Economic model for review question: What is the effectiveness of uterotonics for the prevention of postpartum haemorrhage?

Cost-effectiveness analysis of different uterotonics

Introduction

Postpartum haemorrhage (PPH) can have significant physical and psychological impacts on a woman's health, as well as impacting the woman's birth experience and ability to bond with their baby. There are various uterotonic drugs that can be used prophylactically to reduce the risk of PPH, and the difference in effectiveness and downstream costs of these drugs is important to consider in the context of a resource constrained publicly funded health service and the potentially large resource impact given the number of women treated.

A recent UK health technology assessment (HTA) (Gallos 2019) synthesised clinical evidence comparing uterotonics for prevention of PPH using an NMA, and the HTA also included an economic evaluation. New evidence has been highlighted since this HTA was published including two large carbetocin trials, so it was decided the NMA and health economic model needed to be updated for the committee to make fully informed recommendations on uterotonics for prevention of PPH. The existing economic model included more of the pathway than could be informed by the new NMA evidence, so the NICE guideline developers constructed a new economic model for the purposes of this guideline.

Methods

Setting and population

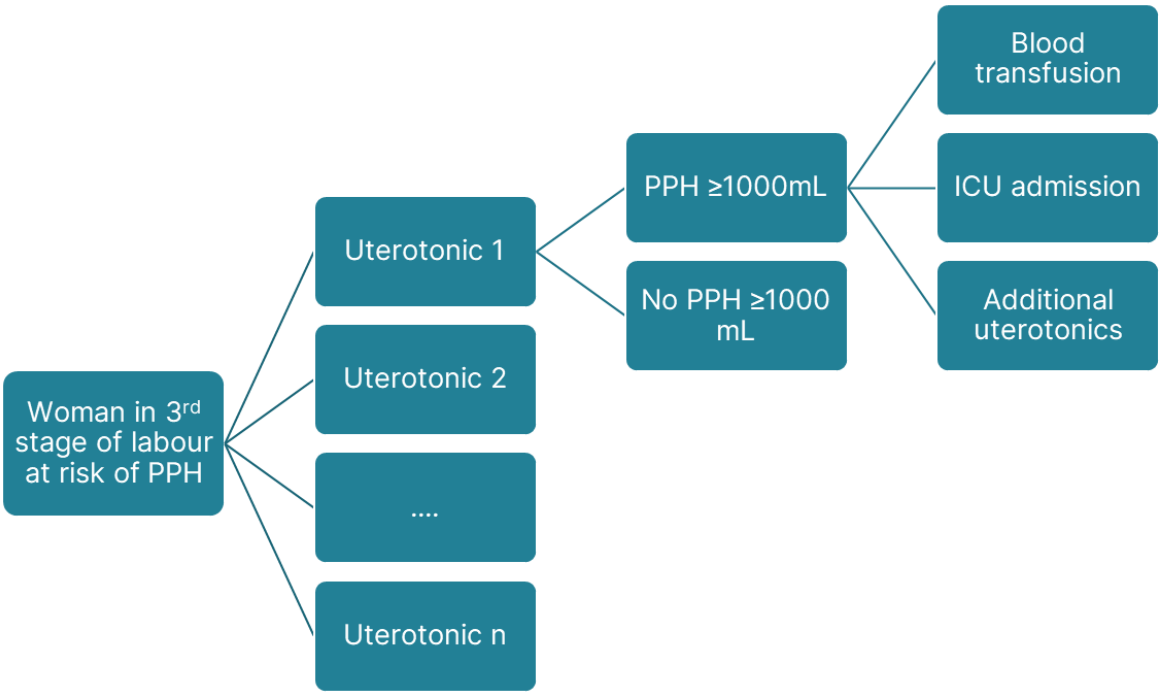
The model was in the NHS setting, and the population was women in the third stage of labour, who are all at risk of PPH. The time horizon was very short, only capturing the immediate postpartum period and the costs and outcomes in the third stage of labour. The model was run for the full population, and also for two mode-of-birth subgroups; vaginal birth and caesarean birth.

Model structure

A decision analytic model was developed in Microsoft Excel® to assess the cost-effectiveness of different uterotonics for prevention of PPH.

The model schematic is shown in Figure 46, and shows the four outcomes considered in the model, with the primary outcome being a PPH of 1000mL or more.

Figure 46: Model schematic



Clinical outcomes

The clinical outcomes incorporated into the model were the same as those considered in the NMA:

- PPH ≥1000mL
- Additional uterotonics
- ICU admission
- Blood transfusions

The continuous outcome of mean blood loss was not used in the economic model, as the committee felt this overlapped and would be correlated with the PPH ≥1000mL outcome. The relative treatment effects for each of these outcomes are informed by the NMAs for the entire population and mode-of-birth subgroups.

Interventions

The uterotonics included in the economic analysis reflected the interventions in which there was evidence from the NMAs, particularly for the PPH ≥1000mL outcome. The committee's clinical opinion was then used to select those uterotonics which were plausible clinical alternatives for PPH prophylaxis in an NHS setting.

The interventions included in the economic model were:

- Carbetocin
- Oxytocin ≤ 1 iu (full population and vaginal birth groups only)
- Oxytocin >1 iu and ≤ 5 iu
- Oxytocin >5 iu and ≤ 10 iu

- Oxytocin > 10 iu
- Ergometrine plus oxytocin

The network of evidence for the PPH ≥1000mL outcome in the caesarean birth subgroup did not include oxytocin ≤ 1 iu, so this dose level was not included in the economic model for the caesarean birth analysis.

There was limited NMA data for the ICU admission outcome, so this was included as a scenario only in the full population and vaginal birth subgroup, with the comparison restricted to just oxytocin >5 iu and ≤ 10 iu and carbetocin.

Baseline

The NMA provided evidence on the relative effectiveness of treatments relative to a reference treatment for each outcome. This analysis used the placebo arm as the reference for the majority of outcomes and population groups, but in two cases (caesarean birth; PPH≥1000mL and blood transfusion) the placebo arm was not included in the network and carbetocin was used as the reference instead.

