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CLINICAL ARTICLE

Obstetrics

Intrapartum use of sildenafil citrate to prevent fetal compromise and emergency operative birth in term pregnancies in the United Kingdom and Australia: A preliminary cost-effectiveness analysis

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Abstract

Objective: To compare cost-effectiveness of oral sildenafil citrate, administered after onset of labor, with standard care to health system funders in the UK and Australia.

Methods: We conducted a modeled cost-effectiveness analysis, measuring costs and quality adjusted life years (QALYs), using a decision-analytic model covering onset of labor to 1 month post-birth. The relative risk of emergency cesarean section and operative vaginal birth was taken from a Phase 2 placebo controlled double blinded randomized control trial.

Results: Both options of care resulted in the same QALYs gained over the model time period (0.08). Sildenafil citrate was cost-saving compared with standard care, saving £92 per birth in the UK (AU$303 per birth in Australia). Sensitivity analyses did not identify any areas of uncertainty that stopped sildenafil citrate being cost saving compared with standard care. Threshold analysis revealed that sildenafil citrate would be cost saving up to a per birth drug or administration cost of £152.32 in the UK (AU$333.61 in Australia).

Conclusion: Oral sildenafil citrate may be cost saving compared with standard care; however, the effects on neonatal outcomes still need to be demonstrated in large randomized trials.

KEYWORDS
cesarean section, cost–benefit analysis, decision-support techniques, economic evaluation, fetal distress, operative birth, value-based health care

1 | INTRODUCTION

Worldwide cesarean section rates have increased from an average of 7% in 1990 to 21% in 2021.[1] In many high income countries and some middle income countries, cesarean rates are often much higher than this global average.[2] In the UK, rates of cesarean section have risen from 25% in 2009, to 31% in 2019.[3] whilst in Australia, this has increased from 32% to 36% over the same

time period.[4] If cesarean sections continue at the current rate, this mode of birth may be the norm for almost one in two of all Australian babies by 2030.[1] In light of this and concerns regarding adverse health and economic consequences following operative birth,[5] there is increasing recognition that prevention of avoidable cesarean births is important, provided it does not increase rates of adverse neonatal or maternal outcome.[6]

Although intrapartum fetal compromise ("fetal distress") is a frequent indication for emergency cesarean section[7] identification of infants at risk is difficult.[8] Low et al. showed that 63% of cases of birth asphyxia occurred in women with no antepartum risk factors, and that these pregnancies accounted for 40% of cases of moderate or severe asphyxia.[9] Fetal distress is usually the result of placental impairment,[10] and the reduced capacity of the fetus to cope with reduction in uterine blood flow during contractions.[11]

Sildenafil citrate (SC) a phosphodiesterase-5 inhibitor and potent vasodilator, is utilized for the treatment of erectile dysfunction in males[12] and severe pulmonary arterial hypertension in adults, neonates and children. It has also been used in pregnancy and has a good safety profile.[13] In a recent Phase 2 double-blind, placebo-controlled randomized controlled trial (RCT)[14] SC reduced the relative risk of operative vaginal birth for fetal compromise (RR 0.49, 95% CI: 0.33–0.73) and the relative risk of emergency cesarean section for fetal compromise of 0.50 (95% CI: 0.28–0.89), compared to placebo.[14]

Based on these preliminary data in 300 women,[14] SC may be a promising preventive treatment for intrapartum fetal compromise, although larger Phase 3 trials are required to evaluate its effects on neonatal and maternal outcome. However, before SC can become a part of routine care, evidence of safety, efficacy and cost-effectiveness would be required, particularly in health systems such as the UK and Australia where demonstration of cost-effectiveness and affordability is a requirement for public subsidization of pharmaceuticals. Therefore, the aim of the present study was to make a preliminary estimate of the cost-effectiveness of intrapartum oral SC if utilized as part of routine labor management, based upon the results produced in the Phase 2 RCT. This cost-effectiveness was measured by assessing differences in costs and outcomes (measured using quality adjusted life years [QALYs]), and the incremental cost per quality adjusted life year (QALY) gained for intrapartum oral SC compared to standard care.

