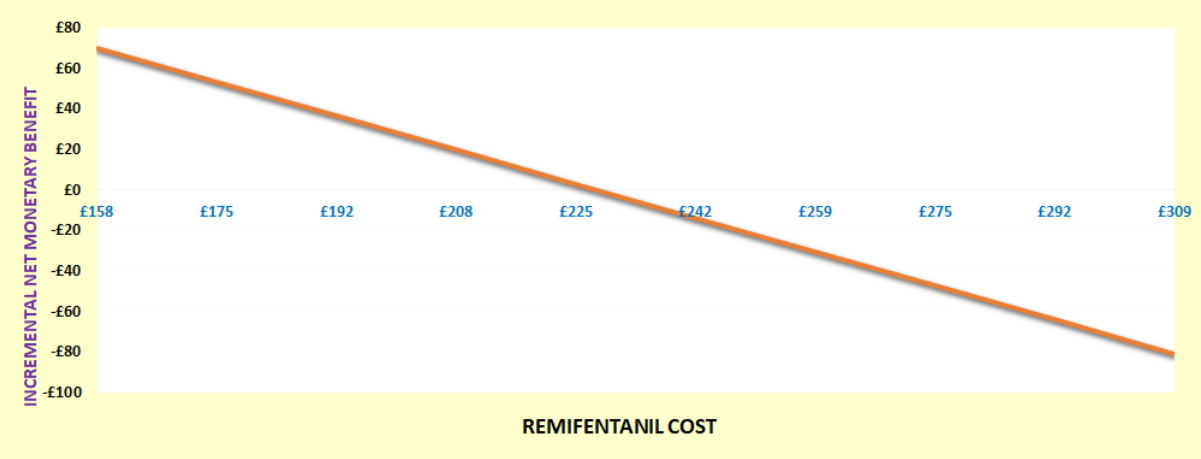
The right hand of Figure 23 lists the variables that were included on the Tornado diagram with the numbers in parentheses indicating the range over which they were varied in order to generate the difference in incremental NMB indicated by the chart bars. The diagram is ordered according to the difference between low and high incremental NMB values in descending order, producing the distinctive Tornado shape. For many variables both the low and high values have a positive incremental NMB indicating that remifentanil is cost-effective even when the input for that variable is set to a "worst case" scenario for remifentanil. The Tornado diagram suggests that pump use per annum, neonatal admission relative risk, rescue analgesia costs and remifentanil costs (of which pump use per annum is a determinant) are key drivers of the model's conclusions.

One-way sensitivity analysis

i. Varying the cost of remifentanil

Figure 24 shows the impact of varying the cost of the IV remifentanil PCA intervention between £158 and £309 on the cost-effectiveness of IV remifentanil relative to IM pethidine as measured by incremental NMB. It suggests that cost-effectiveness of remifentanil is sensitive to changes in this parameter. The chart indicates that remifentanil ceases to be cost-effective at a cost-effectiveness threshold of £20,000 per QALY when the cost exceeds £228 (it is £183 in the base case analysis).

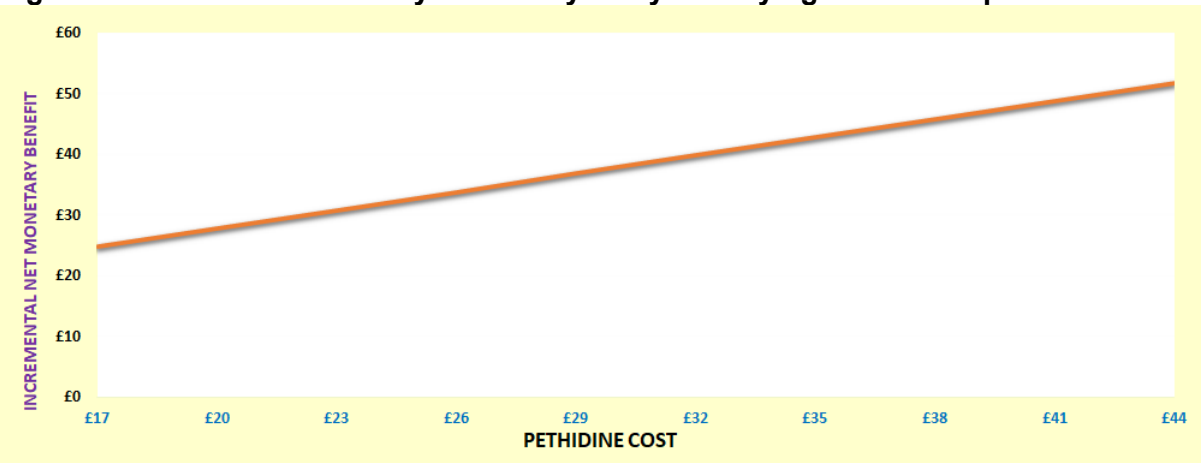
Figure 24: Chart of one-way sensitivity analysis varying the cost of remifentanil



ii. Varying the cost of pethidine

The implications of varying the cost of pethidine is illustrated in Figure 25. It shows intuitively that remifentanil becomes more cost-effective as the cost of pethidine increases. However, even at the lowest cost of pethidine charted, remifentanil remains the more cost-effective option with an incremental NMB of £25.