Probabilities for each of the events in the reference arm were taken from trials included in that NMA that were considered to be in the most similar setting to the UK NHS perspective and are listed in Table 31.

Table 31: Baseline event probabilities

Outcome	Population	Study arm	Probability	Standard error[a]	Source
PPH ≥1000mL	Full	Placebo	11.9%	0.0004	Jans 2016
	VB	Placebo	11.9%	0.0004	Jans 2016
	CB	Carbetocin	4.8%	0.0011	Attilakos 2010
Additional uterotonics	Full	Placebo	23.5%	0.0005	Jans 2016
	VB	Placebo	23.5%	0.0005	Jans 2016
	CB	Placebo	92.0%	0.0106	Rosseland 2013
Blood transfusion	Full	Placebo	1.4%	0.0001	Jans 2016
	VB	Placebo	1.4%	0.0001	Jans 2016
	CB	Carbetocin	2.1%	0.0008	Attilakos 2010
ICU admission	Full	Placebo	0.2%	0.0001	Derman 2006
	VB	Placebo	0.2%	0.0001	Derman 2006

[a]Standard error calculated from the total number of individuals, total number of events, and mean probability Beta distribution used around all probabilities.

Treatment effectiveness

Treatment effect was incorporated in the model by using the outcomes from the NMAs. The NMAs generated relative effectiveness in the form of odds ratios, which are applied to the baseline probabilities detailed in the previous section to calculate the event probabilities specific to each treatment in the economic model. These odds ratios are listed for each treatment, mode-of-birth subgroup, and event, in the Clinical evidence profile for outcomes included in the network meta-analysis.

The odds ratios are applied to baseline probabilities using a logit function:

- Logit = ln (reference treatment probability / (1 – reference treatment probability))

- Log odds (treatment A) = logit + log odds ratio of treatment A
- Absolute probability (treatment A) = exp (log odds) / (1 + exp (log odds))

Adverse events

Treatment-related adverse events were included in the model and are informed by the Gallos 2019 HTA. The probabilities and standard errors used in the economic model are detailed in Table 32 and Table 33. Since the HTA only reported adverse events for the separate subgroups, the adverse event probabilities for the full population are assumed to be the average of the probabilities reported for the two subgroups, and this approach was informed by clinical opinion.

Assumptions have been made where there are evidence gaps. Carboprost was not included in the HTA analysis so adverse events were not reported, and therefore the event probabilities have been assumed equal to the probabilities of oxytocin based on clinical opinion on the similarities in those treatments. Where information was missing for carbetocin the probabilities were set equal to those in the oxytocin arm, given the similarities between the probabilities for carbetocin and oxytocin in other events and other subgroups. Where information was missing for any other treatment three options were considered; average of all other treatments, minimum from other treatments, or maximum from other treatments. The base-case assumed the average of probabilities from other treatments for that subgroup and event.

Table 32: Treatment-related adverse event probabilities (SE), vaginal births

Intervention	Nausea	Vomiting	Hypertension	Headache	Tachycardia	Hypotension	Fever	Shivering	Abdominal pain
Carbetocin	0.028 (0.341)	0.01 (0.305)	0.03 (0.808)	0.054 (0.382)	0.074 (0.498)	0.005* (0.005)	0.02* (0.003)	0.071* (0.007)	0.099 (0.307)
Oxytocin ≤ 1 iu	0.039 (0.005)	0.01 (0.002)	0.021 (0.005)	0.044 (0.009)	0.025 (0.014)	0.005 (0.005)	0.02 (0.003)	0.071 (0.007)	0.134 (0.043)
Oxytocin >1 iu and ≤ 5 iu	0.039 (0.005)	0.01 (0.002)	0.021 (0.005)	0.044 (0.009)	0.025 (0.014)	0.005 (0.005)	0.02 (0.003)	0.071 (0.007)	0.134 (0.043)
Oxytocin >5 iu and ≤ 10 iu	0.039 (0.005)	0.01 (0.002)	0.021 (0.005)	0.044 (0.009)	0.025 (0.014)	0.005 (0.005)	0.02 (0.003)	0.071 (0.007)	0.134 (0.043)
Oxytocin > 10 iu	0.039 (0.005)	0.01 (0.002)	0.021 (0.005)	0.044 (0.009)	0.025 (0.014)	0.005 (0.005)	0.02 (0.003)	0.071 (0.007)	0.134 (0.043)
Ergometrine plus oxytocin (syntometrine)	0.081 (0.202)	0.043 (0.099)	0.059 (0.633)	0.072 (0.294)	0.04 (0.551)	0.0037* (0.7014)	0.02 (0.336)	0.087 (0.282)	0.149 (0.245)
Misoprostol ≤ 600 mcg	0.058 (0.161)	0.029 (0.097)	0.033 (0.655)	0.068 (0.323)	0.036* (0.184)	0.002 (1.63)	0.105 (0.162)	0.271 (0.14)	0.127 (0.158)
Misoprostol >600 mcg and ≤ 800 mcg	0.058 (0.161)	0.029 (0.097)	0.033 (0.655)	0.068 (0.323)	0.036* (0.184)	0.002 (1.63)	0.105 (0.162)	0.271 (0.14)	0.127 (0.158)
Misoprostol >800 mcg and ≤ 1000 mcg	0.058 (0.161)	0.029 (0.097)	0.033 (0.655)	0.068 (0.323)	0.036* (0.184)	0.002 (1.63)	0.105 (0.162)	0.271 (0.14)	0.127 (0.158)
Misoprostol plus oxytocin	0.27 (0.891)	0.039 (0.255)	0.0444* (0.424)	0.0635* (0.2093)	0.036* (0.184)	0.0037* (0.7014)	0.09 (0.229)	0.261 (0.246)	0.1337* (0.1662)
Ergometrine	0.106 (0.226)	0.042 (0.148)	0.172 (0.814)	0.129 (0.412)	0.036* (0.184)	0.0037* (0.7014)	0.02 (0.303)	0.097 (0.265)	0.172 (0.464)
Carboprost	0.039* (0.005)	0.01* (0.002)	0.021* (0.005)	0.044* (0.009)	0.025* (0.014)	0.005* (0.005)	0.02* (0.003)	0.071* (0.007)	0.134* (0.043)

