Late pregnancy ultrasound to screen for and manage potential birth complications in nulliparous women: a cost-effectiveness and value of information analysis

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Concise description:

Late-pregnancy screening is unlikely to be cost-effective, but a rapid presentation-only scan may be. The evidence is uncertain but an RCT is not warranted.

Highlights:

- Foetal growth restriction is a major risk factor for stillbirth. A routine late pregnancy ultrasound scan could detect this, as well as other anomalies such as breech presentation.
- Evidence of effect is scarce, but an RCT powered to detect stillbirth would be extremely large and expensive. It is wise to predict the return on investment from research to ensure the maximum benefit from finite resources.
- Current evidence suggests universal late pregnancy ultrasound scans would not be cost-effective in the UK setting. However, a rapid 'presentation-only' scan may be. An RCT powered to detect stillbirth would not be a value for money investment.

Abstract

Background: Foetal growth restriction (FGR) is a major risk factor for stillbirth. A routine late-pregnancy ultrasound scan could help detect this allowing intervention to reduce the risk of stillbirth. Such a scan could also detect foetal presentation and predict macrosomia. A trial powered to detect stillbirth differences would be extremely large and expensive. It is therefore critical to know whether this would be a good investment of public research funds.

Objective: To estimate the cost-effectiveness of various late-pregnancy screening and management strategies based on current information, and predict the return on investment from further research.

Methods: Synthesis of current evidence structured into a decision model reporting expected costs, QALYs and net benefit over 20 years and value-of-information analysis reporting predicted return on investment from future clinical trials.

Results: Given a willingness to pay of £20,000 per QALY gained, the most cost-effective strategy is a routine presentation-only scan for all women. Universal ultrasound screening for foetal size is unlikely to be cost-effective. Research exploring the cost implications of induction of labour has the greatest predicted return on investment. A randomised controlled trial with an endpoint of stillbirth is extremely unlikely to be a value for money investment.

Conclusion: Given current UK value-for-money thresholds, the most cost-effective strategy is to offer all pregnant women a presentation-only scan in late pregnancy. A randomised controlled trial of screening and intervention to reduce the risk of stillbirth following universal ultrasound to detect macrosomia or FGR is unlikely to represent a value for money investment.

Introduction

Complications of pregnancy, both to mother and baby, are a major determinant of the Global Burden of Disease.[1] Stillbirth, defined as the baby born dead at 24 weeks gestational age or later, is a major contributor to this: there were a total of 2689 stillbirths in England and Wales in 2018, equating to approximately 0.4% of all births.[2] Foetal growth restriction (FGR) is where the baby fails to achieve its genetically determined growth potential, and is a major risk factor for stillbirth.[3] It is possible that offering a routine ultrasound scan to every mother in late pregnancy (around 36 weeks gestational age) could help detect FGR, allowing intervention to reduce the risk of stillbirth. Furthermore, an ultrasound scan has the potential to detect other conditions which place the pregnancy at risk such as macrosomia (birthweight >4kg) and foetal presentation (cephalic or breech).

Under current guidelines in England and the rest of the UK,[4 5] an ultrasound scan after 28 weeks is offered only where clinically indicated, e.g. relevant medical history, or concerns following clinical examination. An alternative approach is to offer an ultrasound scan to all late-stage pregnancies. This would be expected to identify more pregnancies in need of intervention. However, this could also increase false positive diagnoses leading to unnecessary, and possibly harmful, intervention. The overall balance of risk to harm to foetal health, and whether such a screening programme would represent the best use of health care resources is unknown, and the need to evaluate this has been highlighted previously.[6-8]

A Cochrane review (searching to August 2014) of routine ultrasound in late-stage pregnancy concluded that there was insufficient evidence to recommend universal screening.[9] However, none of the 13 trials studied screening followed by an intervention, the different trials applied different definitions of screen positive and performed assessments at different gestational ages, and even the meta-analysis was underpowered for plausible estimates of diagnostic and interventional effectiveness.[10]

The key pieces of information that can be obtained from a scan around 36 weeks are whether the fetus measures small or large for gestational age (SGA or LGA, defined as foetal size in the 1st or 10th decile of the distribution respectively), and whether the fetus is in a cephalic (head down) presentation. An SGA fetus may be suffering FGR and hence be at increased risk of stillbirth, whilst an LGA fetus may be macrosomic at delivery (defined as birthweight over 4kg), which increases the risk of complications during delivery. We previously reported analyses of a Level 1 study of diagnostic effectiveness[11] (where the results of the ultrasound scan were blinded) in relation to extremes of fetal size,[12 13] and we have also reported that, in the same cohort study, a late pregnancy scan identified about 2.5% of women with a previously undiagnosed breech presentation at 36 weeks.[14] Our previous work has also estimated the cost-effectiveness scanning for each of these individually, concluding that scanning for LGA[15] and SGA[16] is unlikely to be worthwhile. However, we predict that a presentation scan could prevent around eight perinatal deaths per annum, and could be cost-neutral to the English National Health Service (NHS) if able to be performed by a midwife as part of a routine antenatal appointment.[14]

In this paper we build on this work, comparing all screening and management strategies simultaneously within one decision model framework. Critically, we use our framework to estimate overall decision uncertainty and perform a value of information analysis[17-19] to determine whether there is sufficient evidence to make a policy recommendation or whether investment in further research, for example a randomised controlled trial or other data gathering exercise, would represent value for money for a major public sector funder of research (the National Institute for Health Research, England, UK). This is of particular importance, given that most existing studies (and systematic review[20]) were underpowered to detect a statistically significant difference in stillbirth rates between routine and selective screening arms. A new and sufficiently powered clinical trial would need to be extremely large, and thus expensive. It is vital, therefore, to consider whether this is the best use of scarce public funds, or whether more health could be generated for the population from investment in other studies, or direct patient care.

Methods

Population

The target population is singleton nulliparous pregnancies (i.e. babies born to new mothers), in England.

Comparator strategies

The comparator strategies comprise both a screening option and subsequent management. Screening options are 'selective', 'universal breech' and 'universal'. All scans are assumed to take place at between 36 weeks and 36 weeks +6 days gestational age. 'Selective' screening means only those mothers who are clinically indicated for a late pregnancy scan receive one, assumed to reflect the status quo.[4 5] The 'universal breech' scanning strategy offers all mothers a simple presentation-only scan, i.e. solely to determine the orientation of the foetus. It is assumed performed by a midwife using a point of care ultrasound device as part of a routine antenatal contact. 'Universal' screening is defined as all mothers receiving an ultrasound scan incorporating measurements to estimate foetal size. Given the simplicity of establishing foetal presentation, this scan would also identify any babies in the breech position. Findings from a presentation scan can be either cephalic or breech, and foetal size could be either appropriate, small or large for gestational age (AGA, SGA and LGA, respectively).

If a breech presentation is identified, all mothers are assumed offered external cephalic version (ECV, manual manipulation of the mother's belly to turn the foetus to a cephalic presentation), unless contraindicated. If this is declined or unsuccessful, an elective Caesarean section may be scheduled. If LGA is detected, the mother may be offered either induction of labour (IoL) or expectant management. If SGA is detected, all mothers are offered induction of labour.

We therefore compare six alternative screening and management policies comprising three possible screening modes and two alternative management plans, numbered 1-6 and summarised in Table 1.

Model structure

The model structure is a decision tree with four sections covering breech, LGA, SGA and AGA (Figure 1 and Appendix 1). It was established by discussion amongst the study team, comprising economists and clinicians. For parsimony, we assume they are all mutually exclusive. This is logically true for LGA, SGA and AGA, but a baby may be both breech and LGA, for example. The structure is arranged hierarchically, with breech position first, as this is most easily and reliably identified.

We assume a presentation-only scan is perfectly predictive of breech (i.e. 100% sensitive and specific). However, our model allows for false negatives which are interpreted as undetected breech deliveries under the selective scanning strategy (node B_B, Figure 1). Where breech is detected, ECV is offered which may be successful or not. If unsuccessful, an elective Caesarean section may be scheduled. In either case, the baby may spontaneously revert to breech or cephalic position. Reversion to breech can lead to a vaginal breech delivery or emergency Caesarean section. Outcomes from delivery comprise none, moderate or severe morbidity, or stillbirth. Surviving infants could subsequently have no long-term complications, special educational needs, severe neurological morbidity or neonatal/infant mortality. The risk of long-term complications increases with neonatal morbidity severity (Appendix 1, Figure A1.1).

An LGA baby may or may not be diagnosed as such, determined by the sensitivity of the scan (Figure 1, node L_B). A positive scan can be managed either with induction of labour or expectant management, determined by the overall strategy (Table 1, Figure 1, node MGT_LGA_TP). Induction is assumed to reduce the risk of emergency Caesarean section (Figure 1, nodes L_C3 and L_C2 respectively). Delivery of a macrosomic baby leads to either no complications or respiratory morbidity, shoulder dystocia (trapping of the shoulder behind the mother's pubic bone) with attendant risk of transient or permanent brachial plexus injury (damage to the nerves of the arm) and acidosis (lowered blood pH usually due to build-up of carbon dioxide), other acidosis (i.e. not related to shoulder dystocia) or neonatal mortality (Appendix 1, Figure A1.2). Long term complications are

divided into none, special educational needs, severe neurological morbidity and neonatal/infant mortality (mirroring the structure of the breech arms, Appendix 1, Figure A1.1).

An SGA baby diagnosed as such will undergo induction of labour, with either a vaginal or emergency Caesarean section as the delivery mode. Undetected SGA babies are not induced and undergo either vaginal or emergency Caesarean section, with differing probabilities (Figure 1, nodes S_B, S_C3 and S_C2 respectively). Infants are then at risk of none, moderate or severe morbidity or stillbirth, with long term outcomes comprising no complications, special educational needs, severe neurological morbidity and neonatal/infant mortality (Appendix 1, Figure A1.3), mirroring the structure of the breech arms (Appendix 1, Figure A1.1).