2 | MATERIALS AND METHODS

We conducted a modeled cost-effectiveness analysis to compare the costs and QALYs from SC and standard care, and the incremental cost per QALY gained for SC compared to standard care. To do this, we constructed a decision-analytic model covering onset of labor to 1 month post-birth. The relative risk of emergency cesarean section and operative vaginal birth was taken from a Phase 2 placebo controlled double blinded randomized control trial.[14]

2.1 | The intervention and population of interest

The intervention to be modeled was SC administered orally as a 50 mg dose at 8-h intervals, to a maximum of three doses in women aged 18–50 years, with a singleton pregnancy, cephalic presentation, planning a vaginal birth at more than >37 + 0 weeks gestation. Women with more than one previous cesarean section are not a part of the target population. We have reported the analysis in line with the Consolidated Health Economics Evaluation Reporting Standards (CHEERS),[15] and designed our study in line with best-practice recommendations.[16]

2.2 | Description of the model and structure

The model is designed as a decision analysis tree, to compare use of SC with current standard care from the health system funder's perspective. Microsimulation modeling was utilized to simulate events and characteristics of birth, and neonatal care. The model covers the onset of labor to 1 month post-birth, and as it is less than 1 year in length no discounting was applied. The model was developed with the TreeAgePro software package (TreeAge Software Inc.).

The abbreviated structure of the model is shown in Figure 1, with only the standard care arm expanded; however, both arms have the same structure. The model commences after the onset of labor (either spontaneous or induction), which is when SC would be administered. Birth outcomes would be either vaginal birth without instruments (normal vaginal birth), operative vaginal birth (vacuum or forceps) for fetal distress, operative vaginal birth for other reasons, emergency cesarean section for fetal distress, or emergency cesarean section for other reasons. The neonate could then be admitted with the mother as a standard postnatal ward inpatient, to the special care nursery (SCN), neonatal intensive care unit (NICU) or be stillborn. Finally, outcomes for liveborn neonates could either be discharge home or neonatal death (≤28 days) before discharge. These transitions all occur within the one cycle of the model.

2.3 | Transition probabilities

To populate the model, measures of likelihood from a whole-of-population linked administrative dataset containing all births in Queensland, Australia between July 1, 2012 and June 31, 2018[17] were utilized. The dataset was limited to women who matched the population of interest, described above ($n = 285\,929$). The transition probabilities generated and utilized in the model are shown in Table 1. For the intervention arm, the relative risk identified from the RIDSTRESS trial[14] of operative birth by vacuum or forceps for fetal compromise (RR 0.49, 95% CI: 0.33–0.73); and a relative risk of emergency cesarean section for fetal compromise (0.50, 95% CI: 0.28–0.89) was applied to the transition probabilities.

