Economic Evaluation of Carbetocin as Prophylaxis for Postpartum Hemorrhage in the Philippines

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Abstract

**Background:** Cost-effectiveness and budget impact of carbetocin was evaluated as an alternative to oxytocin for postpartum hemorrhage (PPH) prophylaxis in the Philippines.

**Methods:** A model-based economic evaluation was employed to assess cost-effectiveness of carbetocin compared to oxytocin for PPH. Population of interest were women undergoing either vaginal delivery (VD) or cesarean section (CS) in a public hospital setting with costs and outcomes evaluated in six weeks. Cost-utility was analyzed using a government and societal perspectives while the budget impact was determined using a third party payer’s perspective. Incremental Cost Effectiveness Ratio (ICER) was evaluated using the set threshold in the country of 150,000 PhP per QALY gained.

**Results:** Carbetocin was not cost-effective in the Philippines. Deterministic results in a government perspective for CS was at 724,081 PhP while for VD was over 2 million PhP. Deterministic and probabilistic results in the societal perspective for CS and VD were near these respective ICER values and did not also favor carbetocin use. Moreover, the treatment effects of carbetocin in reference to oxytocin were identified as the most sensitive parameter used. On budget impact, if 50% of deliveries would switch to carbetocin for the fiscal years assessed, additional incremental cumulative costs of 1.08 billion PhP for VD and 1.86 billion PhP for CS would be needed.

**Conclusion:** The incremental benefit of carbetocin does not justify the additional costs incurred from purchasing the drug given a Philippine context. Price reduction of carbetocin is recommended if the drug would be publicly reimbursed in the country.

**Background**

Postpartum hemorrhage (PPH) is defined as blood loss of more than 500 mL in vaginal delivery (VD) or more than 1000 mL in cesarean section (CS) \(^1-^3\). It remains as the leading cause of maternal morbidity and mortality worldwide, accounting for 13% maternal deaths in developed countries and 28% of maternal deaths in developing countries, further disproportionately affecting those in the world’s poorest countries \(^4,^5\). In the Philippines, 114 deaths per 100,000 live births was registered for 2015 – a far cry from the target of 52 deaths per 100,000 live births\(^6\) – in which 30% are associated
with PPH.

PPH is frequently unpredictable as it occurs without identifiable risk factors hence, strategies such as administration of prophylactic uterotonics, specifically one dose of oxytocin, is recommended by the World Health Organization (WHO) to prevent PPH.\(^7^ \&^8\) Carbetocin, a synthetic analogue of oxytocin, is an alternative to oxytocin as it has a longer duration of action thereby reduces need for additional doses \([\text{RR (95\% CI)}: 0.48 (0.34-0.68)]\) \(^5^ \&^7^ \&^9\). It is also as clinically effective in PPH prevention \([\text{PPH } \geq 500 \text{mL, RR (95\% CI)}: 0.75 (0.58-0.98)]\)\(^5\) with comparable side effect profile. Moreover, a new formulation of carbetocin stable under room temperature has been developed to adapt in hot and humid climates such as in the Philippines\(^10\).

While therapeutic efficacy favors carbetocin, price difference between the two drugs \((\text{carbetocin: }933 \text{ PhP}^{10} \text{ vs oxytocin: }11.05 \text{ PhP}^{11})\) raises the question if purchase would represent value for money, especially in a low-middle income country (LMIC) where its economic efficiency has not yet been examined\(^11^ \&^12\). A systematic review of economic evaluations (EE)\(^13\) suggested cost-effectiveness for CS \((\text{e.g. Colombia}^{14}, \text{Ecuador}^{15}, \text{Malaysia}^{16}, \text{Peru}^{17} \text{ and UK}^{18})\), while it was not cost-effective for VD in Colombia\(^14\). However, the systematic review also rated the quality of evidence low, due to uncertainties around costs, other input variables and incomplete description of methods\(^13\).

Therefore, this study was performed to assess cost-utility of carbetocin compared with oxytocin as prophylaxis for PPH and the budget impact if carbetocin would be included in the public reimbursement list in the Philippines. The study could serve as a reference guide for practice guidelines in choosing a uterotonic, especially that carbetocin is recently recommended by WHO as a prophylactic uterotonic of choice, but only in countries where its cost would be comparable to other effective uterotonics\(^19\).