AGA babies may be falsely diagnosed as SGA or LGA, in which case the management and patient pathways are as per the true positives described above (Figure 1, node B). However, the risks of adverse outcomes vary as described below ('model data'). Babies correctly identified as AGA undergo routine deliveries, with a 'background' risk of conversion to emergency Caesarean section for reasons other than foetal size or presentation (Figure 1, node C1). The expanded tree for AGA babies is shown in Appendix 1, Figure A1.4.

Model data

Data to populate the model were extracted from multiple sources in the literature[12-14 21-63] (Appendix 2, Table A2.1). Good quality systematic reviews and meta-analyses were prioritised, followed by large, good quality clinical trials or cohort studies as appropriate. Where possible, probabilities were expressed as a baseline and odds ratio (or relative risk where odds were not calculable). Unit costs pertained to a 2016/17 price year. Care was taken to appropriately reflect uncertainty in all parameters, as specified in the assigned probability distributions (Appendix 2, Table A2.1). Where no evidence for a parameter existed, we relied on expert opinion either to judge whether a study in a related area provided a sufficient proxy, or to provide a central estimate and credible interval representing beliefs about plausible values for the parameter. Source data for parameters were

assigned a subjective quality rating, high representing a source of directly relevant data, and low representing use of indirectly relevant or no data, revised with expert opinion. Model inputs and details of derivation are reported in Appendix 2.

Analysis

The model was analysed via Monte Carlo simulation, with the appropriate number of simulations determined by the trade-off between minimising Monte Carlo error and computational expense (Appendix 3). Model outcomes comprised mean, variance and covariance of costs and quality-adjusted life years (QALYs), reported as mean and 95% credibility intervals for cost, QALYs and net benefits calculated at £20,000 per QALY. We also report incremental net benefit relative to strategy 1 (selective scanning and induction of labour for SGA and LGA). Decision uncertainty is illustrated with cost-effectiveness acceptability curves (CEACs). All costs were from a third-party (payer) perspective (the English NHS), and the health consequences from a foetal perspective only. All costs and QALYs were discounted by 3.5% annually, as recommended by NICE.[64] The time-horizon was 20 years in the base-case scenario. Costs in other currencies were converted to GBP (£) by the exchange rate of the respective year. All prices were updated to the price level of 2016/17 using the hospital & community health services (HCHS) index.[56]

To complement the probabilistic sensitivity analysis, we also investigated the model's sensitivity to key parameters through one-way sensitivity analysis. Further, our base case analysis assumed early labour induction would only affect long-term foetal outcomes via its impact upon neonatal outcomes. However, there is evidence suggesting that induction of labour may of itself increase the risk of special educational needs in later life.[40] We therefore explore the impact of an independent effect of induction of labour on the risk of special educational needs.

We report the per-patient (i.e. per mother/infant dyad) and population Expected Value of Perfect Information (EVPI) at a willingness to pay of £20,000/QALY and the Expected Value of Perfect Parameter Information (EVPPI) for each parameter individually using the Sheffield Accelerated Value

of Information (SAVI) tool.[65] Parameters with a positive EVPPI were grouped into those which could be collected within a single research study and the EVPPI for that group of parameters calculated. The Expected Value of Sample Information (EVSI) for any parameters or groups of parameters was then calculated using the method of Moment Matching with 30 nested samples.[66] EVPPI and EVSI calculations are traditionally extremely computationally expensive. The SAVI and moment matching methods generate statistical approximations, allowing calculation within a feasible timeframe. Briefly, SAVI estimates the EVPPI via a generalised additive model (GAM) with non-parametric smoothing applied to the sampled input parameter set and resulting net benefits. Our implementation of the MM method relies on the conjugate distribution of the respective prior to estimate the preposterior distribution for a given study sample size (see Appendix 3 for code and walk-through). Population values are calculated over a time horizon of 10 years and as a 'conservative' estimate, assuming the information is only of value to singleton nulliparous pregnancies resulting in a beneficial population of 1,689,663 and again with a broader estimate which assumes the information is of value to all pregnancies in England (n=5,477,940, Appendix 2).

The model was coded in R[67] and associated packages.[68-74] Full model code is available from the corresponding author upon request.

Results

Economic evaluation results are presented based on 100,000 simulations of the model. Value of information analysis statistics are based on 10,000 simulations (stability testing results reported in Appendix 4).

Given current evidence and assuming a willingness to pay of £20,000 per QALY, the strategy associated with the highest net benefit is strategy 3: a presentation-only scan for all women (unless further screening is clinically indicated) with induction of labour where LGA or SGA are suspected. The added benefits from universal ultrasound screening for foetal size are unlikely to justify its added cost (Table 2). However, there is substantial uncertainty associated with this recommendation, with only a 44% probability of this yielding the highest net benefit, and a 39% probability of universal screening being optimal (Table 2, Figure 2). As the willingness to pay threshold rises, the probability that universal screening becomes the most cost-effective strategy also rises (Figure 2).

One-way sensitivity analyses suggested that the cost-effectiveness outcomes were only sensitive to a few parameters: presentation only scanning is the most cost-effective option if the time horizon of the analysis is below 45 years, above which universal screening becomes the most cost-effective option. A presentation-only scan remains the most cost-effective option provided it costs no more than £90, above which status quo is the most cost-effective, and that the baseline stillbirth rate is above 0.28%, at which point universal scanning is most cost-effective. Finally, we found that the impact of induction of labour on risk of special educational needs (SEN) would only change the conclusions if the relative risk of SEN was lower than 0.95, or above 1.3; observational data suggest that the effect is highly unlikely to be outside this range (Appendix 5).[40]

The per patient expected value of perfect information (EVPI) is £31.56. Given a population who can benefit from the information of 1,689,663 (see Appendix 2), the population EVPI to England is £53.3m. If the results of the analysis are assumed generalizable to all pregnancies in England, then the population EVPI is £172.9m (Table 3). Only five input parameters yielded a population EVPPI greater

than £100,000, and these logically group into three clusters of outcome measures that could be collected in possible future studies or RCTs (labelled studies 1, 2 and 3). The parameter with the greatest EVPPI is the difference in net cost of induced versus non-induced deliveries, accounting for 84% of the EVPI. No other parameters individually account for more than 1% of the total EVPI (Table 3).

EVSI analysis of study 1, exploring the net cost difference between early labour induction and expectant management suggests scope for it to yield a positive return on investment. For example, a study with 1000 patients (in each arm of a two-arm study) has an EVSI to England of £11.3m (or £97.2m if this information is of value to all pregnancies in England, not just low risk nulliparous singleton pregnancies, Figure 3). If such a study were to cost £1m, it would yield a net return on investment (ENGS) of at least £10.3m. The EVSI algorithm was not able to estimate an EVSI for studies 2 and 3; following investigation, we concluded that for very low EVSIs, the approximation method is not able to return a value. We therefore conclude that the EVSI is very low and thus studies collecting data on the respective parameters are unlikely to be worth more than the cost of collecting them.

Discussion

Given current information, the most cost-effective strategy for late-pregnancy ultrasound scanning is to offer all women a presentation-only scan (those women who are currently indicated to undergo a full third-trimester ultrasound scan to continue to do so), and where SGA or LGA are suspected, the mother should be offered induction of labour, unless otherwise contraindicated. Given current thresholds,[64] universal routine ultrasound screening to assess foetal size is not cost-effective.

There is substantial decision uncertainty around this recommendation. However, the expected value of eliminating all uncertainty is only worth a maximum of £172.9m, or 8644 QALYs to the population of England (assuming £20,000 per QALY). This represents the expected opportunity loss due to the probability that the above recommendation is incorrect (crudely, the probability of being 'wrong' multiplied by the consequence of being 'wrong'). The majority of the EVPI is concentrated in a single parameter, namely the difference in cost as a result of early induction of labour. This is somewhat surprising, but arises due to the large standard error around the relevant model parameter (Appendix 2, Table A2.1, row "Induction of labour"). This is because the cost encompasses not only the cost of inducing a pregnancy itself, but the costs of delivery and antenatal visits which may or may not be avoided too. Induction also has an uncertain impact on complications and hence long-term cost and outcomes of delivery. On top of this, less than perfect sensitivity and specificity of the scans at detecting LGA and SGA babies magnify the impact of uncertainty in the cost and outcomes of induction of labour. The EVSI of this parameter suggests that a study of 'reasonable' size (eg 1000 mothers per arm with a cost of £1m) would likely yield a highly positive return on investment.

An ideal study design to measure the cost-difference would be a study randomising mothers to induction of labour or not, irrespective of indication. This is likely to raise ethical issues and would require careful consideration of the pros and cons and risks to mothers and their babies, based on current state of knowledge. A non-randomised study design (eg database or cohort analysis) would be feasible but at risk of bias. The mathematics of value of information analysis are blind to whether

reducing uncertainty in a parameter is ethical or not, or even possible or not. Instead, as with all economic evaluation, they provide a guide and input to the decision-making process. An important finding from our analysis is that there is no evidence that a large scale RCT powered to detect a difference in stillbirth would be a worthwhile investment: the EVPPI from reducing uncertainty in stillbirth rates is worth less than £100,000, a sum for which it is not possible to deliver an RCT.

We believe our analysis represents the most plausible summary of the evidence on the costs and effects of different ultrasound screening and subsequent management strategies in late pregnancy. The decision model translates uncertainty in parameters (crudely, the standard errors around mean estimates of effect, cost and health state utilities) to decision uncertainty (standard errors around mean estimates of net benefit). The value of information analysis then predicts the likely return on investment from reducing the SEs of the input parameters.

However, the validity of our conclusion rests entirely on the validity of the model. Whilst we believe we have appropriately captured parameter uncertainty, we have implicitly assumed that the structure of the model itself is 'correct'. Addressing such structural uncertainty is challenging in decision models. In theory it would require constructing many alternative models and comparing or averaging out the results, which would be prohibitively expensive. However, where possible we did explore structural uncertainty, for example our base case assumed that all long-term morbidity was mediated through the risk of neonatal morbidity, whilst there is evidence to suggest an independent effect of induction of labour on risk of special educational needs. We explored this and found our conclusions to be robust to all but implausibly extreme assumptions as to the relative risk. Our analytic perspective was limited to foetal outcomes only, excluding maternal quality of life. This may underestimate the QALY gains from screening and so underestimate cost-effectiveness.