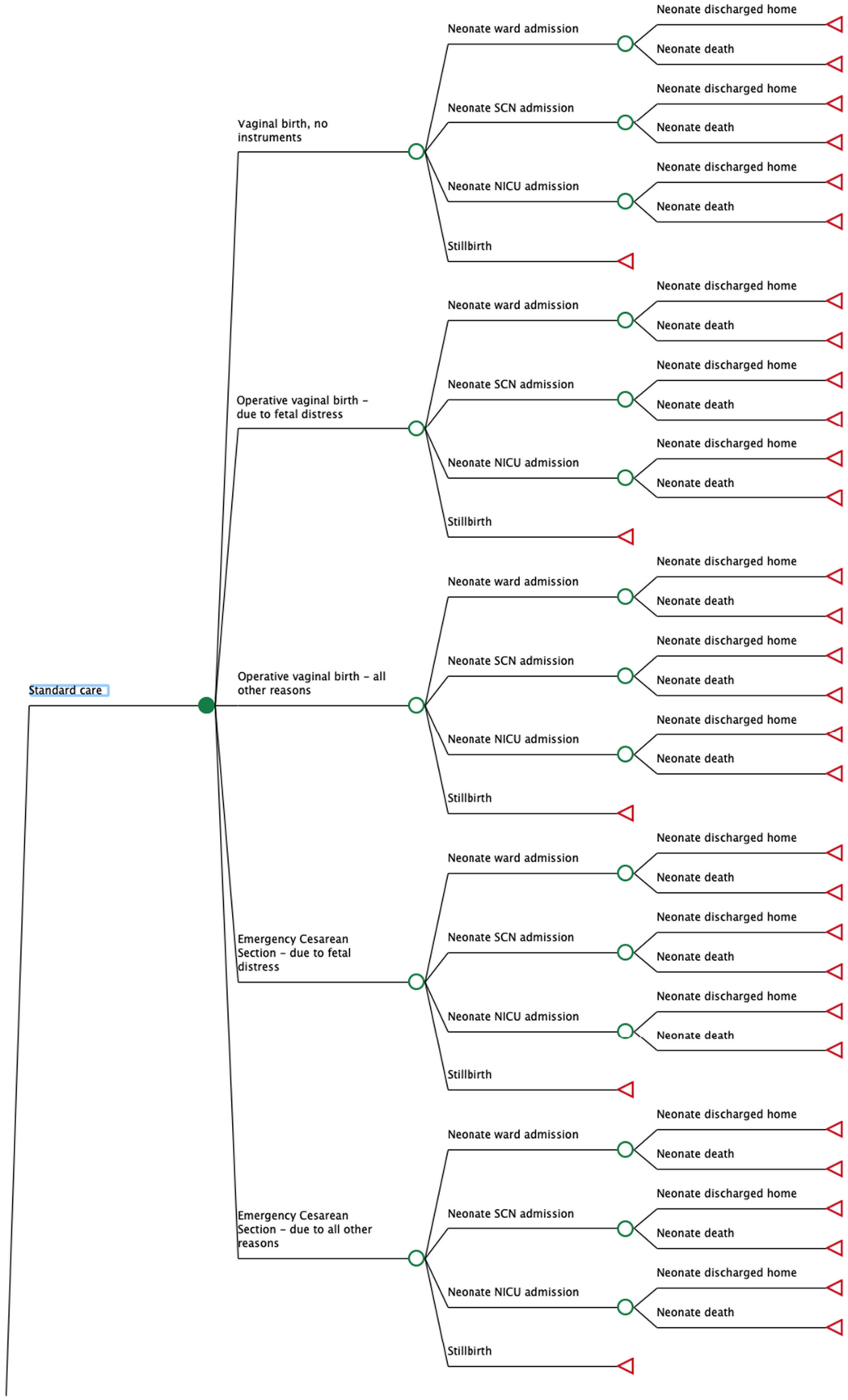

FIGURE 1 Structure of decision analysis tree used to identify cost-effectiveness of Sildenafil citrate compared to standard care. NICU, neonatal intensive care unit; SCN, special care nursery.

TABLE 1 Transition probabilities utilized in the model.

Transition		
Original state	**Subsequent state**	***P* value**
Labor commences (start of model)	Vaginal birth without instruments	0.7298
	Operative birth by vacuum or forceps for fetal distress	0.0694
	Operative birth by vacuum or forceps for all other reasons	0.0672
	Emergency cesarean section for fetal distress	0.0418
	Emergency cesarean section for all other reasons	0.0918
Vaginal birth without instruments	Neonate postnatal ward admission	0.9139
	SCN	0.0802
	NICU	0.0049
	Stillbirth	0.0010
Operative vaginal birth—any reason	Neonate postnatal ward admission	0.8117
	SCN	0.1771
	NICU	0.0106
	Stillbirth	0.0005
Emergency cesarean section for fetal distress	Neonate postnatal ward admission	0.7356
	SCN	0.2398
	NICU	0.0243
	Stillbirth	0.0003
Emergency cesarean section for all other reasons	Neonate postnatal ward admission	0.8004
	SCN	0.1888
	NICU	0.0104
	Stillbirth	0.0004
Neonate admission	Discharged home	0.9998
	Death	0.0002
SCN	Discharged home	0.9981
	Death	0.0019
NICU	Discharged home	0.9871
	Death	0.0129

Abbreviations: NICU, neonatal intensive care unit; SCN, special care nursery.