Figure 25: Chart of one-way sensitivity analysis varying the cost of pethidine



iii. Varying the cost of antiemetic administration

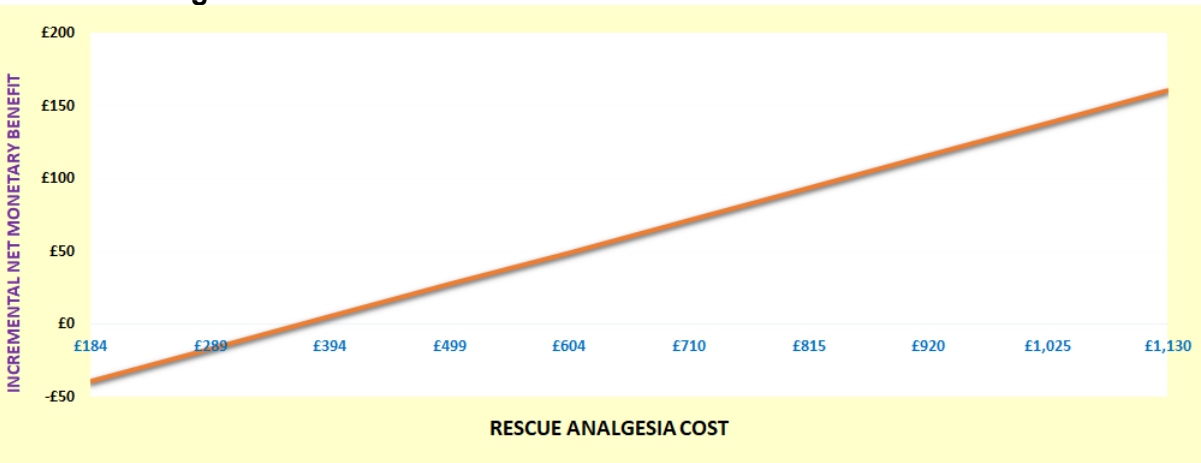
Figure 26 shows that the cost-effectiveness of remifentanil increases as the cost of pethidine rises. This reflects the fact that the model, based on Wilson (2018), results in lower use of antiemetic with remifentanil. The model is not particularly sensitive to changes in this parameter with remifentanil remaining the cost-effective option over the entire range of costs for antiemetic administration.

Figure 26: Chart of one-way sensitivity analysis varying the cost of antiemetic

iv. Varying the cost of rescue analgesia

The implications of varying rescue analgesia are displayed in Figure 27. They show that the model's conclusions could be sensitive to changes in this parameter. Remifentanil remains cost-effective providing the costs of rescue analgesia exceed £371 compared with a base case value of £582. The cost-effectiveness of remifentanil increases with higher rescue analgesia costs because the clinical evidence, on which the model is based, suggests that remifentanil significantly reduces the need for rescue analgesia compared to pethidine.

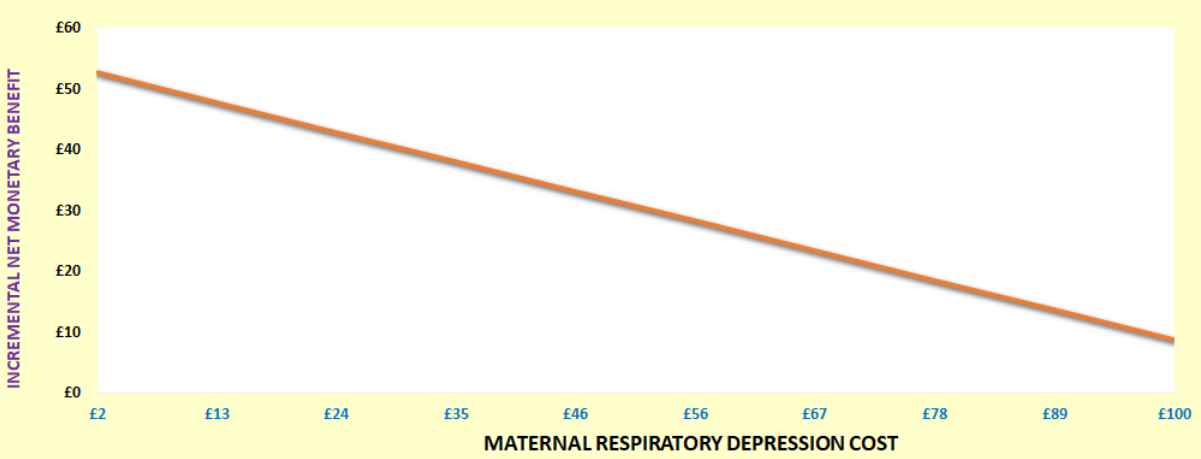
Figure 27: Chart of one-way sensitivity analysis varying the cost of rescue analgesia



v. Varying the cost of maternal respiratory depression

The results of this sensitivity analysis are shown in Figure 28. The outcome of maternal respiratory depression occurs more frequently with remifentanil than pethidine and therefore increasing maternal respiratory depression costs lead to reduced cost-effectiveness for remifentanil as measured by incremental NMB. However, maternal depression costs would have to be in excess of £100 before remifentanil ceased to be cost-effective relative to IM pethidine.

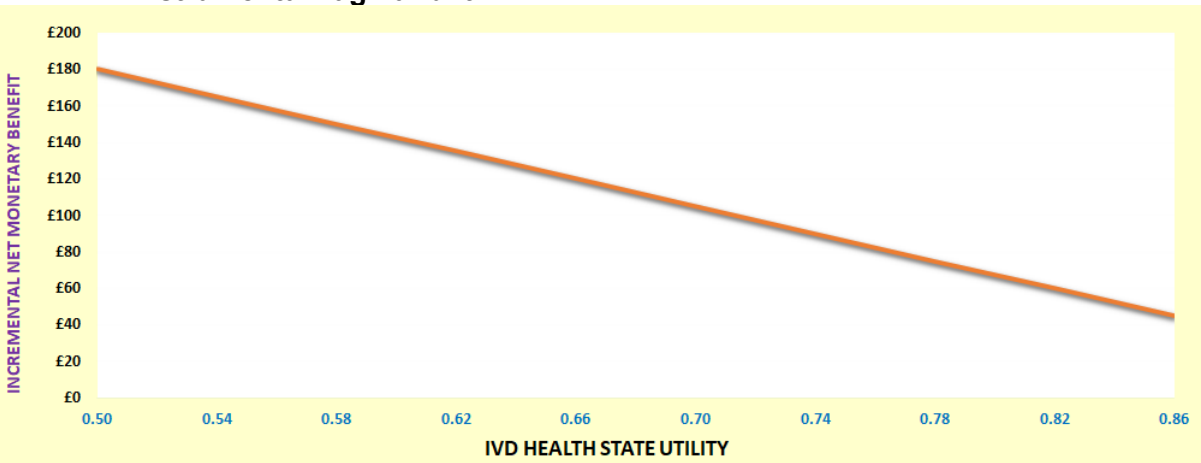
Figure 28: Chart of one-way sensitivity analysis varying the cost of maternal respiratory depression



vi. Varying the health state utility of instrumental vaginal birth

The base case analysis assumes an identical health state utility for all vaginal birth and remifentanil is cost-effective under this assumption. However, it is not plausible that health state utility for an instrumental vaginal birth could be higher than for a spontaneous vaginal birth and Figure 29 shows as expected that the cost-effectiveness of remifentanil for pain relief in labour increases with lower values of health state utility for instrumental vaginal birth, as one of the benefits of remifentanil is that it increases the proportion of spontaneous vaginal births relative to instrumental vaginal births.