**Missing data, completed with assumptions*

Table 33: Treatment-related adverse event probabilities (SE), caesarean births

Intervention	Nausea	Vomiting	Hypertension	Headache	Tachycardia	Hypotension	Fever	Shivering	Abdominal pain
Carbetocin	0.092 (0.327)	0.049 (0.282)	0.167* (0.076)	0.083 (0.151)	0.12 (1.546)	0.157 (0.346)	0.026 (0.785)	0.035 (0.392)	0.178 (0.089)
Oxytocin ≤ 1 iu	0.091 (0.019)	0.056 (0.011)	0.167 (0.076)	0.094 (0.021)	0.024 (0.016)	0.169 (0.065)	0.033 (0.005)	0.05 (0.01)	0.172 (0.071)
Oxytocin >1 iu and ≤ 5 iu	0.091 (0.019)	0.056 (0.011)	0.167 (0.076)	0.094 (0.021)	0.024 (0.016)	0.169 (0.065)	0.033 (0.005)	0.05 (0.01)	0.172 (0.071)
Oxytocin >5 iu and ≤ 10 iu	0.091 (0.019)	0.056 (0.011)	0.167 (0.076)	0.094 (0.021)	0.024 (0.016)	0.169 (0.065)	0.033 (0.005)	0.05 (0.01)	0.172 (0.071)
Oxytocin > 10 iu	0.091 (0.019)	0.056 (0.011)	0.167 (0.076)	0.094 (0.021)	0.024 (0.016)	0.169 (0.065)	0.033 (0.005)	0.05 (0.01)	0.172 (0.071)
Ergometrine plus oxytocin (syntometrine)	0.453 (1.012)	0.337 (1.127)	0.042 (1.08)	0.0863* (0.2404)	0.018 (0.707)	0.141 (0.532)	0.042* (0.3329)	0.1252* (0.2104)	0.1998* (0.1168)
Misoprostol ≤ 600 mcg	0.043 (0.687)	0.048 (0.407)	0.142* (0.2768)	0.059 (0.451)	0.039* (0.386)	0.034 (1.077)	0.049 (0.639)	0.244 (0.4)	0.1998* (0.1168)
Misoprostol >600 mcg and ≤ 800 mcg	0.043 (0.687)	0.048 (0.407)	0.142* (0.2768)	0.059 (0.451)	0.039* (0.386)	0.034 (1.077)	0.049 (0.639)	0.244 (0.4)	0.1998* (0.1168)
Misoprostol >800 mcg and ≤ 1000 mcg	0.043 (0.687)	0.048 (0.407)	0.142* (0.2768)	0.059 (0.451)	0.039* (0.386)	0.034 (1.077)	0.049 (0.639)	0.244 (0.4)	0.1998* (0.1168)
Misoprostol plus oxytocin	0.164 (0.393)	0.085 (0.299)	0.142* (0.2768)	0.141 (0.576)	0.039* (0.386)	0.22 (0.672)	0.073 (0.274)	0.16 (0.262)	0.333 (0.328)
Ergometrine	0.1202* (0.3869)	0.0839* (0.2973)	0.142* (0.2768)	0.0863* (0.2404)	0.039* (0.386)	0.1296* (0.5041)	0.042* (0.3329)	0.1252* (0.2104)	0.1998* (0.1168)
Carboprost	0.091* (0.019)	0.056* (0.011)	0.167* (0.076)	0.094* (0.021)	0.024* (0.016)	0.169* (0.065)	0.033* (0.005)	0.05* (0.01)	0.172* (0.071)

**Missing data, completed with assumptions*

Costs

In accordance with NICE methodology a NHS and Personal Social Services (PSS) perspective was adopted for this analysis. NHS Reference Costs were based on the 2019/20 published costs. Drug costs were taken from the British National Formulary (BNF) at the date of writing. The short time horizon of the model meant that all costs occurred within a few days, meaning that there were no future costs to discount.

Drug costs

Treatment costs for each uterotonic used for prophylaxis are summarised in Table 34. Where a dose range is specified the dose used for costing is assumed to be the upper limit of that range. Drug costs were treated deterministically in the model as the values are based on published prices which are not subject to sampling uncertainty.

Table 34: Drug costs of prophylactic uterotonics

Intervention	Cost	Notes	Source
Carbetocin	£17.64	1x 100mcg dose	BNF, January 2023
Oxytocin ≤ 1 iu	£0.80	1x 5 IU dose Wastage assumed for the rest of the 5 IU ampoule	BNF, January 2023
Oxytocin >1 iu and ≤ 5 iu	£0.80	1x 5 IU dose	BNF, January 2023
Oxytocin >5 iu and ≤ 10 iu	£0.91	1x 10 IU dose	BNF, January 2023
Oxytocin > 10 iu	£2.72	3x 10 IU dose Assumed to be 30 IU as observed in clinical trials	BNF, January 2023
Ergometrine plus oxytocin	£1.57	1x syntometrine (500mcg/5IU)	BNF, January 2023
Misoprostol ≤ 600 mcg	£0.50	3x 200mcg oral tablets	BNF, January 2023
Misoprostol >600 mcg and ≤ 800 mcg	£0.67	4x 200mcg oral tablets	BNF, January 2023
Misoprostol >800 mcg and ≤ 1000 mcg	£0.84	5x 200mcg oral tablets	BNF, January 2023
Misoprostol plus oxytocin	£1.24	2x 200mcg oral misoprostol 1x 10 IU dose oxytocin	BNF, January 2023
Ergometrine	£1.50	1x 500mcg dose	BNF, January 2023
Carboprost	£18.20	1x 250mcg dose	BNF, January 2023

Drug administration costs

Administration costs were informed by clinical opinion and are detailed in Table 35. These costs include staff time only. Misoprostol is assumed to have no administration costs as it is assumed to be given either orally, vaginally or rectally. Based on committee input carbetocin is assumed to be given intravenously in the base case, and all other treatments are given by intramuscular injection for administration costing purposes. A scenario was included in the vaginal birth subgroup where carbetocin was assumed to be given by intramuscular injection.