Secondly, our conclusions regarding the cost-effectiveness of presentation scanning are contingent on midwifes being able to undertake the scan as part of a routine antenatal contact. This is currently unknown and requires a feasibility study to test. It should also be noted that the scans will certainly

increase the burden on midwifes whilst we predict a reduction in delivery complications. This will require a shift in resources from secondary care to (antenatal) midwifery. The budgetary mechanisms underlying this are not considered in our analysis. It is worth noting that our previous work[14] focusing only on presentation scans (and not including the alternative strategies considered here) concluded that a presentation-only scan was cost-effective so long as it could be provided for £19.80 or less. Our analysis here, which models longer term costs and outcomes in greater detail, suggests greater scope for cost-effectiveness, with our one-way sensitivity analysis suggesting the scan remaining cost-effective so long as it can be provided for less than approximately £90 (Appendix 5, Figure A4.2).

To our knowledge this is the first value of information analysis estimating the return on investment from future research into late pregnancy ultrasound scans. Economic evaluations of obstetric investigations commonly include estimates of the value of perfect information, for example there may be value in future studies on quality of life gains and costs of early detection of gestational diabetes,[75] the effects of interventions to prevent postnatal depression,[76] the cost-effectiveness of financial incentives for smoking cessation during pregnancy,[77] and possibly into the effectiveness of a screening programme to reduce periconceptional exposure to methylmercury.[78] However, we are not aware of any attempts to calculate the expected value of sample information from specific study designs in obstetrics.

Conclusion

Our results suggest that universal ultrasound for foetal presentation only may be both clinically and economically justified, but that implementation research is needed before it is adopted into routine care. Specifically, this must explore whether a scan can be conducted by a midwife during a routine antenatal visit. Universal ultrasound including estimation of foetal weight is of borderline cost-effectiveness, and sensitive to certain assumptions. Our formal value of information analysis suggests that future research should be focused on the net cost of induction of labour compared to expectant

management, and that there is unlikely to be value in a large scale RCT of routine vs selective ultrasound screening powered to detect a difference in stillbirth rates.

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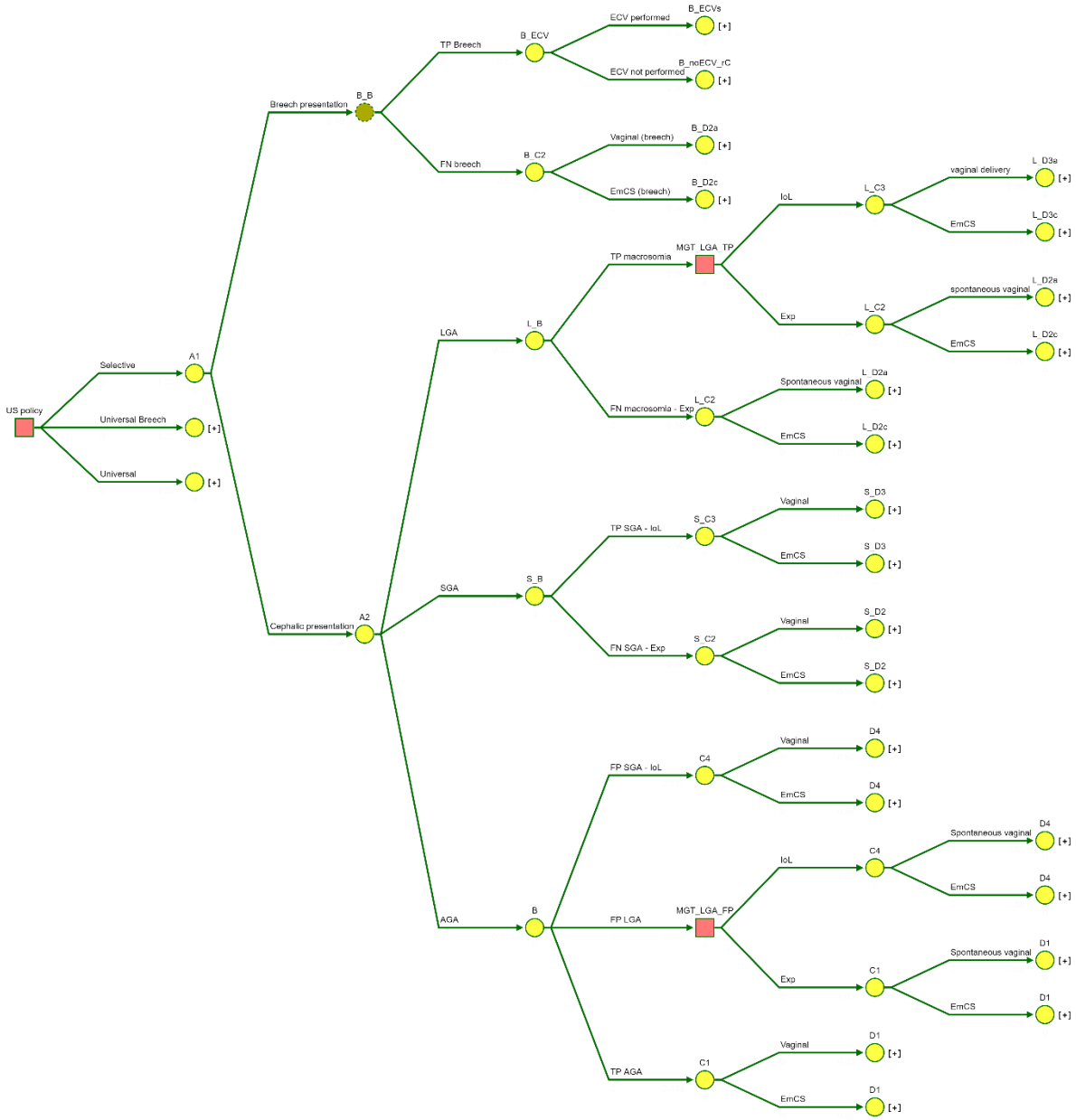
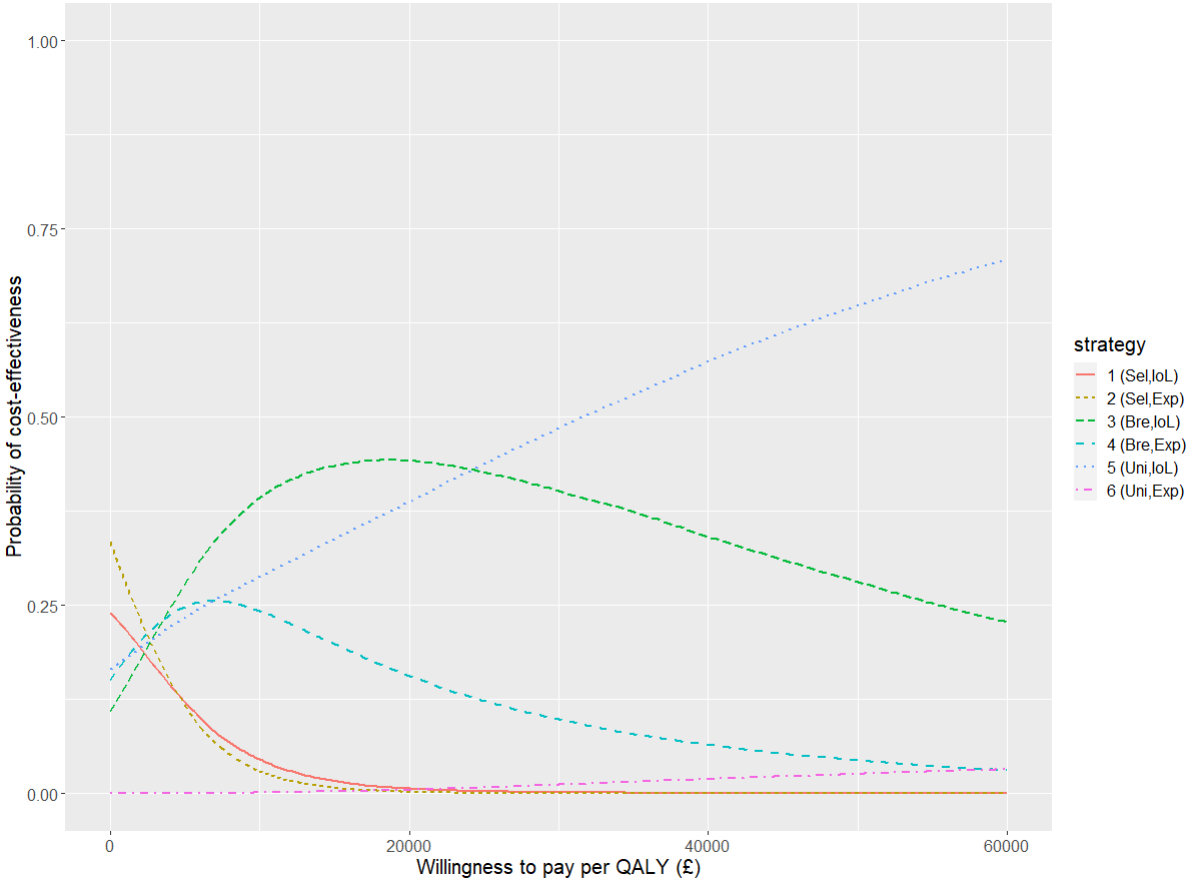
Tables and Figures

Figure 1. Model structure overview: Screening-management options and foetal conditions.