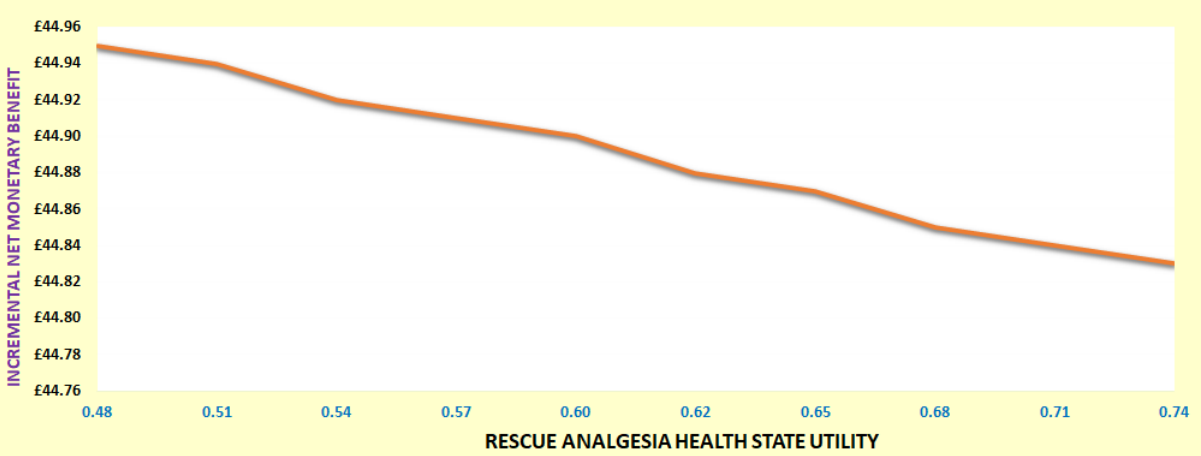
Figure 29: Chart of one-way sensitivity analysis varying the health state utility of instrumental vaginal birth



vii. Varying the health state utility of rescue analgesia

Figure 30 show that model conclusions are highly insensitive to changes in this model input, with a negligible change in incremental NMB across the range of rescue analgesia health state utility values assessed (note values on y-axis). This is because the duration of any health state disutility associated with rescue analgesia is assumed to be experienced for a very short duration of time meaning that any QALY impact will be quite limited even if a large health state disutility is assumed.

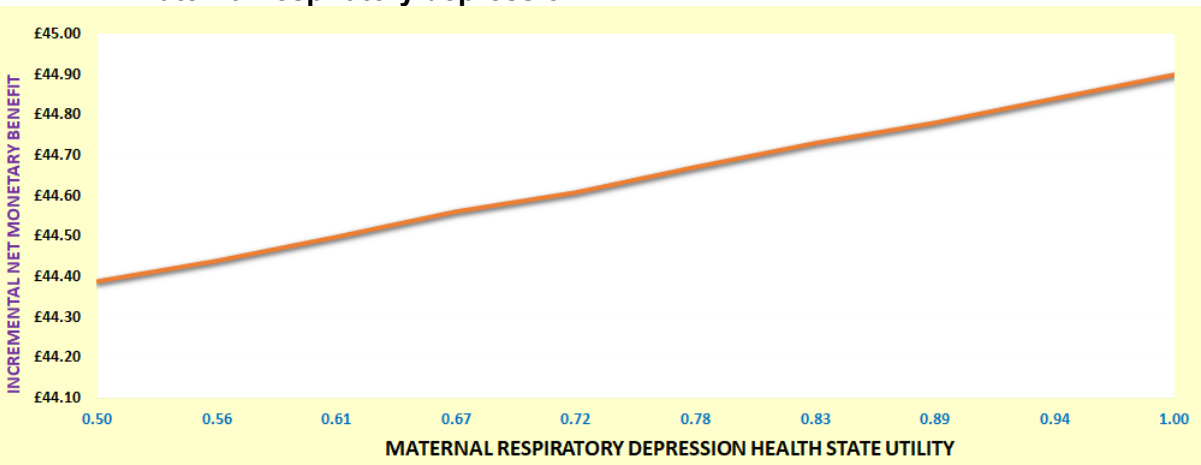
Figure 30: Chart of one-way sensitivity analysis varying the health state utility of rescue analgesia



viii. Varying the health state utility of maternal respiratory depression

As with the health state utility of rescue analgesia the model assumes that health state disutility of maternal respiratory depression (if any) is very short-lived meaning that any QALY impact is negligible. This is reflected in Figure 31, with the chart showing hardly any change in incremental NMB over a large range of health state utility values.