Methods
A model-based economic evaluation was conducted to assess cost-effectiveness of carbetocin \((100 \mu g)\) against oxytocin \((10 \text{ IU})\) as an alternative prophylaxis for PPH in women giving birth in VD and CS in a public hospital setting. A separate decision tree for women in VD and CS was used. For cost-utility
analysis, outcome of interest was ICER (PhP per QALY gained) against a 1 GDP per capita at 150,000 PhP threshold and was evaluated in government and societal perspectives. Discount rate was not applied since costs and utility were evaluated only over a period of six weeks. Additionally, budget impact for five fiscal years was also evaluated (2020-2024) if carbetocin would be included in the public reimbursement list in a third party payer’s perspective.

**Model structure**

The decision tree was based from previous economic evaluations\(^{14, 15, 17, 18, 20, 21}\), review of clinical practice guidelines and consultation from clinical experts in the Philippines. In the model, women can either go through VD or CS (Figure 1). Each model begins when patient would receive a prophylactic dose of either oxytocin or carbetocin. Despite initial dose, patient may still experience uterine atony and would require additional uterotonic doses, therefore used as treatment. If the treatment dose would not suffice, a series of conservative management – such as blood transfusion – would be done. In rare cases, patient may still not respond and in such circumstances, radical invasive surgical procedure such as hysterectomy would be performed.

**Model assumptions**

It is important to note that country differences in the approach for treating PPH was carried through the model. With this, the following hypothetical scenarios were assumed: (1) The model only takes into account PPH caused by uterine atony alone; (2) only immediate PPH or event that occurs within 24 hours of delivery was considered; (3) patients in the treatment stage would receive oxytocin/carbetocin only; (4) patients experiencing PPH would have blood transfusion; (5) PPH episode would have no implications on long-term health care costs since the disease is acute.

**Treatment effects**

We referred to the network meta-analysis by Gallos and colleagues\(^5\) for the clinical efficacy following the definition of PPH for amount of blood loss for each mode of delivery. Probabilities for outcomes additional uterotonics and blood transfusion were derived from the same meta-analysis using absolute probabilities relative to oxytocin as the control arm. Meanwhile, for outcomes hysterectomy
and maternal deaths, incidence data was used from a global survey conducted by the WHO using Philippine country data from seven health facilities\textsuperscript{22}. Remarkably, incidence for hysterectomy and death at discharge were equal from the crude data. Further, incidence was assumed same for VD and CS since data was not disaggregated for the modes of delivery (Table 1).

Table 1. Input values used in the analysis

| Parameters                          | Values | Standard error | Distribution | Source                        |
|-------------------------------------|--------|----------------|--------------|-------------------------------|
| **Cesarean section**               |        |                |              |                               |
| Effect size of carbetocin as prophylaxis (PPH\textgeq 1000 mL) | 0.62   | 0.23           | lognormal    | Meta-analysis\textsuperscript{5} |
| Probability of CS needing treatment dose | 0.2318 | 0.0119         | beta         | Meta-analysis\textsuperscript{5} |
| Probability of CS needing blood transfusion | 0.0287 | 0.0390         | beta         | Meta-analysis\textsuperscript{5} |
| Probability of CS needing hysterectomy | 0.0013 | 0.0003         | beta         | Global survey\textsuperscript{22} |
| Probability of maternal deaths     | 0.0013 | 0.0003         | beta         | Global survey\textsuperscript{22} |
| Utility in CS, no complications    | 0.83   | 0.02           | beta         | EQ-5D-5L, Thailand            |
| Utility in CS, with PPH episode    | 0.67   | 0.15           | beta         | EQ-5D-5L, Thailand            |
| Utility in CS, with hysterectomy   | 0.50   | -              | beta         | Visual analogue scale, expert advise\textsuperscript{23} |
| **Vaginal delivery**               |        |                |              |                               |
| Effect size of carbetocin as prophylaxis (PPH\textgeq 500 mL) | 0.67   | 0.12           | lognormal    | Meta-analysis\textsuperscript{5} |
| Probability of VD needing treatment dose | 0.1067 | 0.0025         | beta         | Meta-analysis\textsuperscript{5} |
| Probability VD needing blood transfusion | 0.0134 | 0.0153         | beta         | Meta-analysis\textsuperscript{5} |
| Probability of VD needing hysterectomy | 0.013  | 0.0003         | beta         | Global survey\textsuperscript{22} |
| Probability of maternal deaths     | 0.0013 | 0.0003         | beta         | Global survey\textsuperscript{22} |
| Utility in VD, no complications    | 0.85   | 0.01           | beta         | EQ-5D-5L, Thailand            |
| Utility in VD, with PPH episode    | 0.78   | 0.03           | beta         | EQ-5D-5L, Thailand            |