TABLE 2 Data inputs for utilities in the model.

State	Utility weight	Source
Inpatient admission	1	
SCN	0.94	Carroll & Downs (2009)[18]
NICU	0.87	Carroll & Downs (2009)[18]
Death	0	

Abbreviations: NICU, neonatal intensive care unit; SCN, special care nursery.

TABLE 3 Data inputs for costs.

Model state	UK: Cost per event (£)	Australia: Cost per event (AU$)
Vaginal birth	£2852	$5136
Operative birth	£4314	$6983
Emergency cesarean section	£5937	$13 287
Neonate inpatient admission	£1416	$3858
SCN admission	£2606	$8483
NICU admission	£29 913	$73 485
Sildenafil citrate, per birth	£59	$28.72

Abbreviations: NICU, neonatal intensive care unit; SCN, special care nursery.

2.4 | Utilities

The effectiveness outcome of interest was quality adjusted life years (QALYs) gained. A utility weight for neonates in each health state was assigned, drawn from the literature. As shown in Table 2, it is assumed that when the baby is unborn, when they are born and an inpatient with the mother (with or without the mother) they are in perfect health (a utility weight of 1). A utility weight of 0.94 and 0.87 were applied to SCN and NICU admission, respectively.[18] It was assumed that the model length was 1 month, and utilities adjusted accordingly to produce QALYs.

2.5 | Costs

Costs are associated with discrete intrapartum events: vaginal birth, operative birth, emergency cesarean section, inpatient admission, SCN and NICU admission (Table 3). Costs for the UK were drawn from the 2019/20 National Cost Collection data; Australian cost data was derived from the equivalent National Hospital Cost Data Collection. These are annual costing estimates produced from hospital costing across the UK and Australia, used as part of hospital financing activities.

The cost of the intervention was limited to costs of drug purchase, as it is expected that oral administration would occur as part of routine care when women are admitted to the labor ward for labor and birth. For the base case, cost per dose was based upon the National Health Service Drug Tariff for the UK, and the Dispensed Price Per Maximum Quantity for SC on the Pharmaceutical Benefits Advisory Committee (as it would be expected that if the drug was used as a part of routine care in Australia, then this price would be utilized). The maximum quantity at this price is four. All costs are presented in 2021 pounds for the UK, and Australian dollars, after adjusting for inflation.

2.6 | Analysis

Our analysis was focused on measuring cost, outcomes (as measured by QALYs) and cost-effectiveness based the incremental cost per QALY gained SC and standard care. The incremental cost per QALY gained represents the incremental cost effectiveness ratio (ICER), and is the difference between the costs of SC and standard care, as a ratio to the difference in QALYs produced by SC and standard care as follows:

$$\text{ICER} = \frac{\left(\text{Cost}_{\text{Sildenafil citrate}} - \text{Cost}_{\text{Standard care}}\right)}{\left(\text{QALYs}_{\text{Sildenafil citrate}} - \text{QALYS}_{\text{Standard care}}\right)}.$$

This was calculated using Monte Carlo simulation with 10000 trials. The number of cesarean sections for any reason and for fetal distress, operative births for any reason and due to fetal distress, SCN admissions, NICU admissions, and vaginal births per 10000 was also reported. All results are reported separately for the UK and Australia. To test the sensitivity of the model we undertook bootstrapping with 1000 samples, and one-way sensitivity analysis to test the impact of different background probabilities of cesarean section for fetal distress, operative birth by vacuum or forceps for fetal distress, and cost of cesarean section and operative birth. We also undertook a threshold analysis to test the maximum cost of the intervention (drug purchase costs and any administration costs) for yielding cost-savings.

Analysis was conducted using SAS9.4 and TreeAge Healthcare Pro 2022. Significance was set at 0.05.