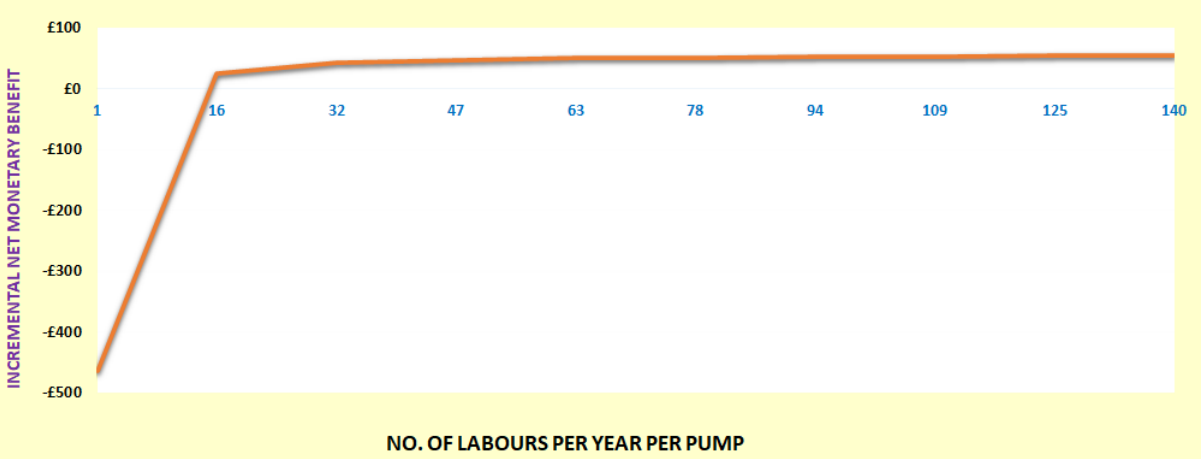
Figure 31: Chart of one-way sensitivity analysis varying the health state utility of maternal respiratory depression



ix. Varying the pump use per annum (number of labours)

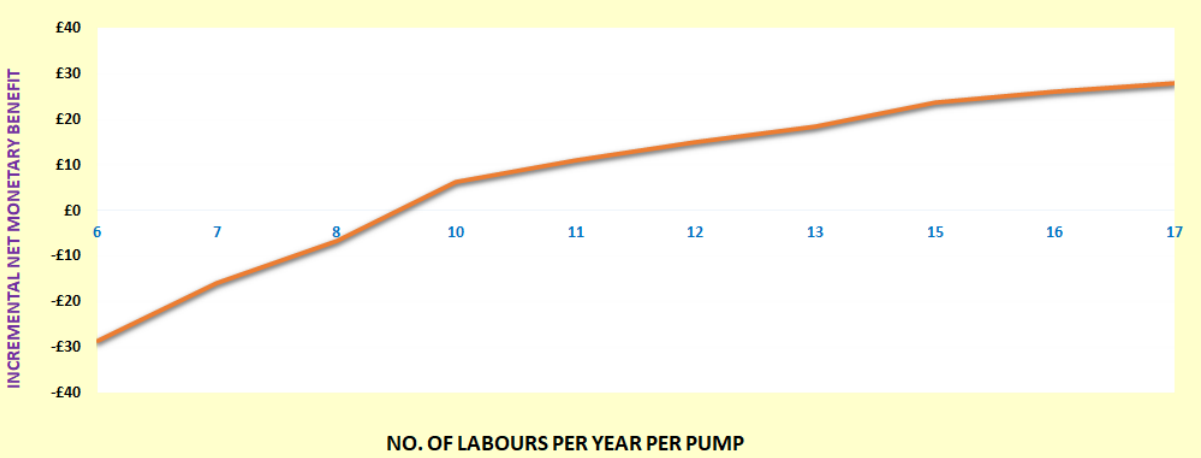
The cost of the pumps used for IV remifentanil feed into the overall treatment cost of remifentanil. The pumps have an equivalent annual cost and as that cost is spread over a greater number of labours the cost per labour falls rapidly at first and then at a much slower rate as is shown in Figure 32.

Figure 32: Chart of one-way sensitivity analysis varying the pump use per annum



The range of Figure 32 is too large to indicate the threshold pump use per annum for IV remifentanil PCA to be cost effective but Figure 33 uses a smaller range to demonstrate that IV remifentanil PCA becomes cost-effective for pain relief providing each pump is used for more than 9 labours per annum.

Figure 33: Cost-effectiveness threshold for pump use per annum

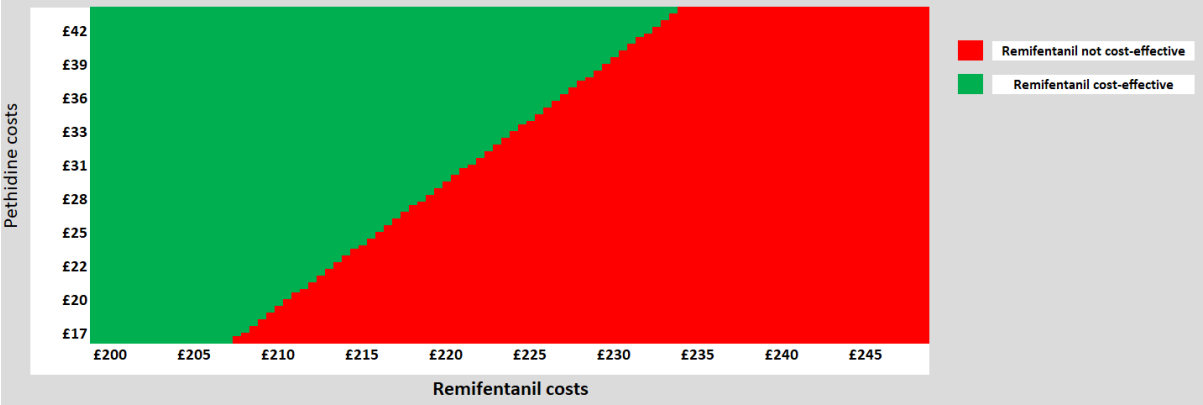


Two-way sensitivity analysis

i. Two-way sensitivity analysis varying the costs of remifentanil and IM pethidine

This two-way sensitivity analysis shown in Figure 34 illustrates the trade-off between the cost of the intervention and cost of the comparator needed for remifentanil to stay cost-effectiveness. The difference in costs rather than their absolute values determines the cost-effectiveness decision and explains why the cost threshold for remifentanil cost-effectiveness falls as the cost of pethidine falls. A smaller range of remifentanil costs was used than for the one-sensitivity analysis to illustrate the trade-off more clearly between the costs of the intervention and comparator.