PPH: Postpartum hemorrhage, CS: Cesarean section, VD: Vaginal delivery

Cost inputs

The average cost of service in VD and CS who may or may not experience PPH-related complications were derived from a separate unpublished study based from hospital-billing records of patients who gave birth in 2018 at Dr. Jose Fabella Memorial Hospital (DJFMH) - a tertiary level birthing hospital in Manila, Philippines with approximately 15,000 deliveries annually.

There were limited patients who underwent hysterectomy following childbirth delivery for the year
2018. Thus, same cost for hysterectomy regardless mode of delivery was considered. Given a scenario of trial of labor for VD, if the patient would go through severe bleeding and would need hysterectomy, she would undergo CS section eventually and considered as an emergency CS patient. Then, it would be justified to assume cost similar in hysterectomy for VD or CS.

To calculate cost in a governmental perspective, direct medical cost (DMC) was identified as costs shouldered by hospital (provider) and fee-for-service reimbursed by Philhealth (payer) – or the total inpatient cost. For a societal perspective, the following were considered: (1) DMC: inpatient cost and out-of-pocket expenses; (2) direct non-medical cost: meals and transportation costs; (3) indirect cost: caregiver’s absenteeism cost computed as a missed day work plus one day of outpatient visit (Table 2).

**Table 2. Costs summary for each mode of delivery (average cost in PhP)**

| Cost categories | Prophylaxis | Additional treatment dose | Blood transfusion | Hysterectomy |
|-----------------|-------------|--------------------------|-------------------|--------------|
| **Cesarean section** |             |                          |                   |              |
| Inpatient cost  | 21,922      | 23,195                   | 27,994            | 48,061       |
| OOP             | 1,130       | 894                      | 2,309             | 3,100        |
| Transportation  | 652         | 928                      | 1,051             | 1,164        |
| Food            | 1,064       | 1,412                    | 1,775             | 1,575        |
| IC due to absenteeism | 7,228    | 12,484                   | 14,419            | 10,948       |
| **Vaginal delivery** |             |                          |                   |              |
| Inpatient cost  | 8,754       | 8,985                    | 14,879            | 48,061       |
| OOP             | 843         | 903                      | 1,959             | 3,100        |
| Transportation  | 597         | 662                      | 1,185             | 1,164        |
| Food            | 1,205       | 1,221                    | 1,399             | 1,575        |
| IC due to absenteeism | 7,644    | 7,676                    | 7,915             | 10,948       |

Cost items included inpatient fees such as drug, medical supplies, laboratory, procedure and other miscellaneous costs, professional fees and room charges. However, carbetocin is not available in the hospital formulary and in order to reflect cost associated with use, price of one dose of oxytocin (11 PhP) was subtracted from the total inpatient cost was replaced with one dose of carbetocin (933 PhP). Only one dose replacement was considered for all decision nodes since carbetocin is intended for single use administration only 24.

Costs were calculated as cost-at-charge and converted to Philippine Consumer Price Index (CPI) for 2019. The Ethics Committee of DJFMH approved this study prior to retrieval of hospital charges (REC-2019-004 ver. 1). Hospital costing data was coded appropriately to protect confidentiality of the patient.
**Utility values**

We adopted health utility values of Thai women who gave birth through VD or CS from an on-going study in Siriraj Hospital, Mahidol University – Bangkok’s largest tertiary and quaternary-care hospital. EQ-5D-5L was used in this study to derive utility weights \(^{25}\). Patients where prophylactic only dose and needing uterotonic treatment dose were assigned with utilities of VD or CS without complications (Table I). Those who needed blood transfusion were assigned with utilities of VD or CS with PPH episode.

The study was conducted after approval of the Institutional Review Board (IRB) of Siriraj Hospital (COA. No. Si 128/2019). Permission from the EuroQoL group was granted before using the EQ-5D-5L questionnaire (Registration ID: L-29103). Written informed consent was obtained before conducting the interview and information gathered were appropriately coded to protect the identity of the patient.