Ethics approval for the administrative data utilized in the model was received from the Townsville Hospital and Health Services Human Research Ethics Committee (HREC) (HREC/16/QTHS/223), and the Australian Institute of Health and Welfare HREC (EO2017-1-338). Consent was not directly obtained, and a waiver of consent was granted under the Public Health Act (RD007377).

3 | RESULTS

Table 4 shows the outcomes that were produced with each option. There was no difference detected in QALYs between SC and standard care. However, routine use of SC is expected to produce 224 less cesarean section births per 10000 women treated; 367 less operative births, 70 SCN fewer admissions and seven fewer NICU admissions. It is also expected to produce an additional 591 unassisted vaginal births per 10000 women treated. When assessing only costs, SC was cost-saving compared to standard care, producing savings of £92 and $303 for the UK and Australia, respectively.

The results of the bootstrapping to illustrate uncertainty in the distribution of costs and outcomes is shown in Figure 2 (for the UK) and Figure 3 (for Australia). Each point in the figures represents a pair of incremental costs and QALYs and the ellipse the 95% confidence intervals. These show a high level of certainty that SC is cost saving compared to standard care, with only a small incremental QALY effect (a difference of less than 0.009). Multiple one-way sensitivity analyses tested the effects of different assumptions on cost-effectiveness, with all thresholds tested (Table 5) resulting in SC remaining cost-saving compared to standard care. Greater cost-savings would be seen in populations with higher rates of cesarean or operative vaginal birth due to fetal distress. Price threshold analysis revealed that SC would remain lower cost up to an intervention cost (SC drug purchase price and any administration costs) of £152 in the UK, and $334 in Australia.

4 | DISCUSSION

Our preliminary cost-effectiveness analysis indicates that SC is potentially cost saving compared to standard care in a UK and Australian population, with a saving of £92 per birth in the UK, and $303 per birth in Australia. Health outcomes as measured in QALYs were similar; however, for every 10000 women treated with SC, there would be 224 fewer cesarean sections and 367 fewer operative births, as well as 70 fewer SCN admissions and seven fewer NICU admissions as a result of the cesarean sections avoided. Threshold analysis indicated that SC would continue to be cost saving up to an additional cost per woman treated of £152 in the UK, and $334 in Australia.

The strength of the present study is the use of a large population-based dataset to generate the probabilities for our model. The use of this dataset allowed us to exactly match the transition probabilities to the population that SC would be used in in practice. Although these data related to Australia, not the UK, our one-way sensitivity analyses were able to demonstrate that our conclusions regarding

TABLE 4 Costs for the UK and Australia and effects of modeled use of sildenafil citrate compared to standard care.

	Sildenafil citrate	Standard care	Difference (sildenafil citrate compared to standard care)
Cost per birth, mean (SD)	UK: £5080 (2277) Australia: $10 931 (5712)	UK: £5172 (2448) Australia: $11 233 (6135)	UK: −£92 Australia: −$303
QALYs, mean (SD)	0.08 (0)	0.08 (0)	0
Cesarean section—any reason, number per 10 000	1146	1370	−224
Cesarean section—for fetal distress, number per 10 000	217	441	−224
Operative vaginal births by vacuum or forceps—for any reason, number per 10 000	1005	1372	−367
Operative vaginal births by vacuum or forceps—due to fetal distress, number per 10 000	310	705	−674
SCN admission, number per 10 000	993	1063	−70
NICU admission, number per 10 000	48	55	−7
Vaginal birth, unassisted, number per 10 000	7849	7258	591