Figure 34: Chart of two-way sensitivity analysis varying the cost of remifentanil and the cost of pethidine



ii. Two-way sensitivity analysis varying the cost of remifentanil and the health state utility of an instrumental vaginal birth

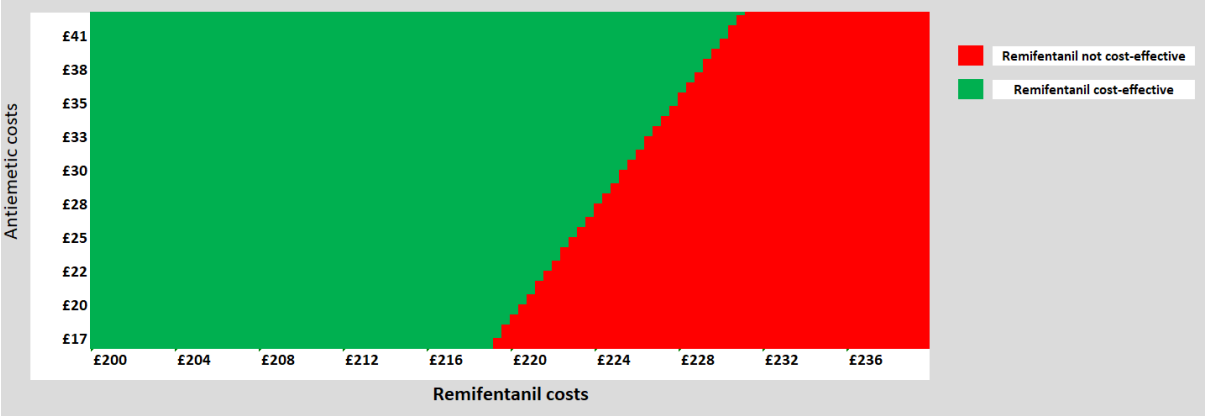
Other things being equal, a lower health state utility for instrumental vaginal birth is more likely to result in remifentanil being considered cost-effective. This is clearly shown in Figure 35 at the higher remifentanil costs, although if the cost of remifentanil is sufficiently low the cost-effectiveness decision is no longer affected by the health state utility of instrumental vaginal birth.

Figure 35: Chart of two-way sensitivity analysis varying the cost of remifentanil and the health state utility of an instrumental vaginal birth

iii. Two-way sensitivity analysis varying the cost of remifentanil and the cost of antiemetic

This analysis is displayed in Figure 36 and shows that remifentanil can be cost-effective at higher costs as the cost of antiemetic cost rises. This is because those costs have a bigger impact on the total costs of pethidine where antiemetic use is more often required.

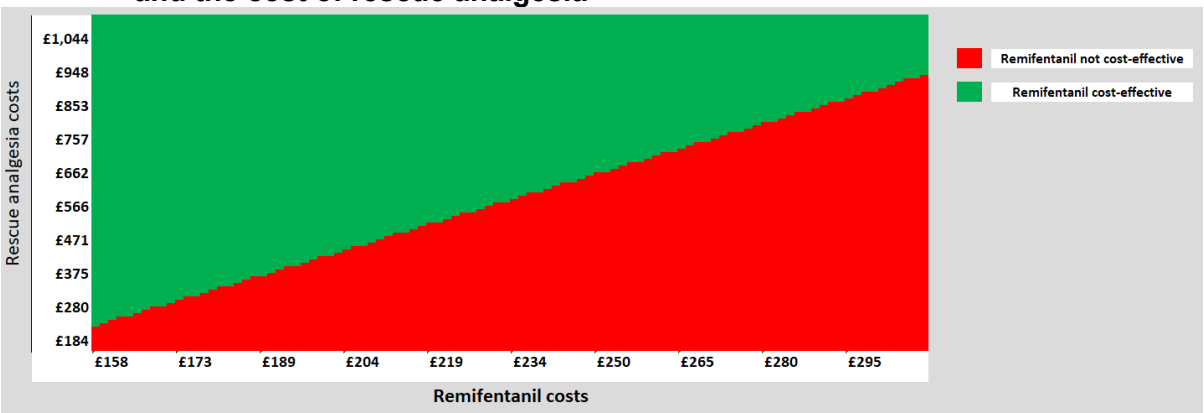
Figure 36: Chart of two-way sensitivity analysis varying the cost remifentanil and the cost of antiemetic



iv. Two-way sensitivity analysis varying the cost of remifentanil and the cost of rescue analgesia

Figure 37, illustrates the cost-effectiveness threshold for the cost of remifentanil for different rescue analgesia costs. As rescue analgesia is used less often when pain relief in labour is provided using remifentanil, then increasing costs of rescue analgesia have a greater relative impact on the cost of pethidine and as a result the threshold for cost-effectiveness for the cost of remifentanil is higher as rescue analgesia costs increase.

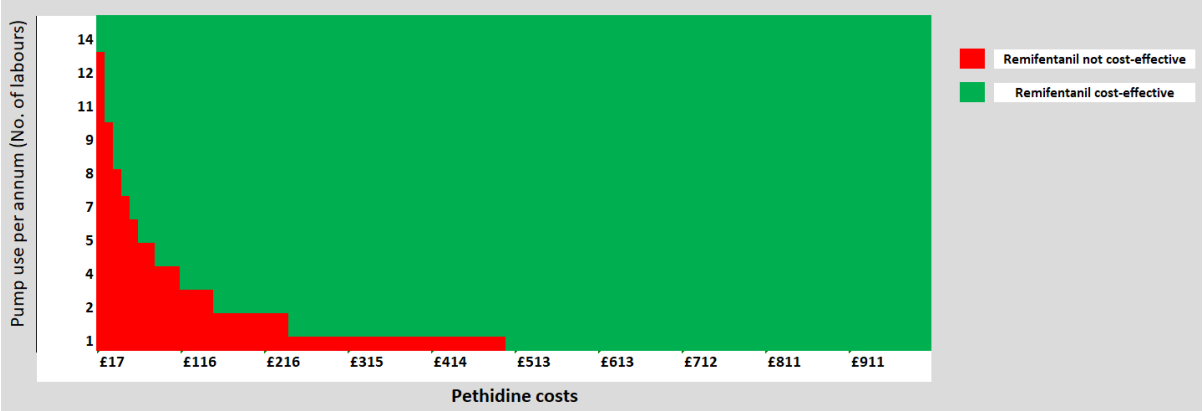
Figure 37: Chart of two-way sensitivity analysis varying the cost of remifentanil and the cost of rescue analgesia



v. Two-way sensitivity analysis varying the cost of pethidine and pump use per annum (number of labours)