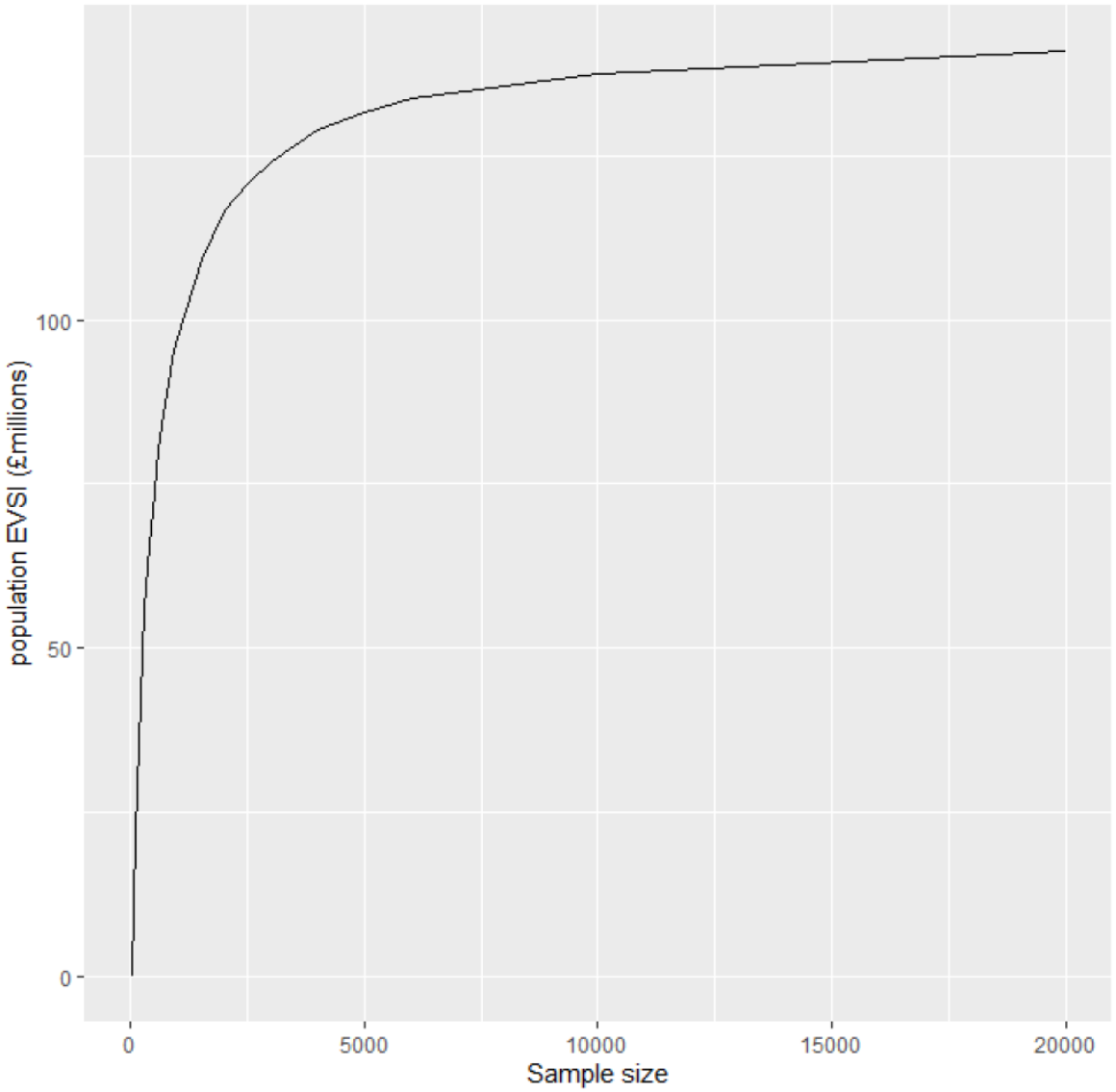
[+] = sub-branches of model collapsed for clarity; see Appendix 1 for expanded nodes. Nodes with the same letter have identical subsequent structures, whilst a different number and lowercase letter indicates different probabilities assigned to the next subbranch. The prefix before the underscore indicates a set of probabilities relevant to breech (B_), LGA (L_) or SGA (S_) For example, nodes D1 and D4 have identical sub-structures, but D1 relates to AGA babies delivered spontaneously, whereas D4 relates to AGA babies wrongly diagnosed as SGA or LGA and undergoing induction of labour unnecessarily. US = ultrasound; TP = true positive; FN = false negative; FP = false positive; TN = true negative; ECV = external cephalic version; EmCS = Emergency Caesarean section; Exp = Expectant management; IoL = Induction of labour

Figure 2. Cost-effectiveness acceptability curves showing probability of cost-effectiveness as a function of willingness-to-pay for an additional quality-adjusted life year.



Sel = selective scanning; Bre = Universal presentation-only scan; Uni = Universal scan of foetal biometry and presentation; IoL = Induction of labour if LGA suspected; Exp = Expectant management if LGA suspected.

Figure 3: Expected Value of Sample Information of Study 1.



Expected value of sample information as a function of sample size for a study of the cost-difference between early induction of labour versus expectant management.

Table 1: Comparator strategies / policies

Strategy	Screen	Offered management if diagnosed:		
		Breech+	Macrosomia+	SGA+
1	Selective	ECV	IoL	IoL
2	Selective	ECV	Exp	IoL
3	Universal Breech	ECV	IoL	IoL
4	Universal Breech	ECV	Exp	IoL
5	Universal	ECV	IoL	IoL
6	Universal	ECV	Exp	IoL

ECV = External cephalic version; Exp = Expectant management; IoL = Induction of labour; SGA = Small for gestational age

Table 2. Cost effectiveness results (per mother scanned).

Screening + management	Cost (£)	QALYs	NB|£20k	INB|£20k	P_CE|£20k
1. Selective US + IoL for LGA	6090	13.640	£266,719	£0	0.65%
	(4420, 7890)	(13.441, 13.841)	(£262,333, £271,079)	(£0, £0)	
2. Selective US + Exp for LGA	6091	13.639	£266,682	-£37.09	0.22%
	(4424, 7889)	(13.439, 13.839)	(£262,297, £271,040)	(-£124.7, £35.24)	
3. **Universal US for breech + + IoL for LGA ***	**6101**	**13.645**	**£266,806**	**£87.36**	**44.19%**
	(4443, 7887)	**(13.446, 13.846)**	**(£262,426, £271,154)**	**(£4.88, £205.68)**	
4. Universal US for breech + Exp for LGA	6102	13.644	£266,769	£50.29	15.63%
	(4446, 7887)	(13.444, 13.844)	(£262,389, £271,120)	(-£68.06, £186.43)	
6. Universal US + Exp for LGA	6178	13.646	£266,734	£14.47	0.51%
	(4508, 7972)	(13.446, 13.846)	(£262,351, £271,099)	(-£133.98, £173.31)	
5. Universal US + IoL for LGA	6180	13.648	£266,779	£60.24	38.81%
	(4498, 7983)	(13.448, 13.849)	(£262,386, £271,147)	(-£151.43, £281.7)	

*Strategies are listed in order of increasing cost (1,2,3,4,6,5). Management refers to management strategy when LGA is suspected, all cases of suspected SGA are assumed induced and breech to be offered ECV. * Strategy with highest expected net benefit (shown in bold). IoL = Induction of Labour; Exp = Expectant Management; INB = Incremental net benefit relative to current practice (strategy 1, selective US + induction of labour); NB = Net benefit ; P_CE|£20k = Probability of being the most cost-effective strategy given a willingness to pay of £20,000 per QALY gained.*

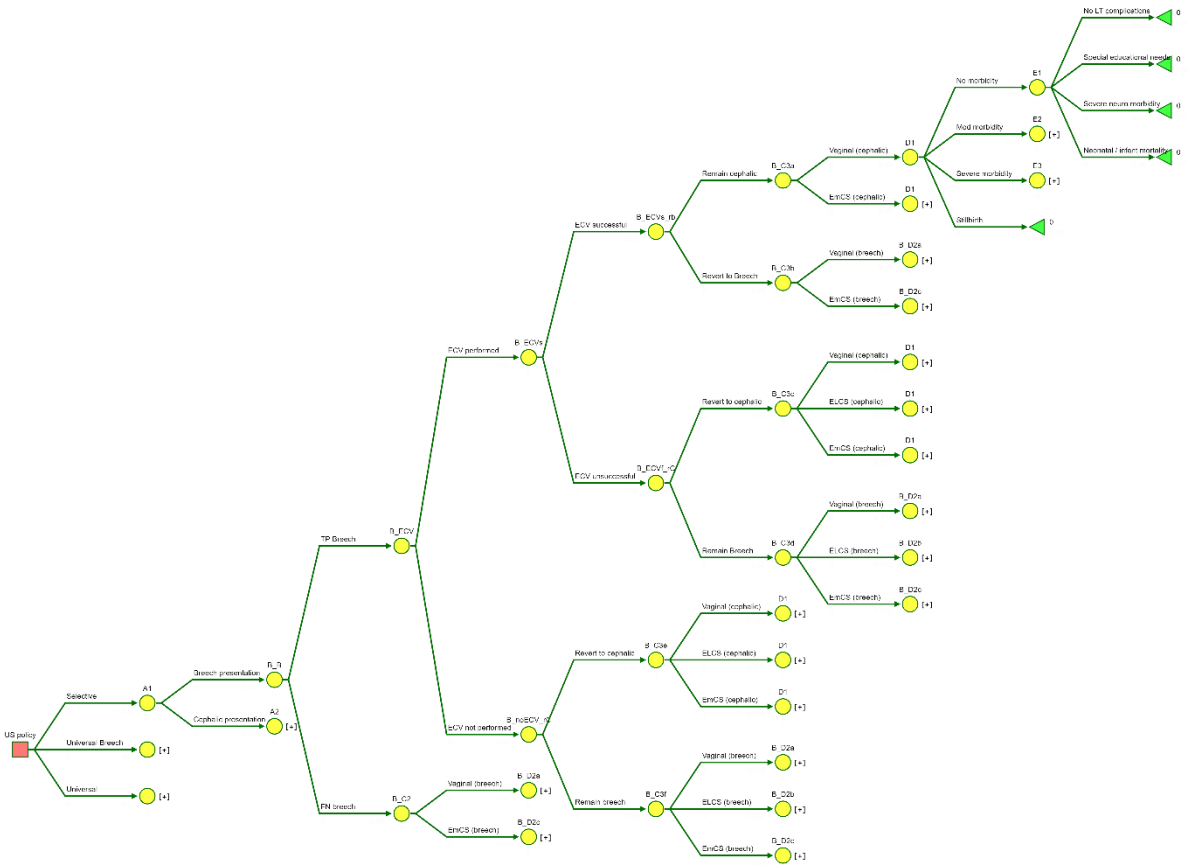
Table 3. Expected value of perfect information.