The cost per working hour for one midwife is assumed to be £51.00 which is the cost for an hour of band 6 nurse time, as reported in the most recently published PSSRU document.

Table 35: Drug administration costs

Route of administration	Staff requirements	Cost
Intravenous slow infusion	2x midwives	£25.50

Route of administration	Staff requirements	Cost
	15 minutes for drawing up, checking, and delivering the drug	
Intramuscular injection	2x midwives 10 minutes for drawing up, checking, and delivering the drug	£17.00

Treatment-related adverse event costs

Adverse event costs are applied to the proportions of women expected to experience the events for each treatment, as detailed in the earlier section. Management of each event is based on that reported in the Gallos 2019 HTA, and all costs have been recalculated with drug costs taken from the BNF (accessed January 2023) and excess bed day costs from the NHS reference costs. The costs applied in the economic model are detailed in Table 36.

Table 36: Adverse event costs

Event	Total cost	Notes[1][2][3]
Nausea	£5.45	2x 50mg injection of cyclizine (£3.45) 2x 4mg injection of ondansetron (£2.00)
Vomiting	£758.75	3x 12.5mg injection prochlorperazine (£1.57) 1x excess bed day (£757.18)
Hypertension	£784.87	200mg labetalol over 24 hours (£27.60) 20mg nifedipine over 24 hours (£0.09) 1x excess bed day (£757.18)
Headache	£1.29	Paracetamol for 24 hours (£0.60) Codeine for 24 hours (£0.69)
Tachycardia	£757.18	1x excess bed day (£757.18)
Hypotension	£757.18	1x excess bed day (£757.18)
Fever	£759.70	Paracetamol (£0.60) Amoxicillin (£1.92) 1x excess bed day (£757.18)
Shivering	£757.18	1x excess bed day (£757.18)
Abdominal pain	£1.76	Paracetamol for 24 hours (£0.60) Ibuprofen for 24 hours (£1.16)

[1]Drug costs are taken from the BNF, accessed in January 2023
[2]Excess bed days are costed as the weighted average of all currency codes related to delivery (normal, assisted, planned caesarean, and emergency caesarean) in the National schedule of NHS reference costs
[3]For drugs where the amount has not been specified the cost of a full pack has been used, taking the least costly pack price from the BNF

Cost of additional uterotonics

Based on clinical input, assumptions were made on which uterotonics could be used as second line. It was assumed that it was not appropriate for single agent or combinations of either misoprostol or ergometrine to be repeated whereas repeat oxytocin can be. The model uses an average cost of all potential second line treatments following each prophylactic uterotonic. The cost associated with second line uterotonics used in the model is summarised in Table 37.

Table 37: Cost of subsequent uterotonics

Uterotonic used as prophylaxis	Cost	Uterotonics included in average
Carbetocin	£3.95	All uterotonics

Uterotonic used as prophylaxis	Cost	Uterotonics included in average
Oxytocin ≤ 1 iu	£3.95	All uterotonics
Oxytocin >1 iu and ≤ 5 iu	£3.95	All uterotonics
Oxytocin >5 iu and ≤ 10 iu	£3.95	All uterotonics
Oxytocin > 10 iu	£3.95	All uterotonics
Ergometrine plus oxytocin	£4.43	All options except ergometrine and syntometrine
Misoprostol ≤ 600 mcg	£5.52	All options except misoprostol
Misoprostol >600 mcg and ≤ 800 mcg	£5.52	All options except misoprostol
Misoprostol >800 mcg and ≤ 1000 mcg	£5.52	All options except misoprostol
Misoprostol plus oxytocin	£5.52	All options except misoprostol
Ergometrine	£4.43	All options except ergometrine and syntometrine
Carboprost	£3.95	All uterotonics

Cost of blood transfusions

The cost of blood transfusions is calculated using the cost per unit, administration cost, and the estimated number of units required. The cost per unit is £153.30 and was taken from the NHS blood and transplant price list 2022/23. The mean number of units was assumed to be two units based on committee clinical opinion and is varied in a gamma distribution with a confidence interval of 1-4 units which allows for rare events where many more units are required. The administration cost is £586.85, taken as the cost of a single plasma exchange or other intravenous blood transfusion as reported in the National schedule of NHS reference costs. The total cost of blood transfusion used in the model is £893.45 and is applied to the proportion of women having this outcome, as reported in the NMA.

Cost of ICU admission

The cost of ICU admission is only applied in scenario analysis due to the limited NMA evidence on this outcome. The cost used in the analysis is £2,303.38 which is the weighted average of all codes for obstetric critical care (Service code CCU12 with currency codes XC02Z, XC03Z, XC04Z, XC05Z, XC06Z, XC07Z) in the National schedule of NHS reference costs.

Cost-effectiveness measure

In general NICE prefers a cost-utility approach in economic analyses, using QALYs to measure the health benefits of an intervention, however other approaches can be used if it is not possible to quantify benefits using QALYs. The Gallos 2019 HTA presented an analysis based on cost per PPH ≥500mL avoided, and noted that QALYs could not be used due to the lack of appropriate utility data in the literature. For this analysis a similar approach was taken, using cost per PPH ≥1000mL avoided, after a non-systematic review of the literature did not identify any utility data for PPH.

The Gallos 2019 HTA detailed a method of considering ICERs based on hard outcomes (i.e., PPH ≥1000mL) against a willingness-to-pay threshold of £30,000 per QALY gained, without having QALYs as an outcome of the analysis. This analysis also uses this approach to aid interpretation of the results for the committee given there isn't an agreed price that the NHS is willing to pay for avoidance of PPH. This analysis uses the ICER and a cost-effectiveness threshold of £20,000 per QALY to calculate how many days in perfect health must be considered acceptable to trade off to avoid one PPH event. An illustrative example of this calculation is given below.