For utility weight associated with hysterectomy, we referred to a study in Israel where they determined utility values for patients who underwent cesarean section following hysterectomy \(^{23}\).

**Uncertainty analysis**

One-way sensitivity analysis was performed to determine which of the parameters (i.e. efficacy, transition probability, costs and utility weights) would cause greatest variation in ICER. Standard errors were computed from relative probabilities. Where no standard errors for probabilities were provided in literature estimates, they were calculated as 20% of the mean. For unreported 95% confidence intervals (CI), these were assumed as ±10% of the mean. A threshold analysis was also done to determine the price at which the drug is cost effective for VD and CS at 150,000 PhP threshold in a government’s perspective.

The effect of multiple parameter uncertainties on ICER was also explored by probabilistic sensitivity analysis (PSA) using Monte Carlo simulation with 1,000 iterations and illustrated through the cost effectiveness plane. Analyses performed used costs incurred in a societal perspective. Microsoft Excel 2013© was used to enter and process data for all the analyses.
**Budget impact analysis (BIA)**

BIA was evaluated using a third party payer’s perspective for fiscal years 2020-2024 using the same Excel-based model for CUA. Patients who would receive prophylactic uterotonic was assumed as the total registered births in hospitals. The latest report by Philippine Statistics Office was for 2017 with a total registered 1,700,618 live births. Since the number of registered live births declined by five percent from 2012-2017 - a one percent decline from the previous year’s live births was assumed to calculate eligible population\(^{26}\). Moreover, proportion of patients attended by health professionals (93.3% for 2017) and proportion of mode of delivery (19%, CS) was applied\(^{27}\). With this, total patients likely to give birth in VD and CS was predicted for 2020-2024.

For cost inputs, we only considered costs incurred by Philhealth, which is the entity that reimburses fee-for-services or case rates as commonly known in the country. The published case rates for 2017 were used as the input values for costs\(^{28}\). In addition, we considered a scenario of a 50-50 product uptake of oxytocin and carbetocin. In reality, product uptake between the two interventions evaluated would vary yearly. However, we assume a constant 50-50 product uptake for each to reflect on budget impact, if one is chosen over the other.

**Results**

**Cost-effectiveness analysis**

For deterministic results, ICER of carbetocin versus oxytocin in CS resulted at 724,081 PHP per QALY gained using government perspective with a lower ICER at 613,282 PHP for a societal perspective. For results of probabilistic analysis, ICER was at 644,808 PHP per QALY gained. In VD, ICER results were over 2 million per QALY gained in all scenarios tested. Regardless the mode of delivery and all the scenarios tested, ICER values were over than the presumed 1 GDP threshold at 150,000 PhP (Table 3).

**Table 3.** Summary of ICER results (ICER in PhP/QALY gained)
| Cesarean section | Deterministic; Societal | Probabilistic; Societal |
|------------------|-------------------------|-------------------------|
| Total cost       | Total QALY | Total cost | Total QALY | Total cost | Total QALY |
| Cesarean section | 23,050       | 0.82761    | 28,712      | 0.82761    | 28,760      | 0.82797 |
| Oxytocin         | 22,260       | 0.82652    | 28,043      | 0.82652    | 28,077      | 0.82697 |
| Mean difference  | 790          | 0.001091   | 669         | 0.001091   | 683         | 0.001000 |
| ICER per QALY gained | 724,081     | 613,282    | 683,103     |

| Vaginal delivery | Deterministic; Societal | Probabilistic; Societal |
|------------------|-------------------------|-------------------------|
| Total cost       | Total QALY | Total cost | Total QALY | Total cost | Total QALY |
| Vaginal delivery | 9,450       | 0.84541    | 15,086      | 0.84541    | 15,107      | 0.84535 |
| Oxytocin         | 8,540       | 0.84498    | 14,183      | 0.84498    | 14,202      | 0.84494 |
| Mean difference  | 909         | 0.000435   | 902         | 0.000435   | 906         | 0.000405 |
| ICER per QALY gained | 2,088,691   | 2,072,491  | 2,235,909   |

**Uncertainty analysis**

Based on one-way sensitivity analysis results, the tornado diagram presents ten parameters which influence the ICER values the most for VD and CS (Figure 2). In VD, effective size of carbetocin over oxytocin for PPH ≥ 500 mL had the most influence in ICER with over 250% change in range followed by utility in VD (23%) then cost of carbetocin (21%). Almost the same parameters were observed to influence ICER in CS. ICER in CS was most sensitive to effective size of carbetocin over oxytocin for PPH ≥1000 mL in CS delivery with 370% change followed by utility in CS following PPH (53%), then probability in CS following blood transfusion (49%).