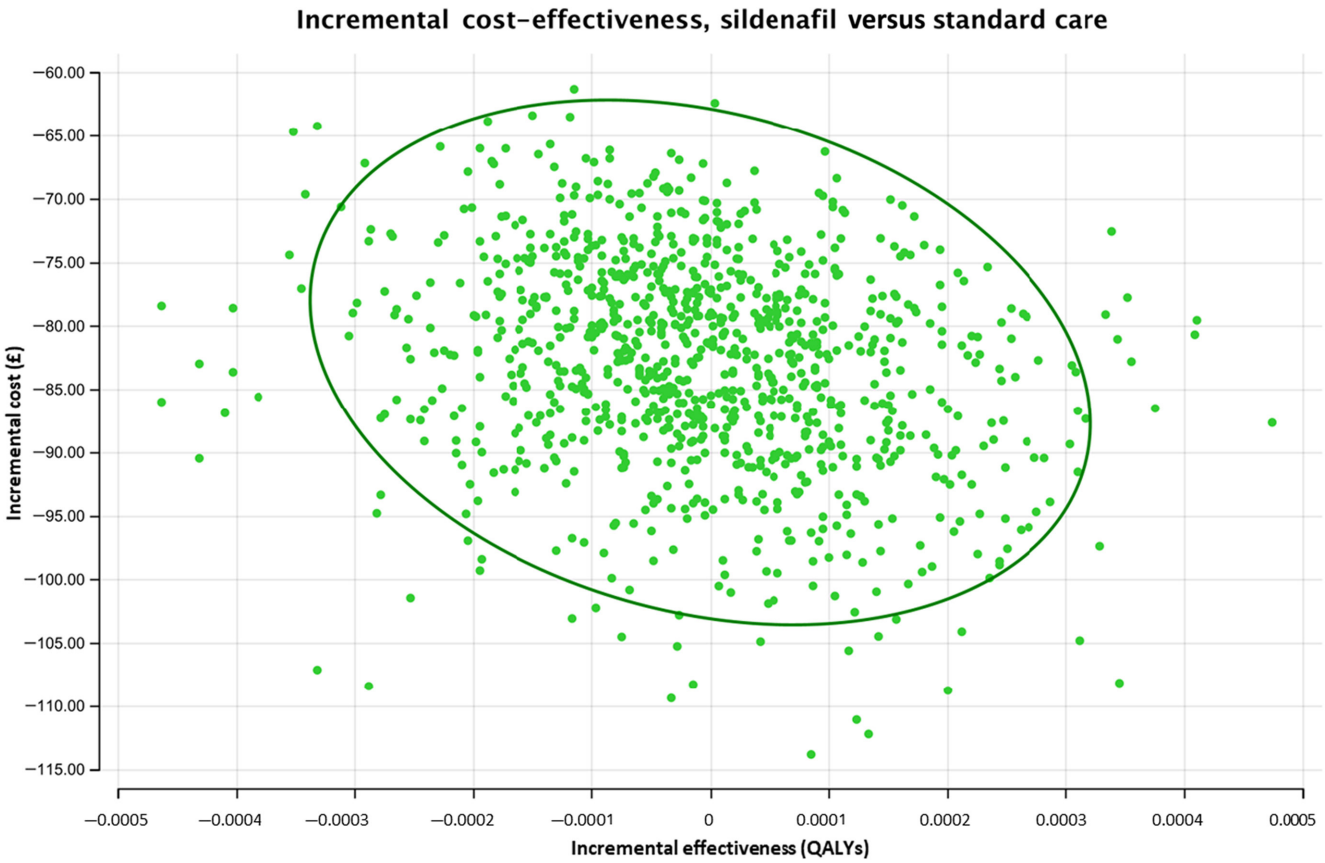

FIGURE 2 Cost effectiveness plane for sildenafil compared to standard care in the United Kingdom. Costs in 2021 GB Pounds.

the cost savings of SC would be unchanged even with different background probabilities for cesarean section and operative birth.