Example:

- Suppose carbetocin is associated with £10 more costs and 0.01 less PPH≥1000mL events than oxytocin and therefore has an ICER of £1,000 per PPH≥1000mL avoided

- First, we divide the ICER by the cost-effectiveness threshold of £20,000 to calculate the QALYs needed in this scenario to justify the incremental cost (£1,000 / £20,000 = 0.05)
- We then calculate the number of "perfect health" days that would need to be traded off to avoid one PPH≥1000mL event i.e. the number of days in full health equivalent to the calculated number of QALYs (0.05 / (1 / 365.25) = 18.26 days)
- Therefore, for carbetocin to be considered cost-effective compared with oxytocin at an ICER of £1,000 per PPH≥1000mL avoided, we must be willing to trade off 18 days in full health to avoid having a PPH≥1000mL.

This calculation is also performed at the £30,000 per QALY threshold to provide a range of trade-off days for each result.

Cost-effectiveness was only based on the PPH≥1000mL event, not the additional outcomes included in the economic model.

Sensitivity analysis

All results are presented using PSA to reflect uncertainty with respect to the precise value of model parameters. This involved running a total of 10,000 Monte Carlo simulations where, with the exception of a small number of deterministic parameters, model inputs are sampled from a probability distribution. In each simulation the total costs and outcomes (PPH ≥1000mL, additional uterotonics, blood transfusions) are calculated for each uterotonic treatment, which are then used to calculate the average total costs and outcomes and subsequently the cost-effectiveness measure using the methods detailed above.

Simulations of relative treatment effectiveness were undertaken using Bayesian Markov chain Monte Carlo (MCMC) simulation, which sampled directly from the joint posterior distribution from the NMAs, thereby maintaining any correlation between them, in the WinBugs® package. The results output (CODA) was then imported into the Microsoft Excel® spreadsheet model. When running the simulations in Excel a random number was used to select a row of data (reflecting a single WinBugs® simulation) so that any correlation between the LORs would be preserved.

In addition to the probabilistic base case and the deterministic results, two scenarios were run around parameters the committee considered important; exclusion of adverse events, and inclusion of ICU admission as an outcome. In the vaginal birth subgroup a scenario was explored assuming that carbetocin is administered by intramuscular injection.

Results

Full population

The results of the base-case analysis in the full population are summarised in Table 38, with absolute costs and numbers of events from the probabilistic analysis presented for each treatment.

As Table 38 shows, carbetocin is considered cost-effective compared with ergometrine plus oxytocin, and would be considered cost-effective compared with oxytocin >1 iu and ≤ 5 iu if we are willing to trade off 79 days in full health to avoid one PPH ≥1000mL.

Table 38: Probabilistic (deterministic)* results, full population

Strategy	Absolute Costs	Total PPH ≥1000mL events	Total additional uterotonics	Total blood transfusions	Incremental costs	PPH ≥1000mL avoided	Additional uterotonics avoided	Blood transfusions avoided	Cost-effectiveness (cost/PPH≥1000mL avoided)
Oxytocin >1 iu and ≤ 5 iu	£274.80 (£274.16)	0.069 (0.069)	0.063 (0.061)	0.008 (0.007)	-	-	-	-	-
Oxytocin >5 iu and ≤ 10 iu	£275.85 (£275.63)	0.070 (0.069)	0.099 (0.097)	0.009 (0.008)	£1.04 (£1.47)	-0.0006 (-0.0007)	-0.0361 (-0.0363)	-0.0011 (-0.0014)	Dominated by oxytocin >1 iu and ≤ 5 iu
Oxytocin ≤ 1 iu	£280.20 (£281.01)	0.122 (0.100)	0.155 (0.121)	0.014 (0.014)	£5.39 (£6.86)	-0.0527 (-0.0308)	-0.0917 (-0.0599)	-0.0067 (-0.0074)	Dominated by oxytocin >1 iu and ≤ 5 iu
Oxytocin > 10 iu	£282.76 (£281.65)	0.099 (0.097)	0.128 (0.125)	0.014 (0.013)	£7.95 (£7.49)	-0.0296 (-0.0287)	-0.0650 (-0.0639)	-0.0063 (-0.0060)	Dominated by oxytocin >1 iu and ≤ 5 iu
Carbetocin	£340.46 (£339.01)	0.054 (0.054)	0.027 (0.026)	0.004 (0.003)	£65.66 (£64.86)	0.0152 (0.0147)	0.0360 (0.0347)	0.0040 (0.0036)	More costly but more effective than oxytocin>1 iu and ≤ 5 iu Cost-effective if willing to trade off 79 days in full health to avoid one PPH ≥1000mL at the £20,000 per QALY threshold or 53 days at the £30,000 per QALY threshold.

Strategy	Absolute Costs	Total PPH ≥1000mL events	Total additional uterotonics	Total blood transfusions	Incremental costs	PPH ≥1000mL avoided	Additional uterotonics avoided	Blood transfusions avoided	Cost-effectiveness (cost/PPH≥1000mL avoided)
Ergometrine plus oxytocin	£380.77 (£390.66)	0.057 (0.057)	0.056 (0.055)	0.007 (0.006)	£40.31 (£51.64)	-0.0032 (-0.0029)	-0.0291 (-0.0287)	-0.0029 (-0.0028)	Dominated by carbetocin

**Deterministic results are given in parentheses for comparison.*

Table 39 and Table 40 summarise the results of the scenarios where adverse events were excluded and ICU events were included, respectively. The scenarios use the deterministic values only.

In the adverse events scenario (Table 39) the absolute costs are significantly lower and ergometrine plus oxytocin is likely to be cost-effective.

In the ICU admissions scenario (Table 40) only oxytocin >5 iu and ≤ 10 iu and carbetocin can be compared, and carbetocin would be considered cost-effective compared with oxytocin if we are willing to trade off 75 days in full health to avoid one PPH≥1000mL.