According to PSA results shown in a cost-effectiveness plane, cross marks indicate simulations for oxytocin while dots are for carbetocin (Figure 2). In the uncertainty analysis, 49.5% and 55% of the scenarios fell on the two quadrants on the right hand of the plane for VD and CS, respectively. For the cost-effectiveness acceptability curve, it was only analyzed for CS population since the ICER values derived from VD was too high. At 3 GDP threshold (3 GDP = 450,000 PhP), the probability of carbetocin to be cost effective is at 25%. At around 900,000 PhP ceiling ratio, the probability of carbetocin to be cost effective would be equal to oxytocin. With an ICER threshold at 150,000 PhP in the Philippines (1 GDP), carbetocin would be cost effective if the price were lowered from the current price offered at 933 PhP to 428 PhP for CS, and 96 PhP for VD.

**Budget impact analysis**

At the current listed price of carbetocin, inclusion of carbetocin would require an additional budget of 184 million PhP for VD and 318 million PhP for CS for 2020 if half of the assumed births would receive...
carbetocin instead of oxytocin. Almost 1.08 billion PhP for VD and 1.86 billion PhP for CS would be needed for the implementation for the five fiscal years estimated when compared to costs if oxytocin only were used (Table 4).

Table 4. BIA results: Scenario: 50-50 treatment mix (in PhP)

| Year  | Cesarean section | Vaginal delivery |
|-------|-----------------|-----------------|
|       | Oxytocin        | Carbetocin      | Incremental cost | Oxytocin | Carbetocin | Incremental cost |
| 2020  | 2,512,634,250   | 2,695,352,486   | 318,128,124      | 2,538,014,394 | 2,722,578,269 | 184,563,875 |
| 2021  | 2,574,570,684   | 2,761,792,925   | 314,946,842      | 2,512,634,250 | 2,695,352,486 | 182,718,236 |
| 2022  | 2,638,033,852   | 2,829,871,120   | 311,797,374      | 2,487,507,907 | 2,668,398,961 | 180,891,054 |
| 2023  | 2,703,061,386   | 2,899,627,443   | 308,679,400      | 2,462,632,828 | 2,641,714,971 | 179,082,143 |
| 2024  | 2,769,691,849   | 2,971,103,260   | 305,592,606      | 2,438,006,500 | 2,615,297,822 | 177,291,322 |

Discussion

Although carbetocin reduces incidence of PPH-related complications, our results did not reflect an economic advantage of carbetocin over oxytocin. We employed several scenarios such as evaluation using governmental and societal perspectives through deterministic and probabilistic analysis, all of which did not favor carbetocin use in both VD and CS delivery.

Results of analysis in Colombia also found carbetocin not cost-effective in VD population. On another hand, our study had contrasting results compared to other published studies when CS population is considered. Carbetocin was consistently cost-effective for use in CS population on studies in a high-income country such as UK and upper-middle income countries such as Malaysia, Peru, Colombia and Ecuador. The difference between our results could be attributed with the difference in input values for costs – cost of treatment for PPH-related complications is low from the data we retrieved.