A key limitation is that this cost effectiveness analysis is based on outcomes from a Phase 2 randomized controlled trial in only 300 Australian women,[14] that only captured outcomes related to mode of birth and not including neonatal outcomes nor longer term maternal and infant or childhood sequelae. As such, for the cost-effectiveness analysis we have only demonstrated preliminary cost-effectiveness, with further analysis required to include health impacts of SC relevant to maternal, infant or childhood outcomes, including NICU

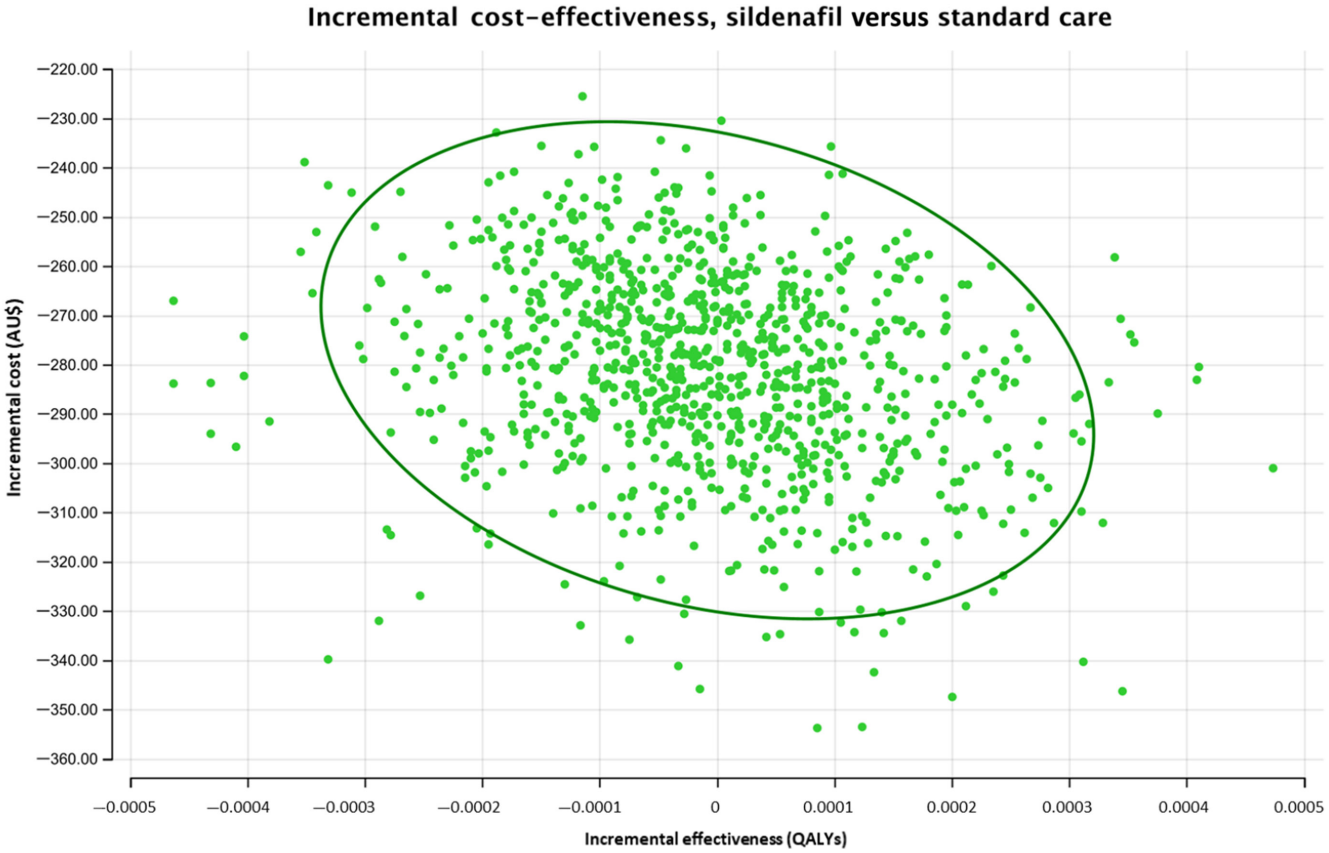

FIGURE 3 Cost effectiveness plane for sildenafil compared to standard care in Australia. Costs in 2021 Australian dollars.