Table 39: Scenario results, adverse events excluded, full population

Strategy	Absolute Costs	Total PPH ≥1000mL events	Total additional uterotonics	Total blood transfusions	Incremental costs	PPH ≥1000mL avoided	Additional uterotonics avoided	Blood transfusions avoided	Cost-effectiveness (cost/PPH≥1000mL avoided)
Oxytocin >1 iu and ≤ 5 iu	£24.26	0.069	0.061	0.007	-	-	-	-	-
Ergometrine plus oxytocin	£24.35	0.057	0.055	0.006	£0.09	0.0118	0.0060	0.0008	More costly but more effective than oxytocin Cost-effective if willing to trade off 0.14 days in full health to avoid one PPH ≥1000mL at the £20,000 per QALY threshold or 0.09 days at the £30,000 per QALY threshold.
Oxytocin >5 iu and ≤ 10 iu	£25.73	0.069	0.097	0.008	£1.38	-0.0126	-0.0423	-0.0021	Dominated by ergometrine plus oxytocin

Strategy	Absolute Costs	Total PPH ≥1000mL events	Total additional uterotonics	Total blood transfusions	Incremental costs	PPH ≥1000mL avoided	Additional uterotonics avoided	Blood transfusions avoided	Cost-effectiveness (cost/PPH≥1000mL avoided)
Oxytocin ≤ 1 iu	£31.12	0.100	0.121	0.014	£6.77	-0.0427	-0.0659	-0.0082	Dominated by ergometrine plus oxytocin
Oxytocin > 10 iu	£31.75	0.097	0.125	0.013	£7.40	-0.0405	-0.0699	-0.0067	Dominated by ergometrine plus oxytocin
Carbetocin	£46.28	0.054	0.026	0.003	£21.93	0.0029	0.0287	0.0028	More costly but more effective than ergometrine plus oxytocin Cost-effective if willing to trade off 138 days in full health to avoid one PPH ≥1000mL at the £20,000 per QALY threshold or 92 days at the £30,000 per QALY threshold.

Table 40: Scenario results, ICU admission events included, full population

Strategy	Absolute Costs	Total PPH ≥1000mL events	Total additional uterotonics	Total blood transfusions	Incremental costs	PPH ≥1000mL avoided	Additional uterotonics avoided	Blood transfusions avoided	Cost-effectiveness (cost/PPH≥1000mL avoided)
Oxytocin >5 iu and ≤ 10 iu	£280.07	0.069	0.097	0.008	-	-	-	-	-
Carbetocin	£343.69	0.054	0.026	0.003	£63.62	0.0155	0.0710	0.0049	More costly but more effective than oxytocin Cost-effective if

Strategy	Absolute Costs	Total PPH ≥1000mL events	Total additional uterotonics	Total blood transfusions	Incremental costs	PPH ≥1000mL avoided	Additional uterotonics avoided	Blood transfusions avoided	Cost-effectiveness (cost/PPH≥1000mL avoided)
									willing to trade off 75 days in full health to avoid one PPH ≥1000mL at the £20,000 per QALY threshold or 50 days at the £30,000 per QALY threshold.

Vaginal birth subgroup

The results of the base-case analysis in the vaginal birth subgroup are summarised in Table 41, with absolute costs and numbers of events from the probabilistic analysis presented for each treatment.

The results in Table 41 suggest that oxytocin >5 iu and ≤ 10 iu was the most cost-effective option, and oxytocin plus ergometrine was more costly and more effective but would be cost-effective if we are willing to trade off 91 days in full health to avoid one PPH ≥1000mL.

Table 41: Probabilistic (deterministic)* results, vaginal birth subgroup

Strategy	Absolute Costs	Total PPH ≥1000mL events	Total additional uterotonics	Total blood transfusions	Incremental costs	PPH ≥1000mL avoided	Additional uterotonics avoided	Blood transfusions avoided	Cost-effectiveness (cost/PPH≥1000mL avoided)
Oxytocin >5 iu and ≤ 10 iu	£141.28 (£141.14)	0.070 (0.069)	0.104 (0.103)	0.008 (0.007)	-	-	-	-	-
Oxytocin >1 iu and ≤ 5 iu	£142.78 (£141.88)	0.069 (0.069)	0.095 (0.092)	0.009 (0.008)	£1.50 (£0.75)	0.0013 (0.0009)	0.0092 (0.0101)	-0.0015 (-0.0010)	More costly and marginally more effective than oxytocin >5 iu and ≤ 10 iu Cost-effective if willing to trade off 21 days in full health to

Strategy	Absolute Costs	Total PPH ≥1000mL events	Total additional uterotonics	Total blood transfusions	Incremental costs	PPH ≥1000mL avoided	Additional uterotonics avoided	Blood transfusions avoided	Cost-effectiveness (cost/PPH≥1000mL avoided)
									avoid one PPH ≥1000mL at the £20,000 per QALY threshold or 14 days at the £30,000 per QALY threshold.
Oxytocin > 10 iu	£144.80 (£143.74)	0.100 (0.093)	0.150 (0.142)	0.009 (0.008)	£2.02 (£1.85)	-0.0309 (-0.0244)	-0.0548 (-0.0500)	-0.0001 (0.0003)	Dominated by oxytocin >1 iu and ≤ 5 iu
Oxytocin ≤ 1 iu	£148.10 (£147.81)	0.130 (0.104)	0.235 (0.235)	0.014 (0.014)	£5.32 (£5.93)	-0.0609 (-0.0357)	-0.1397 (-0.1425)	-0.0052 (-0.0060)	Dominated by oxytocin >1 iu and ≤ 5 iu
Ergometrine plus oxytocin	£202.14 (£218.62)	0.058 (0.058)	0.065 (0.063)	0.007 (0.007)	£59.36 (£76.73)	0.0109 (0.011)	0.0306 (0.0295)	0.0023 (0.0018)	More costly and more effective than oxytocin >5 iu and ≤ 10 iu Cost-effective if willing to trade off 91 days in full health to avoid one PPH ≥1000mL at the £20,000 per QALY threshold or 60 days at the £30,000 per QALY threshold. Dominant over carbetocin in PSA
Carbetocin	£210.03 (£209.70)	0.061 (0.059)	0.043 (0.041)	0.007 (0.007)	£7.89 (-£8.91)	-0.0026 (-0.0019)	0.0215 (0.0215)	-0.0005 (-0.0003)	Dominated (on PPH ≥1000mL) by ergometrine plus oxytocin in PSA

**Deterministic results are given in parentheses for comparison.*

Table 42 and Table 43 summarise the results of the scenarios where adverse events were excluded and ICU events were included, respectively. The scenarios use the deterministic values only.