	Per Person EVPPI (£expected, SE)	% of EVPI	pEVPPI (£)*	pEVPPI (£)*
Study 1				
Cost difference from early induction of labour	26.51 (0.07)	84	44,790,000	145,200,000
Study 2				
RR for acidosis in macrosomic fetuses if induced early	0.27 (0.04)	1%	456,000	1,478,000
OR for mortality if fetus is macrosomic	0.26 (0.03)	1%	438,900	1,423,000
Group	0.72 (0.07)	2%	1,215,199	3,939,513
Study 3				
RR for emergency CS among SGA fetuses following early labour induction	0.06 (0.01)	0%	99,290	321,900
OR for severe neonatal morbidity if fetus is SGA	0.03 (0.01)	0%	48,740	158,000
Group	0.26 (0.04)	1%	443,104	1,436,484
Expected Value of Perfect Information	31.56 (-)	100%	53,326,764	172,883,786

** First pEVPPI column assumes information is applicable just to the target population (nulliparous singleton pregnancies), second assumes the information is equally applicable to all births in England. CS = Caesarean section; EVPI = Expected value of information; EVPPI = Expected value of partial perfect information; OR = Odds ratio; SE = Standard error; RR = Relative risk. Standard error around estimates of EVPPI are a result of the SAVI[74] approximation algorithm. The EVPI is calculated directly and thus has no associated standard error. Note sum of EVPPI will not usually equal the EVPI due to interactions / correlations between input parameters.*

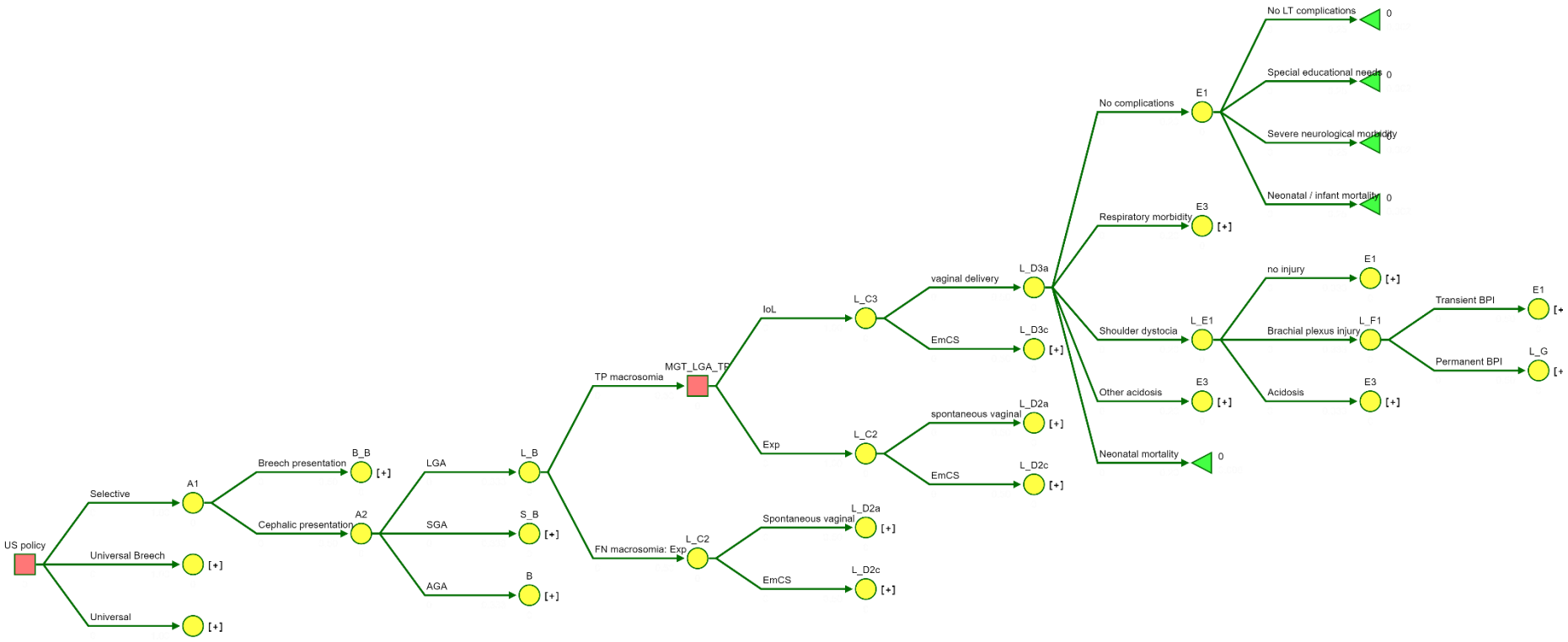
Appendix 1: Model structure – Breech, LGA and SGA

Figure A1.1. Outcomes associated with breech.



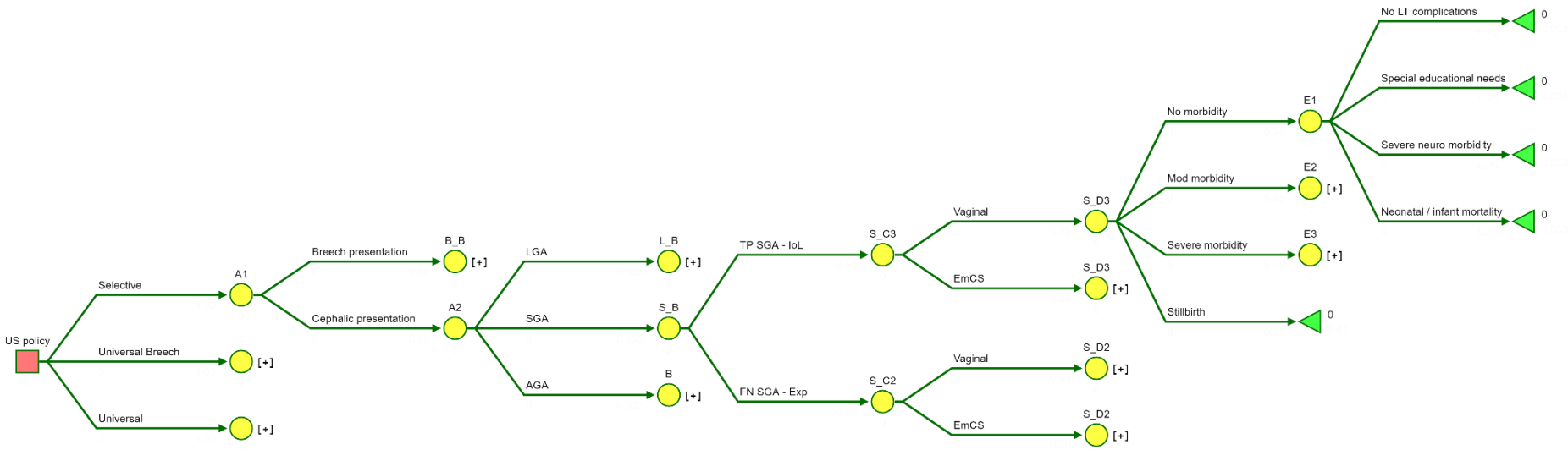
[+] = collapsed sub-branches. Nodes with the same letter have identical subsequent structures, whilst a different number and lowercase letter indicates different probabilities assigned to the next subbranch. The prefix before the underscore indicates a set of probabilities relevant to breech (B_). US = ultrasound; TP = true positive; FN = false negative; FP = false positive; TN = true negative; ECV = external cephalic version; ELCS = Elective Caesarean section; EmCS = Emergency Caesarean section; Exp = Expectant management; IoL = Induction of labour

Figure A1.2. Outcomes associated with LGA.



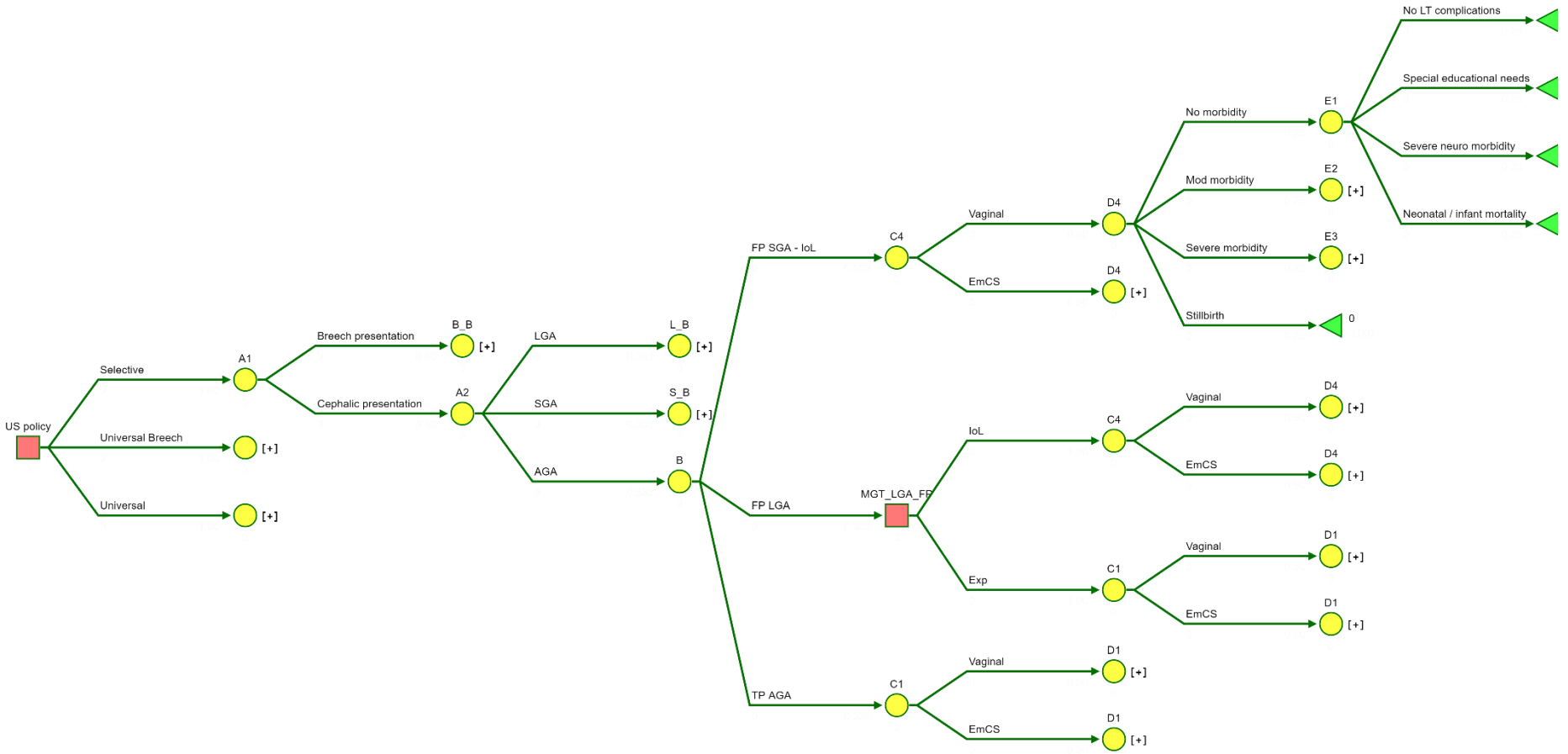
[+] = collapsed sub-branches. Nodes with the same letter have identical subsequent structures, whilst a different number and lowercase letter indicates different probabilities assigned to the next subbranch. The prefix before the underscore indicates a set of probabilities relevant to LGA (L_). US = ultrasound; TP = true positive; FN = false negative; FP = false positive; TN = true negative; EmCS = Emergency Caesarean section; Exp = Expectant management; IoL = Induction of labour