This two-way sensitivity analysis shown in Figure 38 indicates the trade-off between pump use per annum and the cost of pethidine. As pump use increases from low levels, there is a steep fall in the cost of remifentanil as a fixed equipment cost is spread over more labours. Therefore, the threshold for the cost-effectiveness of pethidine indicates that its cost must fall rapidly as pump use increases. However, as pump use continues to increase the impact on the cost of remifentanil lessens and smaller reductions in pethidine cost are required to maintain the cost-effectiveness of pethidine. A much higher cost has been used for pethidine cost than that used for the one-way sensitivity analysis to better illustrate that how much more sensitive the cost-effectiveness of remifentanil is to the cost of pethidine at low pump use.

Figure 38: Chart of two-way sensitivity analysis varying the cost of pethidine and pump use per annum



Discussion

Clearly any model is only as good as the inputs that go into it and any limitations in the clinical evidence will be reflected in a model utilising that evidence. Therefore, it is important that the results of this model are interpreted with an awareness of the quality of the clinical evidence that informed it (see Table 5).

The results presented in this analysis provide some evidence for the cost-effectiveness of IV remifentanil PCA for pain relief compared to IM pethidine. Deterministic analyses suggested that remifentanil dominated pethidine and probabilistic sensitivity analyses suggested that when factoring in parameter uncertainty across those input parameters with a well-defined probability distribution, there was an approximately 57% probability that remifentanil was cost-effective.

Deterministic sensitivity analyses suggested that the model results were not particularly sensitive to changes in model input parameters, especially those relating to health state utility. This reflects that the principal driver of the cost-effectiveness of remifentanil in the model is reduced costs with “downstream” effects just offsetting the higher costs of the remifentanil intervention. Whilst the clinical evidence suggests that IV remifentanil PCA can reduce the rate of instrumental vaginal birth relative to IM pethidine, no health state utility gain arises from this in the base case analysis and therefore there is no impact on QALYs as a result of this difference. The small QALY gains in the model for remifentanil arise from a lower rate of neonatal admission, although this is a small relative effect with considerable uncertainty around the point estimate, and the reduction in the requirement for rescue analgesia. However, the model assumes that the duration in disutility arising from rescue analgesia is limited to 1 hour and therefore the QALY gain from any reduction in the need for rescue analgesia is very small.

The estimation of health state utilities is a limitation of the model as it relied on either proxies for the outcome of interest or published data on the relevant outcome but in a different population from that in this analysis. However, the Tornado diagram in Figure 23 suggests that uncertainty with respect to the value of these health state utility estimates is unlikely to lead to a different conclusion about the cost-effectiveness of remifentanil providing that the assumption that any disutility associated with maternal respiratory depression is of short duration was reasonable. The Tornado diagram shows changes to the values of health state utility for maternal respiratory depression and rescue analgesia have a negligible impact on the incremental NMB. Any changes to the base case value for health state utility for instrumental vaginal birth could only improve the relative cost-effectiveness of remifentanil as

the base case analysis does not as assume any QALY gain from a reduced rate of instrumental vaginal birth with remifentanil.

The only variables where the Tornado diagram suggested that different model inputs could lead to an alternative conclusion were remifentanil costs (or perhaps more comprehensively the difference in costs between remifentanil and pethidine), pump use per annum (which is a component of remifentanil treatment costs), the relative risk of neonatal admission and rescue analgesia costs. The uncertainty around the difference in neonatal admission is accounted for in the probabilistic analysis which gives a high probability that remifentanil is cost-effective. Whilst very low pump use could theoretically lead to cost ineffective remifentanil, such low use does not seem to a plausible scenario in a context where an NHS Trust had purchased pumps, and their use was supported by NICE guidance. Even in an NHS Trust with a low number of births per annum (e.g., 2,500), pump use would comfortably exceed the threshold for cost-effectiveness if only used in 1% of labours.

Therefore, it is the difference in costs between IV remifentanil PCA and IM pethidine (£146 in the base case analysis, see Table 11) that presents the biggest uncertainty with respect to the model conclusion that remifentanil is cost effective. Both the intervention and the comparator were costed using a micro or “ingredient’s based” approach. The costs of many of the consumables, such as the drug cost, are known with certainty and are available from published sources. So, providing the consumables have been correctly identified this should not be an important source of uncertainty within the micro costing. However, staffing costs are the most important component of the costs, and here reliable costing depends on accurately estimating staff time on the various tasks associated with providing the intervention. These estimates were provided by guideline committee members with relevant expertise and experience, but they are not based on actual timings and there will always be variation across different individual staff members. Nevertheless, Figure 24 showed that, providing the cost of remifentanil was not more than £45 greater than the base case assumption (difference between remifentanil and pethidine was not greater than £191) then remifentanil would remain cost-effective.

Conclusion

This analysis provides some evidence to suggest that IV remifentanil PCA is cost-effective relative to an alternative of IM pethidine for pain relief in labour. This finding is driven by the fact that reductions in the cost of rescue analgesia, antiemetic use and instrumental vaginal births with remifentanil just offset the higher intervention costs associated with remifentanil.

Therefore, there is economic evidence to support the committee’s recommendation that intravenous remifentanil patient-controlled analgesia (PCA) can be considered instead of IM pethidine for women who want ongoing pain relief during active labour, but who do not want an epidural.

Validation

Calculations for the deterministic analysis were undertaken in spreadsheet cells. However, most calculations for the PSA were performed using Visual Basic for Excel®. To check these calculations were correct an extra macro was added which allowed the PSA to be run in a deterministic fashion, with sampled input values always taking their base case value. This validation found that PSA using deterministic “samples” produced an identical result to the deterministic analysis giving a high degree of confidence that the VBA coding accurately mirrored the calculations undertaken in spreadsheet cells.