In the adverse events scenario (Table 42) the absolute costs are significantly lower and ergometrine plus oxytocin is dominant over all other strategies.

In the ICU admissions scenario (Table 43) only oxytocin >5 iu and ≤ 10 iu and carbetocin can be compared, and carbetocin would be considered cost-effective compared with oxytocin if we are willing to trade off 125 days in full health to avoid one PPH≥1000mL.

Table 42: Scenario results, adverse events excluded, vaginal birth subgroup

Strategy	Absolute Costs	Total PPH ≥1000mL events	Total additional uterotonics	Total blood transfusions	Incremental costs	PPH ≥1000mL avoided	Additional uterotonics avoided	Blood transfusions avoided	Cost-effectiveness (cost/PPH≥1000mL avoided)
Ergometrine plus oxytocin	£24.72	0.058	0.063	0.007	-	-	-	-	-
Oxytocin >5 iu and ≤ 10 iu	£24.89	0.069	0.103	0.007	£0.17	0.0119	0.0396	0.0008	Dominated by ergometrine plus oxytocin
Oxytocin >1 iu and ≤ 5 iu	£25.64	0.069	0.092	0.008	£0.92	0.0110	0.0295	0.0018	Dominated by ergometrine plus oxytocin
Oxytocin > 10 iu	£27.49	0.093	0.142	0.008	£2.77	0.0354	0.0794	0.0015	Dominated by ergometrine plus oxytocin
Oxytocin ≤ 1 iu	£31.57	0.104	0.235	0.014	£6.85	0.0467	0.1720	0.0078	Dominated by ergometrine plus oxytocin
Carbetocin*	£49.40*	0.059	0.041	0.007	£24.68	0.0019	-0.0215	0.0003	Dominated by ergometrine plus oxytocin

**When intramuscular injection costs rather than intravenous costs are used for carbetocin administration the only change to results here is that the total cost is reduced to £40.90 for carbetocin.*

Table 43: Scenario results, ICU admission events included, vaginal birth subgroup

Strategy	Absolute Costs	Total PPH ≥1000mL events	Total additional uterotonics	Total blood transfusions	Incremental costs	PPH ≥1000mL avoided	Additional uterotonics avoided	Blood transfusions avoided	Cost-effectiveness (cost/PPH≥1000mL avoided)
Oxytocin >5 iu and ≤ 10 iu	£145.19	0.069	0.103	0.007	-	-	-	-	-
Carbetocin	£213.96	0.059	0.041	0.007	£68.76	0.0100	0.0611	0.0005	More costly but more effective than oxytocin Cost-effective if willing to trade off 125 days in full health to avoid one PPH ≥1000mL at the £20,000 per QALY threshold or 84 days at the £30,000 per QALY threshold.

Table 44 summarises the results of the scenario where intramuscular injection costs are used for carbetocin administration. In this scenario carbetocin became slightly less costly than oxytocin plus ergometrine, but remained more costly and more effective than any dose of oxytocin, and could be considered cost-effective compared with oxytocin >1 iu and ≤ 5 iu if we are willing to trade off 79 days in full health to avoid one PPH ≥1000mL.

Table 44: Scenario results, intramuscular carbetocin, vaginal birth subgroup

Strategy	Absolute Costs	Total PPH ≥1000mL events	Total additional uterotonics	Total blood transfusions	Incremental costs	PPH ≥1000mL avoided	Additional uterotonics avoided	Blood transfusions avoided	Cost-effectiveness (cost/PPH≥1000mL avoided)
Oxytocin >5 iu and ≤ 10 iu	£141.14	0.069	0.103	0.007	-	-	-	-	-
Oxytocin >1 iu and ≤ 5 iu	£141.88	0.069	0.092	0.008	£0.75	-0.0009	-0.0101	0.0010	More costly and more effective than oxytocin >5 iu and ≤

Strategy	Absolute Costs	Total PPH ≥1000mL events	Total additional uterotonics	Total blood transfusions	Incremental costs	PPH ≥1000mL avoided	Additional uterotonics avoided	Blood transfusions avoided	Cost-effectiveness (cost/PPH≥1000mL avoided)
									10 iu Cost-effective if willing to trade off 15 days in full health to avoid one PPH ≥1000mL at the £20,000 per QALY threshold or 10 days at the £30,000 per QALY threshold.
Oxytocin > 10 iu	£143.74	0.093	0.142	0.008	£1.85	0.0244	0.0398	0.0007	Dominated by oxytocin >1 iu and ≤ 5 iu
Oxytocin ≤ 1 iu	£147.81	0.104	0.235	0.014	£5.93	0.0357	0.1324	0.0070	Dominated by oxytocin >1 iu and ≤ 5 iu
Carbetocin	£201.20	0.059	0.041	0.007	£59.32	-0.0091	-0.0611	-0.0005	More costly and more effective than oxytocin >1 iu and ≤ 5 iu Cost-effective if willing to trade off 119 days in full health to avoid one PPH ≥1000mL at the £20,000 per QALY threshold or 79 days at the £30,000 per QALY threshold.
Ergometrine plus oxytocin	£218.62	0.058	0.063	0.007	£17.41	-0.0019	-0.0396	-0.0008	More costly and more effective than carbetocin Cost-effective if

Strategy	Absolute Costs	Total PPH ≥1000mL events	Total additional uterotonics	Total blood transfusions	Incremental costs	PPH ≥1000mL avoided	Additional uterotonics avoided	Blood transfusions avoided	Cost-effectiveness (cost/PPH≥1000mL avoided)
									willing to trade off 169 days in full health to avoid one PPH ≥1000mL at the £20,000 per QALY threshold or 113 days at the £30,000 per QALY threshold.

Caesarean birth subgroup

The results of the base-case analysis in the caesarean birth subgroup are summarised in Table 45, with absolute costs and numbers of events from the probabilistic analysis presented for each treatment.

The results in Table 45 indicate that carbetocin is the most cost-effective option of the uterotonics as carbetocin was more costly but more effective than oxytocin >1 iu and ≤ 5 iu, and dominant over other oxytocin doses and oxytocin plus ergometrine. Using the cost-effectiveness measure described, carbetocin would be considered cost effective compared with oxytocin if we are willing to trade off 17 days in full health to avoid one PPH ≥1000mL.