Figure A1.3. Outcomes associated with SGA.



[+] = collapsed sub-branches. Nodes with the same letter have identical subsequent structures, whilst a different number and lowercase letter indicates different probabilities assigned to the next subbranch. The prefix before the underscore indicates a set of probabilities relevant to SGA (S_). US = ultrasound; TP = true positive; FN = false negative; FP = false positive; TN = true negative; EmCS = Emergency Caesarean section; Exp = Expectant management; IoL = Induction of labour

Figure A1.4. Model structure overview: Neonatal and long-term outcomes (Appropriate for Gestational Age)



[+] = collapsed sub-branches. Nodes with the same letter have identical subsequent structures, whilst a different number and lowercase letter indicates different probabilities assigned to the next subbranch. US = ultrasound; TP = true positive; FN = false negative; FP = false positive; TN = true negative; EmCS = Emergency Caesarean section; Exp = Expectant management; IoL = Induction of labour

Appendix *2: Model parameter input values*

Summary of model input values: probabilities and costs

Table A2.1 Model inputs for probabilities.

Parameter	Mean	95%CI	Probability distribution	Node	Source	Quality of evidence
Diagnostic Performance						
Prevalence of breech	4.60%	3.98%, 5.30%	~B(179, 3700)	A1	Wastlund et al. (2019)[14]	H
Prevalence of LGA	10.00%	10%, 10%	N/A	A2	By definition	H
Prevalence of SGA	10.00%	10%, 10%	N/A	A2	By definition	H
Selective US						
Specificity SGA - Selective US	98.10%	97.63%, 98.52%	~B(3556, 69)	B	Sovio et al. (2015)[12]	H
Specificity LGA – Selective US	98.67%	98.28%, 99.02%	~B(3640, 49)	B	Sovio et al. (2018)[13]	H
Sensitivity SGA - Selective US	19.60%	15.63%, 23.90%	~B(69, 283)	S_B	Sovio et al. (2015) [12]	H
Sensitivity LGA - Selective US	26.55%	20.33%, 33.28%	~B(47, 130)	L_B	Sovio et al. (2018) [13]	H
Sensitivity breech – selective US	45.10%	37.85%, 52.54%	~B(79, 96)	B_B	Wastlund et al. (2019) [14]	H
Universal US for fetal size and presentation						
Specificity SGA - Universal US	89.99%	88.99%, 90.94%	~B(3262, 363)	B	Sovio et al. (2015) [12]	H
Specificity LGA – Universal US	96.56%	95.95%, 97.12%	~B(3562, 127)	B	Sovio et al. (2018) [13]	H
Sensitivity SGA - Universal US	56.53%	52.33%, 61.67%	~B(199, 153)	S_B	Sovio et al. (2015) [12]	H
Sensitivity LGA - Universal US	37.85%	30.87%, 45.10%	~B(67, 110)	L_B	Sovio et al. (2018) [13]	H
Sensitivity breech – Universal US	100%	100%, 100%	N/A	B_B	Assumption	N/A
Universal US for fetal presentation only						
Specificity SGA – Presentation-only scan	98.10%	97.63%, 98.52%	~B(3556, 69)	B	Sovio et al. (2015) [12]	H
Specificity LGA – Presentation-only scan	98.67%	98.28%, 99.02%	~B(3640, 49)	B	Sovio et al. (2018) [13]	H
Sensitivity SGA – Presentation-only scan	19.60%	15.63%, 23.90%	~B(69, 283)	S_B	Sovio et al. (2015) [12]	H
Sensitivity LGA – Presentation-only scan	26.55%	20.33%, 33.28%	~B(47, 130)	L_B	Sovio et al. (2018) [13]	H
Sensitivity breech – Presentation-only scan	100%	100%, 100%	N/A	B_B	Assumption	N/A
Mode of delivery						
EmCS delivery | AGA and Exp Mgt	20.70%	19.4%, 22.06%	~B(735, 2813)	C1	Wastlund et al.[14]	H

Parameter	Mean	95%CI	Probability distribution	Node	Source	Quality of evidence
RR EmCS delivery | SGA and Exp Mgt [FN] vs. C1	1.9	1.4, 2.5	~LN(0.642, 0.14)	S_C2	Monier et al.[21]	M
RR EMCS | induced, SGA [TP] vs. C1	2.9	1.8, 4.7	~LN(1.065, 0.246)	S_C3	Monier et al.[21]	L
RR EMCS | induced, AGA, [FP SGA] vs. C1	0.84	0.76, 0.93	~LN(-0.174, 0.052)	C4	Grobman et al.[22]	H
OR of EmCS delivery | LGA and Exp Mgt [FN] vs. C1	1.792	0.718, 4.471	~LN(0.583, 0.466)	L_C2	Blackwell et al.[23]	M
OR of EmCS delivery | LGA and Induce [TP] vs. L_C2	0.92	0.85, 0.99	~LN(-0.083, 0.037)	L_C3	Middleton et al.[24]	L
EmCS delivery | Breech and Exp Mgt [FN]	57.69%	38.67%, 75.62%	~B(15, 11)	B_C2	Leung et al.[25]	M
EmCS delivery | breech, ECV success, remain cephalic	27.27%	6.69%, 55.64%	~B(3, 8)	B_C3a	Wastlund et al.[14]	H
EmCS delivery | breech, ECV success, revert breech	57.69%	38.67%, 75.62%	~B(15, 11)	B_C3b	Leung et al.[25]	M
Vaginal delivery | breech, ECV fail, revert cephalic	52.38%	31.51%, 72.80%	~D(11, 1, 9)	B_C3c	Wastlund et al.[14]	H
ELCS delivery | breech, ECV fail, revert cephalic	4.76%	0.13%, 16.84%	-	B_C3c	Wastlund et al.[14]	
EmCS delivery | breech, ECV fail, revert cephalic	42.86%	23.07%, 63.97%	-	B_C3c	Wastlund et al.[14]	
Vaginal delivery | breech, ECV fail, remain breech	0%	0%, 0%	~D(0, 54, 18)	B_C3d	Wastlund et al.[14]	H
ELCS delivery | breech, ECV fail, remain breech	75%	64.47%, 84.22%	-	B_C3d	Wastlund et al.[14]	
EmCS delivery | breech, ECV fail, remain breech	25%	15.78%, 35.53%	-	B_C3d	Wastlund et al.[14]	
Vaginal delivery | breech, no ECV, revert cephalic	52.38%	31.51%, 72.80%	~D(11, 1, 9)	B_C3e	Wastlund et al.[14]	H
ELCS delivery | breech, no ECV, revert cephalic	4.76%	0.13%, 16.84%	-	B_C3e	Wastlund et al.[14]	
EmCS delivery | breech, no ECV, revert cephalic	42.86%	23.07%, 63.97%	-	B_C3e	Wastlund et al.[14]	
Vaginal delivery | breech, no ECV, remain breech	0%	0%, 0%	~D(0, 52, 20)	B_C3f	Wastlund et al.[14]	H
ELCS delivery | breech, no ECV, remain breech	72.22%	61.38%, 81.88%	-	B_C3f	Wastlund et al.[14]	
EmCS delivery | breech, no ECV, remain breech	27.77%	18.12%, 38.62%	-	B_C3f	Wastlund et al.[14]	
External cephalic version						
ECV attempted	47.46%	40.16%, 54.81%	~B(84, 93)	B_ECV	Wastlund et al.[14]	H
ECV not attempted, spontaneous reversion to cephalic	22.58%	14.72%, 31.56%	~B(21, 72)	B_noECV_rc	Wastlund et al.[14]	H
Probability ECV successful	14.29%	7.70%, 22.48%	~B(12, 72)	B_ECVs	Wastlund et al.[14]	H
Probability of reverting to breech post successful ECV	8.33%	0.23%, 28.49%	~B(1, 11)	B_ECVs_rb	Wastlund et al.[14]	H
Probability of spontaneous reversion to cephalic post ECV failure	2.31%	0.48%, 5.49%	~B(3, 127)	B_ECVf_rc	Ben-Meir et al.[26]	H
Outcomes for LGA model						
Respiratory morbidity, baseline	0.32%	0.20%, 0.46%	~B(22, 6933)	-	Morrison et al.[27]	H