All one-way and two-way sensitivity analyses produced the anticipated change in the relative strength of cost-effectiveness in response to changes in input values.

Albers 1999

Albers, L.L. (1999) The duration of labour in healthy women. Journal of Perinatology 19(2):114-9

Bergendahl 2019

Bergendahl, S., Ankarcrona, V., Leijonhufvud, Å., et al. (2019) Lateral episiotomy versus no episiotomy to reduce obstetric anal sphincter injury in vacuum-assisted delivery in nulliparous women: study protocol on a randomised controlled trial. BMJ Open 9(3)

Fairlie 1999

Fairlie, F.M., Marshall, L., Walker, J.J., Elbourne, D. (1999) Intramuscular opioids for maternal pain relief in labour: A randomised controlled trial comparing pethidine with diamorphine. British Journal of Obstetrics and Gynaecology 106: 1181–7

Jones 2021

Jones, K., Burns, A. (2021) Unit Costs of Health and Social Care 2021, Personal Social Services Research Unit, University of Kent, Canterbury.

Tan 2010

Tan, J.M., Macario, A., Carvalho, B., Druzin, M.L., El-Sayed, Y.Y. (2010) Cost-effectiveness of external cephalic version for term breech presentation. BMC Pregnancy and Childbirth 10(3)

Turner 2008

Turner, C.E., Young, J.M., Solomon, M.J., Ludlow, J., Benness, C., Phipps, H. (2008) Vaginal delivery compared with elective caesarean section: the views of pregnant women and clinicians. British Journal of Obstetrics and Gynaecology 115:1494–1502

Wetherington 2014

Wetherington, S., Delong, D., Kini, S., Veledar, E., Schaufele, M.K., Mckenzie-Brown, A.M., Chen, S.C. (2014) Pain quality of life as measured by utilities. Pain Medicine 15(5):865-870

Appendix J Excluded studies

Excluded studies for review question: What is the effectiveness of remifentanil administered by intravenous patient-controlled analgesia (PCA) compared to other intramuscular opioids?

Excluded effectiveness studies

Table 40: Excluded studies and reasons for their exclusion

Study	Reason
Bhagvandas, J., Foon, R., Fong, K. et al. (2022) The effect of remifentanil patient-controlled analgesia versus epidural in labour: maternal and neonatal outcomes. Anaesthesia 77(suppl2): 9	- Conference abstract.
Blair, J. M., Dobson, G. T., Hill, D. A. et al. (2001) Patient-controlled analgesia for labor: a comparison of remifentanil and pethidine. Anesthesiology 95: abstractnoa1063	- Conference abstract.
Blair, J. M., Dobson, G. T., Hill, D. A. et al. (2005) Patient controlled analgesia for labour: a comparison of remifentanil with pethidine. Anaesthesia 60(1): 22-27	- Comparator not in PICO Pethidine administered intravenously via PCA
Bricker, Leanne and Lavender, Tina (2002) Parenteral opioids for labor pain relief: a systematic review. American journal of obstetrics and gynecology 186(5supplnature): 94-109	- Intervention not in PICO Systematic review does not include remifentanil PCA
Calderon, E., Martinez, E., Roman, M. D. et al. (2006) Intravenous remifentanil delivered through an elastomeric device versus intramuscular meperidine comparative study for obstetric analgesia. Revista de la sociedad espanola del dolor 13(7): 462-467	- Article not in English
Douma, M. R., Verwey, R. A., Kam-Endtz, C. E. et al. (2010) Obstetric analgesia: a comparison of patient-controlled meperidine, remifentanil, and fentanyl in labour. British journal of anaesthesia 104(2): 209-215	- Comparator not in PICO Comparator opioids (meperidine and fentanyl) administered intravenously via PCA
Elbourne D and Wiseman RA (2000) Types of intra-muscular opioids for maternal pain relief in labour. The Cochrane database of systematic reviews: CD001237	- Intervention not in PICO Systematic review does not include remifentanil PCA
Fairlie, F M, Marshall, L, Walker, J J et al. (1999) Intramuscular opioids for maternal pain relief in labour: a randomised controlled trial comparing pethidine with diamorphine. British journal of obstetrics and gynaecology 106(11): 1181-7	- Intervention not in PICO Study does not include remifentanil PCA
Haslam, D., Donaldson, H., Davies, S. et al. (2021) Low-dose remifentanil patient-controlled analgesia: Efficacy and safety in two North West obstetric units. Anaesthesia 76(suppl6): 40	- Conference abstract.
Isenor, L and Penny-MacGillivray, T (1993)	- Intervention not in PICO