It is important to note that the estimated cost adopted in this study was rather conservative. Input for cost was from a government hospital that caters to the most underprivileged population in the country. Government facilities are mandated to implement the No Balance Billing policy which subsidizes inpatient costs not covered by the fee-for-services reimbursed by social health insurance provider, Philhealth, given that patients would be eligible. This was reflected with the retrieved data since out-of-pocket expenses for all the health states evaluated were less than 5% – mainly from patients who did not satisfy eligibility criteria for subsidy. Considering that Philippines has a high
proportion of private hospitals of around 60%, the costs derived from the reference would be entirely
different if costs were also determined in a private facility. Additionally, hospital charge in a public
hospital is significantly lower compared to private health care facilities in the country. Nevertheless,
since the aim of this study is to inform coverage decisions, using input for costs incurred in publicly
managed and funded institution would be permissible.
Regarding utility values, we adopted this from Thai population as there was no study available in the
country. It could be argued that utility values of Filipinas and Thai women would be different as there
is higher prevalence of PPH in the country. If anything, even if the lower confidence values of the
utility values were used in the analysis as illustrated in the tornado diagram, the drug would still not
be cost-effective.
Among the parameters, relative treatment effects of carbetocin in outcomes leading to blood loss of
\( \geq 500 \text{ mL in VD; } \geq 1000 \text{ mL in CS} \) were found to be a major cause of uncertainty in our analysis.
There are several reasons for the uncertainty: (1) several methods used to quantify blood loss among
the pooled studies; (2) different oxytocin doses used as a prophylaxis among studies pooled – some
used intravenous bolus plus an infusion of any dose, some used an intravenous infusion only of any
dose. Albeit uncertainties, point estimates would still be a reasonable guide on the relative treatment
effects of carbetocin for these outcomes.
For threshold analysis on carbetocin cost, a substantial decrease would be necessary for cost-
effectiveness – from the current listed price at 933 PhP to 427 PhP for CS, and 96 PhP for VD at
150,000 PhP threshold. This suggested price maybe a drastic reduction however attainable, since the
manufacturer has offered the new heat-stable formulation of carbetocin at 0.31 USD (approximately
16.12 PhP) in LMICs, specifically in public healthcare facilities. This would favor carbetocin use
regardless of the mode of delivery.
On the budget impact analyses, results illustrate that there is no financial advantage of carbetocin
over oxytocin. Given that the projected cumulative 5-year budget impact at around 1.08 billion PhP
for VD and 1.86 billion PhP for CS, carbetocin use in the public sector should be re-evaluated and
carefully considered.
This is the first cost-effectiveness study on carbetocin in a LMIC context. Actual cost of events was incorporate using the Philippine context, where costs were derived in the largest public maternity hospital. However, we reiterate the lack actual costs associated with carbetocin use - a parameter we had no choice but to estimate since it was just recently included in the national formulary. Another constraint is the absence of epidemiological data on some health states, which were addressed through sensitivity analysis. Side-effects were not accounted as well. Ultimately, the results of this study remain reasonable within our context and highly relevant in other LMICs.

Conclusion
Overall, the results of this study suggest that carbetocin would not be a cost-effective choice in PPH prevention in the Philippines for both modes of delivery. Moreover, given that the projected cumulative 5-year budget impact at around 1.08 billion PhP for VD and 1.86 billion PhP for CS, carbetocin use in the public setting should be re-evaluated. Nonetheless, cost-effectiveness is beyond efficiency concerns. Given a possible intervention to address maternal morbidities, further work must be done. It is highly desirable to lower the price of carbetocin for use in a publicly-funded healthcare system, particularly in an LMIC where the drug would have greater impact. Limiting use in cases such as patients with risk factors for PPH such as age and emergency CS patients may also be sensible as they may gain the most from the intervention. Furthermore, effective treatment is not always available in all settings, particularly when there are delays in referral such as in community hospital setting where prophylactic regimens would be useful. These scenarios were not analyzed given the limited available literature. Once data is made available, future research could adopt this model using parameters in their respective settings. Although, one should note that prophylactic uterotonic is only one component of PPH prevention and would not work if other obstetric care components were not improved.

Declarations

Ethical approval and consent to participate
Hospital billing charges were gathered after the approval of the Ethics Committee of Dr. Jose Fabella Memorial Hospital - Manila, Philippines (REC-2019-004 ver. 1). Written consent was waived since the
billing charges were gathered retrospectively and patients were not interviewed. For health utility scores, these was gathered after approval of the Institutional Review Board (IRB) of Siriraj Hospital – Bangkok, Thailand (COA. No. Si 128/2019) where written consent was obtained before administering the EQ-5D-5L questionnaire.

Consent for publication

Not applicable

Availability of data and materials

Cost and health utility data generated and analyzed during this study are available from the corresponding author on a reasonable request. Other parameters used in the economic model are cited accordingly.

Competing interests

The authors declare that they have no competing interests.

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Author’s contribution

JRB performed the research, collected and analyzed data and drafted manuscript. UC designed the research, validated and interpreted data, as well as drafted manuscript. PT and MT interpreted clinical and utility data and drafted manuscript. All authors have agreed and approved the author’s contribution and final manuscript.

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Figures
Figure 1
Decision tree for the cost utility analysis