Parameter	Mean	95%CI	Probability distribution	Node	Source	Quality of evidence
Shoulder dystocia, baseline	0.63%	0.60%, 0.66%	~B(1686, 265542)	-	Ouzounian et al.[28]	M
Other acidosis, baseline	0.68%	0.22%, 1.40%	~B(5, 726)	-	Middleton et al.[24]	H
Perinatal mortality, baseline	0.155%	0.145%, 0.165%	~B(984, 634412)	-	Moraitis et al.[29]	M
RR respiratory morbidity, LGA vs. AGA [FN & ExpMan LGA policy]	0.75	0.5125, 0.9875	~U(0.5, 1)	L_D2a	Expert opinion	L
OR shoulder dystocia, LGA vs. AGA [FN & ExpMan LGA policy]	7.18	2.06, 25.00	~LN(1.971, 0.637)	L_D2a	Rossi et al.[30]	H
OR other acidosis, LGA vs. AGA [FN & ExpMan LGA policy]	2.88	1.34, 6.22	~LN(1.058, 0.393)	L_D2a	Rossi et al.[30]	M
OR perinatal mortality, LGA vs. AGA [FN & ExpMan LGA policy]	1.77	0.30, 10.34	~LN(0.571, 0.901)	L_D2a	Rossi et al.[30]	M
OR respiratory morbidity, LGA vs. AGA, EMCS [FN & ExpMan LGA policy]	5.33	3.50, 7.40	~LN(1.674, 0.167)	L_D2c	Morrison et al.[27]	H
P shoulder dystocia, LGA, EMCS [FN & ExpMan LGA policy]	0	0, 0	N/A	L_D2c	Assumption	H
OR other acidosis, LGA, EMCS [FN & ExpMan LGA policy]	1.867	1.217, 2.865	~LN(0.625, 0.218)	L_D2c	Chongsuvivatwong et al.[31]	M
OR perinatal mortality, LGA, EMCS [FN & ExpMan LGA policy]	1.781	1.266, 2.505	~LN(0.577, 0.174)	L_D2c	Chongsuvivatwong et al.[31]	M
OR respiratory morbidity, LGA, Induction of labour, vaginal delivery [TP]	0.54	0.373, 0.783	~LN(-0.616, 0.19)	L_D3a	Gibson et al.[32]	M
RR shoulder dystocia, LGA, Induction of labour, vaginal delivery [TP]	0.6	0.37, 0.98	~LN(-0.511, 0.25)	L_D3a	Boulvain et al.[33]	M
RR acidosis, LGA, Induction of labour, vaginal delivery [TP]	1.66	0.61, 4.55	~LN(0.507, 0.514)	L_D3a	Middleton et al.[24]	M
RR perinatal mortality, LGA, Induction of labour, vaginal delivery [TP]	0.33	0.14, 0.78	~LN(-1.109, 0.439)	L_D3a	Middleton et al.[24]	M
OR respiratory morbidity, LGA, Induction of labour, EmCS [TP]	0.54	0.373, 0.783	~LN(-0.616, 0.19)	L_D3c	Gibson et al.[32]	M
P shoulder dystocia, LGA, Induction of labour, EmCS [TP]	0	0, 0	N/A	L_D3c	Assumption	H
RR acidosis, LGA, Induction of labour, EmCS [TP]	1.66	0.61, 4.55	~LN(0.507, 0.514)	L_D3c	Middleton et al.[24]	M
RR perinatal mortality, LGA, Induction of labour, EmCS [TP]	0.33	0.14, 0.78	~LN(-1.109, 0.439)	L_D3c	Middleton et al.[24]	M
Risk of acidosis | shoulder dystocia	0.07	0.0630, 0.1112	~B(36, 478)	L_E1	MacKenzie et al.[34]	L
Risk of BPI | shoulder dystocia	0.0856	0.0496, 0.0936	~B(44, 470)	L_E1	MacKenzie et al.[34 c]	L
Risk of permanent BPI	0.055	0.024, 0.098	~B(8, 137)	L_F1	Sandmire et al.[35 c]	M
Neonatal morbidity						
Risk of moderate neonatal morbidity (AGA) [FP]	5.62%	0.0488, 0.0641	~B(198, 3325)	D1	The POP study [c]	H
Risk of severe neonatal morbidity (AGA) [FP]	0.62%	0.0039, 0.0091	~B(22, 3501)	D1	The POP study [c]	H
Risk of perinatal death (AGA) [FP]	0.155%	0.145%, 0.165%	~B(984, 634412)	D1	Moraitis et al.[29]	M
OR moderate neonatal morbidity (SGA vs. AGA, ExpMan)	2.48	1.75, 3.51	~LN(0.91, 0.18)	S_D2	The POP Study [c]	H
OR severe neonatal morbidity (SGA vs. AGA, ExpMan)	1.88	0.65, 5.50	~LN(0.63, 0.55)	S_D2	The POP Study [c]	H

Parameter	Mean	95%CI	Probability distribution	Node	Source	Quality of evidence
OR perinatal death (SGA vs. AGA, ExpMan)	4.39	3.84, 5.03	~LN(1.48, 0.07)	S_D2	Moraitis et al.[29]	H
RR moderate morbidity | induce SGA vs. not inducing SGA [TP]	0.7	0.50, 0.98	~LN(-0.357, 0.172)	S_D3	Middleton et al.[24]	L
RR severe morbidity | induce SGA vs. not inducing SGA [TP]	0.7	0.50, 0.98	~LN(-0.357, 0.172)	S_D3	Middleton et al.[24]	L
RR perinatal death | induce SGA vs. not inducing SGA [TP]	0.33	0.11, 0.96	~LN(-1.109, 0.553)	S_D3	Middleton et al.[24]	L
OR of moderate neonatal morbidity if induce | AGA [FP SGA or LGA]	1.92	1.71, 2.15	~LN(0.652, 0.058)	D4	Stock et al.[36]	H
OR of severe neonatal morbidity if induce | AGA [FP SGA or LGA]	1.92	1.71, 2.15	~LN(0.652, 0.058)	D4	Stock et al.[36]	H
OR of perinatal death if induce | AGA [FP SGA or LGA]	0.15	0.03, 0.68	~LN(-1.897, 0.771)	D4	Stock et al.[36]	H
OR of moderate neonatal morbidity | vaginal breech vs. vaginal cephalic delivery	6.70	5.9, 7.6	~LN(1.902, 0.064)	B_D2a	Thorngren-Jerneck et al.[37]	H
OR of severe neonatal morbidity | vaginal breech vs. vaginal cephalic delivery	6.70	5.9, 7.6	~LN(1.902, 0.064)	B_D2a	Thorngren-Jerneck et al.[37]	H
OR of perinatal death | vaginal breech vs. vaginal cephalic delivery	6.68	2.75, 16.22	~LN(1.899, 0.453)	B_D2a	Moraitis et al.[29]	H
RR of moderate morbidity | ELCS vs. vaginal breech delivery	0.43	0.12, 1.47	~LN(-0.844, 0.627)	B_D2b	Hofmeyr et al.[38]	H
RR of severe morbidity | ELCS vs. vaginal breech delivery	0.11	0.01, 0.87	~LN(-2.207, 1.055)	B_D2b	Hofmeyr et al.[38]	H
RR of perinatal death | ELCS vs. vaginal breech delivery	0.29	0.1, 0.86	~LN(-1.238, 0.555)	B_D2b	Hofmeyr et al.[38]	H
OR of moderate morbidity | EmCS vs. vaginal breech delivery	0.533	0.192, 1.482	~LN(-0.629, 0.522)	B_D2c	Pasupathy et al.[39 c]	M
OR of severe morbidity | EmCS vs. vaginal breech delivery	0.533	0.192, 1.482	~LN(-0.629, 0.522)	B_D2c	Pasupathy et al.[39 c]	M
OR of perinatal death | EmCS vs. vaginal breech delivery	0.533	0.192, 1.482	~LN(-0.629, 0.522)	B_D2c	Pasupathy et al.[39 c]	M
Risk of long-term outcomes from neonatal morbidity						
Risk of SEN | no neonatal morbidity	0.0474	0.0467, 0.0480	~B(18736, 376891)	E1	MacKay et al.[40]	H
Risk of neurological morbidity | no neonatal morbidity	0.0008	0.0007, 0.0008	~B(906, 1193647)	E1	Persson et al.[41]	H
Risk of neonatal/infant mortality | no neonatal morbidity	0.002	0.0020, 0.0021	~B(2074, 1011289)	E1	Iliodromiti et al.[42]	H
OR of SEN | moderate neonatal morbidity	1.55	1.43, 1.67	~LN(0.438, 0.038)	E2	MacKay et al.[40]	H
RR of neurological morbidity | moderate neonatal morbidity	10.4	7.8, 13.9	~LN(2.34, 0.149)	E2	Persson et al.[41]	H
RR of neonatal/infant mortality | moderate morbidity	12.82	9.33, 17.61	~LN(2.551, 0.162)	E2	Iliodromiti et al.[42]	H
OR of SEN | severe neonatal morbidity	1.66	1.46, 1.88	~LN(0.507, 0.063)	E3	MacKay et al.[40]	H
RR of neurological morbidity | severe morbidity	145.5	104.0, 204.1	~LN(4.98, 0.173)	E3	Persson et al.[41]	H
RR of neonatal/infant mortality | severe morbidity	60.61	48.17, 76.26	~LN(4.104, 0.117)	E3	Iliodromiti et al.[42]	H