Study	Reason
Intravenous meperidine infusion for obstetric analgesia. Journal of obstetric, gynecologic, and neonatal nursing : JOGNN 22(4): 349-56	Study does not include remifentanil PCA
Jelting, Y., Weibel, S., Jokinen, J. et al. (2017) Patient-controlled analgesia with remifentanil vs. alternative parenteral methods for pain management in labour: a Cochrane systematic review. Anaesthesia 72(8): 1016-1028	- Systematic review- comparator not in PICO Includes studies with comparators delivered intravenously
Keskin, H L, Keskin, E Aktepe, Avsar, A F et al. (2003) Pethidine versus tramadol for pain relief during labor. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics 82(1): 11-6	- Intervention not in PICO Study does not include remifentanil PCA
Leong, Wan Ling; Sng, Ban Leong; Sia, Alex Tiong Heng (2011) A comparison between remifentanil and meperidine for labor analgesia: A systematic review. Anesthesia and Analgesia 113(4): 818-825	- Systematic review- comparator not in PICO Includes studies with comparators delivered intravenously
MacArthur, C., Hewitt, C., Handley, K. et al. (2019) Remifentanil patient-controlled analgesia versus intramuscular pethidine for pain relief in labour: The RESPITE randomised controlled trial. BJOG: An International Journal of Obstetrics and Gynaecology 126(supplement2): 128	- Conference abstract.
McInnes, Rhona J, Hillan, Edith, Clark, Diana et al. (2004) Diamorphine for pain relief in labour : a randomised controlled trial comparing intramuscular injection and patient-controlled analgesia. BJOG : an international journal of obstetrics and gynaecology 111(10): 1081-9	- Intervention not in PICO Study does not include remifentanil PCA
Moran, V. H., Thomson, G., Cook, J. et al. (2019) Qualitative exploration of women's experiences of intramuscular pethidine or remifentanil patient-controlled analgesia for labour pain. BMJ open 9(12): e032203	- Qualitative study Relevant quantitative outcomes reported in main trial data (included article)
Morley-Forster, P K; Reid, D W; Vandeberghe, H (2000) A comparison of patient-controlled analgesia fentanyl and alfentanil for labour analgesia. Canadian journal of anaesthesia = Journal canadien d'anesthesie 47(2): 113-9	- Intervention not in PICO Study does not include remifentanil PCA
Nelson, Kenneth E and Eisenach, James C (2005) Intravenous butorphanol, meperidine, and their combination relieve pain and distress in women in labor. Anesthesiology 102(5): 1008-13	- Intervention not in PICO Study does not include remifentanil PCA
Schnabel, Alexander, Hahn, Niklas, Broscheit, Jens et al. (2012) Remifentanil for labour analgesia: a meta-analysis of randomised controlled trials. European journal of anaesthesiology 29(4): 177-85	- Systematic review- comparator not in PICO Includes studies with comparators not administered intramuscularly
Smith, Lesley A.; Burns, Ethel; Cuthbert, Anna (2018) Parenteral opioids for maternal pain management in labour. Cochrane Database of Systematic Reviews 2018(6): cd007396	- Systematic review- comparator not in PICO Comparator administered intravenously via PCA

Study	Reason
Soontrapa, Sukree, Somboonporn, Woraluk, Komwilaisak, Ratana et al. (2002) Effectiveness of intravenous meperidine for pain relief in the first stage of labour. Journal of the Medical Association of Thailand = Chotmaihet thangphaet 85(11): 1169-75	- Intervention not in PICO Study does not include remifentanil PCA
Sosa, Claudio G, Balaguer, Erica, Alonso, Justo G et al. (2004) Meperidine for dystocia during the first stage of labor: A randomized controlled trial. American journal of obstetrics and gynecology 191(4): 1212-8	- Intervention not in PICO Study does not include remifentanil PCA
Stourac, Petr, Kosinova, Martina, Harazim, Hana et al. (2016) The analgesic efficacy of remifentanil for labour. Systematic review of the recent literature. Biomedical papers of the Medical Faculty of the University Palacky, Olomouc, Czechoslovakia 160(1): 30-38	- Systematic review- comparator not in PICO Includes studies with comparators delivered intravenously or epidural
Tan, A., Wilson, A.N., Eghrari, D. et al. (2022) Outcomes to measure the effects of pharmacological interventions for pain management for women during labour and birth: a review of systematic reviews and randomised trials. BJOG: An International Journal of Obstetrics and Gynaecology 129(6): 845-854	- Systematic review - intervention not in PICO Does not include Remifentanil
Thurlow, J. A., Laxton, C. H., Dick, A. et al. (2000) Comparison of patient controlled analgesia (PCA) using remifentanil with intramuscular pethidine for pain relief in labour. International journal of obstetric anesthesia 9: 200	- Conference abstract.
Tsui, Michelle H Y, Ngan Kee, Warwick D, Ng, Floria F et al. (2004) A double blinded randomised placebo-controlled study of intramuscular pethidine for pain relief in the first stage of labour. BJOG : an international journal of obstetrics and gynaecology 111(7): 648-55	- Intervention not in PICO Study does not include remifentanil PCA
Tveit, T. O., Seiler, S., Halvorsen, A. et al. (2012) Labour analgesia: a randomised, controlled trial comparing intravenous remifentanil and epidural analgesia with ropivacaine and fentanyl. European journal of anaesthesiology 29(3): 129-136	- Comparator not in PICO Comparator is epidural
Volikas, I. and Male, D. (2001) A comparison of pethidine and remifentanil patient-controlled analgesia in labour. International journal of obstetric anesthesia 10(2): 86-90	- Comparator not in PICO Comparator is administered intravenously
Weibel, S., Jelting, Y., Afshari, A. et al. (2017) Patient-controlled analgesia with remifentanil versus alternative parenteral methods for pain management in labour. Cochrane Database of Systematic Reviews	- Systematic review- comparator not in PICO Includes studies with comparators administered intravenously
Wilson, M. J., MacArthur, C., Smith, F. G. et al. (2017) A randomised controlled trial of remifentanil intravenous patient controlled analgesia (PCA) versus intramuscular pethidine for pain relief in labour (RESPITE trial). International journal of obstetric anesthesia 31:	- Conference abstract.

Study	Reason
S8	
Xu, Shiqin, Shen, Xiaofeng, Wang, Fuzhou et al. (2012) Effectiveness of remifentanil for labor pain control: A systematic review and meta-analysis. HealthMED 6(7): 2407-2418	- Systematic review- comparator not in PICO Includes studies with comparators not delivered intramuscularly
Zhang, Peijun, Yu, Zhiqiang, Zhai, Meili et al. (2021) Effect and Safety of Remifentanil Patient-Controlled Analgesia Compared with Epidural Analgesia in Labor: An Updated Meta-Analysis of Randomized Controlled Trials. Gynecologic and obstetric investigation 86(3): 231-238	- Systematic review- comparator not in PICO Comparator is epidural analgesia

Excluded economic studies

Study	Reason
Freeman, Liv, Middeldorp, Johanna, van den Akker, Eline et al. (2018) An economic analysis of patient controlled remifentanil and epidural analgesia as pain relief in labour (RAVEL trial); a randomised controlled trial. PloS one 13(10): e0205220	- Cost analysis only

Appendix K Research recommendations – full details

Research recommendations for review question: What is the effectiveness of remifentanil administered by intravenous patient-controlled analgesia (PCA) compared to other intramuscular opioids?

No research recommendations were made for this review question.