Table 45: Probabilistic (deterministic)* results, caesarean birth subgroup

Strategy	Absolute Costs	Total PPH ≥1000mL events	Total additional uterotonics	Total blood transfusions	Incremental costs	PPH ≥1000mL avoided	Additional uterotonics avoided	Blood transfusions avoided	Cost-effectiveness (cost/PPH≥1000mL avoided)
Oxytocin >1 iu and ≤ 5 iu	£464.42 (£446.45)	0.072 (0.068)	0.489 (0.430)	0.068 (0.049)	-	-	-	-	-
Carbetocin	£487.65 (£488.40)	0.048 (0.048)	0.354 (0.275)	0.021 (0.021)	£23.24 (£41.95)	0.0244 (0.0197)	0.1344 (0.1551)	0.0464 (0.0273)	More costly and more effective than oxytocin >1 iu and ≤ 5 iu Cost-effective if willing to trade off 17

Strategy	Absolute Costs	Total PPH ≥1000mL events	Total additional uterotonics	Total blood transfusions	Incremental costs	PPH ≥1000mL avoided	Additional uterotonics avoided	Blood transfusions avoided	Cost-effectiveness (cost/PPH≥1000mL avoided)
									days in full health to avoid one PPH ≥1000mL at the £20,000 per QALY threshold or 12 days at the £30,000 per QALY threshold.
Oxytocin > 10 iu	£535.16 (£522.60)	0.123 (0.119)	0.703 (0.696)	0.145 (0.130)	£47.51 (£34.20)	-0.0749 (-0.0713)	-0.3492 (-0.4206)	-0.1237 (-0.1092)	Dominated by carbetocin
Oxytocin >5 iu and ≤ 10 iu	£587.68 (£576.75)	0.073 (0.069)	0.726 (0.723)	0.208 (0.193)	£100.03 (£88.34)	-0.0252 (-0.0215)	-0.3718 (-0.4482)	-0.1863 (-0.1717)	Dominated by carbetocin
Ergometrine plus oxytocin	£615.50 (£591.26)	0.071 (0.066)	0.553 (0.510)	0.063 (0.035)	£127.85 (£102.86)	-0.0228 (-0.0178)	-0.1990 (-0.2346)	-0.0415 (-0.0142)	Dominated by carbetocin

**Deterministic results are given in parentheses for comparison.*

Table 46 summarises the results of the scenario analysis where adverse events were excluded. The scenario uses the deterministic values only.

In the adverse events scenario (Table 46) all oxytocin doses are dominated, and carbetocin would be considered cost-effective compared with ergometrine plus oxytocin if we are willing to trade off 11 healthy days to avoid one PPH≥1000mL.

Table 46: Scenario results, adverse events excluded, caesarean birth subgroup

Strategy	Absolute Costs	Total PPH ≥1000mL events	Total additional uterotonics	Total blood transfusions	Incremental costs	PPH ≥1000mL avoided	Additional uterotonics avoided	Blood transfusions avoided	Cost-effectiveness (cost/PPH≥1000mL avoided)
Ergometrine plus oxytocin	£52.55	0.066	0.510	0.035	-	-	-	-	-
Oxytocin >1 iu and ≤ 5 iu	£62.90	0.068	0.430	0.049	£10.35	-0.0019	0.0795	-0.0131	Dominated by ergometrine plus oxytocin
Carbetocin	£63.24	0.048	0.275	0.021	£10.69	0.0178	0.2346	0.0142	More costly and more effective than ergometrine plus

Strategy	Absolute Costs	Total PPH ≥1000mL events	Total additional uterotonics	Total blood transfusions	Incremental costs	PPH ≥1000mL avoided	Additional uterotonics avoided	Blood transfusions avoided	Cost-effectiveness (cost/PPH≥1000mL avoided)
									oxytocin Cost-effective if willing to trade off 11 days in full health to avoid one PPH ≥1000mL at the £20,000 per QALY threshold or 7 days at the £30,000 per QALY threshold.
Oxytocin > 10 iu	£139.05	0.119	0.696	0.130	£75.81	-0.0713	-0.4206	-0.1092	Dominated by carbetocin
Oxytocin >5 iu and ≤ 10 iu	£193.20	0.069	0.723	0.193	£129.96	-0.0215	-0.4482	-0.1717	Dominated by carbetocin

Conclusion

In the full population, the model indicated that carbetocin is considered cost-effective compared with ergometrine plus oxytocin and would be considered cost-effective compared with oxytocin >1 iu and ≤ 5 iu if we are willing to trade off 79 days in full health to avoid one PPH ≥1000mL. In the scenario where adverse events are excluded, oxytocin plus ergometrine is likely to be the most cost-effective, as compared with oxytocin we would only need to be willing to trade off 0.14 days in full health to avoid one PPH ≥1000mL.

In the base-case model for the vaginal birth subgroup there was evidence suggesting that oxytocin >5 iu and ≤ 10 iu was the most cost-effective option, and oxytocin plus ergometrine was more costly and more effective but would be cost-effective if we are willing to trade off 91 days in full health to avoid one PPH ≥1000mL. Oxytocin >1 iu and ≤ 5 iu was more costly and marginally more effective than the >5 iu and ≤ 10 iu dose range, and would be considered cost-effective compared with this dose if we are willing to trade off 21 days in full health to avoid one PPH ≥1000mL. If adverse events are excluded from the analysis then oxytocin plus ergometrine becomes likely to be the most cost-effective option, being less costly and more effective than the other strategies. Carbetocin is not likely to be considered cost-effective for the vaginal birth subgroup.

There was strong evidence in the caesarean birth subgroup suggesting carbetocin to be the most cost-effective option of the uterotonics. Carbetocin was more costly but more effective than oxytocin >1 iu and ≤ 5 iu, and dominant over other oxytocin doses and oxytocin plus ergometrine. Using the cost-effectiveness measure described, carbetocin would be considered cost effective compared with oxytocin if we are willing to trade off 17 days in full health to avoid one PPH ≥1000mL.