admission. Clinically, it is essential to determine the direct effect of SC on neonatal outcomes, as SC has not been routinely utilized in pregnancy and as such the safety in this population needs to be fully determined. However, if SC improves neonatal outcomes in the short- and long-term, it may prove more cost-saving than has been identified in this study. A Phase 3 clinical trial has been planned to test the effect of SC on neonatal outcomes.[19] Furthermore, we also did not capture any of the longer-term savings associated with reduction in primary cesarean section. Given the increased risk of subsequent cesarean section and adverse outcomes in subsequent pregnancies such as preterm birth,[5] avoiding a primary cesarean section may confer additional cost-savings for women in subsequent pregnancies.[20]

The high rates of cesarean section in high and middle income countries[2] have led to rising concerns of short and long-term maternal and offspring consequences. However, there are surprisingly few clinical interventions tested in randomized controlled trials for safely reducing operative birth rates. The ARRIVE trial[21] demonstrated a 16% reduction in the risk of cesarean section of (RR 0.84, 95% CI: 0.76–0.93) for women undergoing routine induction of labor at 39 weeks compared to expectant management whilst a Cochrane Review[22] showed that active management of labor also reduced the risk of cesarean section (RR 0.77, 95% CI: 0.63–0.94).[22] However, in the ARRIVE trial only 25% of eligible women consented to being enrolled, raising questions about acceptability for routine induction

TABLE 5 One-way sensitivity analysis showing effect on incremental costs for use of sildenafil citrate compared to standard care.

Variable	Value	Incremental cost per birth (sildenafil citrate compared to standard care), UK (Australia)
Probability of CS for fetal distress (base case: 0.0418)	0.1	£211 ($610)
	0.2	£388 ($1097)
	0.3	£582 ($1630)
	0.4	£779 ($2160)
	0.5	£928 ($2545)
Probability of operative vaginal birth for fetal distress (base case: 0.0694)	0.1	£123 ($347)
	0.2	£207 ($475)
	0.3	£301 ($631)
	0.4	£375 ($740)
	0.5	£460 ($870)
Cost of cesarean section	−50%	£1 ($139)
	−25%	£40 ($206)
	+25%	£80 ($341)
	+50%	£160 ($408)
Cost of operative vaginal birth (base case: $7586)	−50%	£19 ($156)
	−25%	£29 ($211)
	+25%	£124 ($322)
	+50%	£172 ($376)

of labor in low risk women. As such, SC might be an important component of efforts to reduce overall cesarean section rates.

There is also an ongoing clinical need for safe and acceptable interventions to reduce the likelihood of intrapartum fetal compromise.[23] Fetal distress is associated with intrapartum stillbirth and significant morbidity for the neonate, including hypoxic ischaemic encephalopathy, and cerebral palsy.[24,25] This is a global health issue across high, middle and low income countries.[26] Whilst some indicators of fetal distress have been identified, including low fetal cerebroplacental ratio on ultrasound[27] and low prelabor levels of placental growth factor,[28] neither are good enough predictors for this outcome. As such, there remains an unmet need for interventions in this area, which SC may fill.

Whilst there is an urgent clinical need for interventions to safely improve outcomes for women and infants, such interventions also need to demonstrate cost-effectiveness. The public funding systems of many countries, including the UK and Australia, require new interventions to demonstrate cost-effectiveness. Previous studies have demonstrated the cost-effectiveness of induction of labor.[29] To our knowledge, this is the first economic evaluation for the intrapartum use of SC.

SC was found to be cost-effective compared to standard care. SC resulted in fewer cesarean section and operative births, SCN and NICU admissions, and was overall cost-saving in UK and Australian populations. SC might be an important clinical intervention to reduce the need for cesarean section and reduce fetal distress, but information from much larger Phase 3 trials including evaluating its effects on neonatal and maternal outcomes is required before it can be recommended as part of routine care.

AUTHOR CONTRIBUTIONS

Emily J. Callander designed and conducted the cost-effectiveness analysis and drafted the manuscript. Sailesh Kumar, William Tarnow-Mordi, Rachael Morton provided input to the study design and interpretation of the results. All authors contributed to the drafting of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT

Research data are not shared.

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