Parameter	Mean	95%CI	Probability distribution	Node	Source	Quality of evidence
Unit costs and related probabilities						
Ultrasound scan	£107.06	£70.98, 134.92	~G(4.9604, 22.8062)	A	NHS reference costs 2016-17 [43 c]	H
Presentation-only scan	£48.71	£8.96, 88.46	~U(6.87, 90.55)	A	Expert opinion	N/A
Proportion scanned with US (selective screening)	0.3499	0.3349, 0.3650	~B(1351, 2510)	A	Sovio et al.[12]	H
Induction of labour (difference vs. normal delivery)	£125	-£1343, 1594	~N(125.3, 749.2)	B1, B2	Vijgen et al.[44]	M
Cost of vaginal (cephalic) delivery	£1,834	£1750, 2236	~G(7.2606, 252.5824)	C1 – C4	NHS reference costs 2016-17 [43 c]	H
Relative cost difference (vaginal breech vs. cephalic delivery)	1.1633	1.0982, 1.2284	~N(1.1633, 0.0332)	B_C3b, B_C3d, B_C3f, B_C2,	Palencia et al.[45]	M
Cost of ECV	£292.30	£287.5, 297.1	~U(287.22, 297.38)	B_ECV	James et al.[46 c]	M
Cost of emergency Caesarean section	£4,688	£3816, 5443	~G(14.7329, 318.1354)	C1 – C4	NHS reference costs 2016-17 [43 c]	H
Cost of elective Caesarean section	£3,412	£2680, 4038	~G(11.1212, 307.0169)	C1 - C4	NHS reference costs 2016-17 [43 c]	H
Cost of Special Care Baby Unit admission	£1,064	£487, 1862	~G(9.0371, 117.7307)	D1 - D4	NHS reference costs 2016-17 [43 c]	H
Cost of Neonatal High Dependency Unit admission	£1,346	£807, 2020	~G(18.7696, 71.7047)	D1 - D4	NHS reference costs 2016-17 [43 c]	H
Cost of Neonatal Intensive Care Unit admission	£2,590	£1280, 4352	~G(10.7403, 241.0768)	D1 - D4	NHS reference costs 2016-17 [43 c]	H
Proportion of neonates admitted to SCBU	74%	65%, 82%	~D(74, 7, 19)	D1 - D4	Alfirevic et al.[47]	M
Proportion of neonates admitted to NHDU	7%	3%, 13%	-	D1 - D4	Alfirevic et al.[47]	
Proportion of neonates admitted to NICU	19%	12%, 27%	-	D1 - D4	Alfirevic et al.[47]	
Probability of admission to care | no neonatal morbidity	0.074	0.066, 0.082	~B(292, 3659)	D1 - D4	Sovio et al.[12]	H
Odds ratio of admission to care | Moderate neonatal morbidity	11.29	5.90, 21.60	~LN(2.424, 0.331)	D1 - D4	Sovio et al.[12]	H
Probability of admission to care | Severe neonatal morbidity	1	1, 1	N/A	D1 - D4	Assumption	N/A
Short-term cost of acidosis / anoxia	£3,240	£806, 7328	~G(3.6143, 895.6169)	L_E1, L_D2a	Own estimation [c]	L
Short-term cost of respiratory morbidity	£2,011	£993, 3381	~G(10.7125, 187.6316)	L_D2a, L_D3a	Own estimation [c]	L
Cost of transient BPI	£2,066	£1033, 4132	~LN(7.6334, 0.3536)	L_F1	Culligan et al.[48]	M
Cost of permanent BPI	£14,134	£7068, 28264	~LN(9.5563, 0.03536)	L_F1	Culligan et a.[48 c]	M
Cost of perinatal or infant mortality	£1,664	£1372, 1956	~U(1357, 1971)	D1 & E1 – 3	Mistry et al.[49]	M
Long term costs and health state utilities						

Parameter	Mean	95%CI	Probability distribution	Node	Source	Quality of evidence
Special educational needs (per annum)	£7,428	£4467, 10389	~N(7428.1, 1511)	E1 – E3	Barrett et al.[50]	M
Severe neurological morbidity (per annum)	£2,930	£1465, 5859	~LN(7.9826, 0.3536)	E1 – E3	Access economics[51]	M
Utility associated with permanent brachial plexus injury	0.5	0.31, 0.69	~U(0.3, 0.7)	L_G	Culligan et al.[48]	M
Disutility associated with SEN	0		n/a	E1 – E3	Assumption	L
% GMFCS 1 (mild)	22.2%	15.4%, 29.8%	~D(28, 15, 23, 32, 28)	E1 – E3	Young et al.[52]	H
% GMFCS 2 (mild)	11.9%	6.9%, 18.1%	-	E1 – E3	Young et al.[52]	
% GMFCS 3 (moderate)	18.3%	12.0%, 25.4%	-	E1 – E3	Young et al.[52]	
% GMFCS 4 (severe)	25.4%	18.2%, 33.3%	-	E1 – E3	Young et al.[52]	
% GMFCS 5 (severe)	22.2%	15.4%, 29.8%	-	E1 – E3	Young et al.[52]	
Utility, age 0 to 24	0.94	0.926, 0.954	~N(0.94, 0.007)	E1 – E3	Szende et al.[53]	H
Utility, age 25 to 34	0.927	0.915, 0.939	~N(0.927, 0.006)	E1 – E3	Szende et al.[53]	H
Utility, age 35 to 44	0.911	0.897, 0.925	~N(0.911, 0.007)	E1 – E3	Szende et al.[53]	H
Utility, age 45 to 54	0.847	0.825, 0.869	~N(0.847, 0.011)	E1 – E3	Szende et al.[53]	H
Utility, age 55 to 64	0.799	0.775, 0.823	~N(0.799, 0.012)	E1 – E3	Szende et al.[53]	H
Utility, age 65 to 74	0.779	0.755, 0.803	~N(0.779, 0.012)	E1 – E3	Szende et al.[53]	H
Utility, age 75+	0.726	0.697, 0.755	~N(0.726, 0.015)	E1 – E3	Szende et al.[53]	H
Disutility, GMFCS 1	0.124	0.003, 0.466	~G(0.95, 0.13)	E1 – E3	Leigh et al.[54]	M
Disutility, GMFCS 2	0.322	0.123, 0.614	~G(6.43, 0.05)	E1 – E3	Leigh et al.[54]	M
Disutility, GMFCS 3	0.497	0.201, 0.924	~G(7.1, 0.07)	E1 – E3	Leigh et al.[54]	M
Disutility, GMFCS 4	1.035	0.845, 1.244	~G(103.5, 0.01)	E1 – E3	Leigh et al.[54]	M
Disutility, GMFCS 5	1.35	0.985, 1.772	~G(45, 0.03)	E1 – E3	Leigh et al.[54]	M

[a] *Distributions: B = Beta, D = Dirichlet; G = Gamma, LN = Log-normal, N = Normal, U = Uniform*

[b] Quality assessment: H = High – good quality directly relevant evidence (e.g. directly relevant population, well conducted RCT for relative effects, or cohort for baseline effects). M = Medium – directly relevant evidence but poorer quality source (e.g. retrospective cohort for relative treatment effect). L = Low – lack of direct evidence or informed by expert opinion.

[c] Parameter estimated based upon data from the source, rather than directly from the source. Details are provided in text below.

BPI = Brachial plexus injury, ECV = External cephalic version, NHDU = Neonatal high-dependency unit, NICU = Neonatal intensive care unit, SCBU = Special care baby unit, US = Ultrasound. GMFCS = Gross Motor Function Classification System, ranging from 1 (mild) to 5 (severe).

All costs in pound sterling (£) and updated to the cost-year of 2016-17 using the HCHS Index[56].

Derivation of input values for costs

Costs of ultrasound scan for foetal size

The cost of an ultrasound scan was extracted from the national schedule of reference costs (Outpatient procedures, 'Ante-Natal Standard Ultrasound scan (NZ21Z)').[43] Weighted average mean and inter-quartile ranges for costs were calculated, and a gamma distribution fit to these. Resulting parameters: $\alpha = 4.6904$, $\beta = 22.8062$, yielding a mean of £107.06 (95% CI: 70.89, 134.92).

Cost of ultrasound scan for foetal presentation only

There is no published unit cost for a presentation-only scan as it is not routinely undertaken in the NHS. Therefore, we costed two alternative scenarios:

Midwife-led screening in primary care setting

We hypothesised that a midwife could perform a scan as part of a standard antenatal visit in primary care, using a basic handheld scanner connected to a mobile phone or tablet computer (point of care ultrasound). Following the methodology for Wastlund et al.[14], the cost for the presentation-only scan was estimated as a function of the midwife's time, equipment cost, and overheads (room/facilities).

The hourly cost for a Band 5 nurse in 2017 was £36.[56] The scan is assumed to take 5-10 minutes comprising time to make the mother comfortable, the scan itself and documentation of results. In the absence of data on the cost of ultrasound equipment and midwife training, we estimated a total cost of between £1,000 - 20,000 and the average scanner is operated 400 to 3000 times annually over its 5-year life-span. Room costs are assumed between £4,500 and £6,000 annually[58], and in use for the scans 1,573 hours per year.[56]

The total cost was simulated using uniform distributions 100,000 times, and a gamma distribution fitted to the resulting distribution. The resulting parameters of the gamma are alpha = 43.8259, beta = 0.2159, yielding a mean cost of £9.46 (95% CI: £6.87, 12.46).

Sonographer-led ultrasound in designated setting

If the midwife-led scenario proves infeasible, the alternative is referral to a designated ultrasonography unit. A presentation-only scan is much swifter and technically less complicated than a standard antenatal scan. Reference cost 'Diagnostic imaging , Ultrasound Scan with duration of less than 20 minutes, without Contrast (RD40Z)' was used reporting mean (£52) and inter-quartile range (£37-60), to which a gamma distribution was fitted (alpha = 9.2207, beta = 5.6395), yielding a mean of £52.00 and 95% CI: £24.05, £90.55.

Cost for base-case scenario

To incorporate uncertainty over the feasibility of a midwife-led presentation-only scan, we used a uniform distribution of costs, ranging between the lower end of the 95% CI for a midwife-led scan (£6.87) and the upper end of the CI for sonographer-led scan (£90.55).

Cost per mode of delivery

For each of the three modes of deliveries (cephalic vaginal, planned CS and emergency CS), weighted averages of cost by admission type (in/out patient, elective/non-elective etc) and level of complications reported in NHS reference costs[43] were calculated, to which a gamma distribution was fitted. For vaginal delivery, this yielded $\alpha = 7.2606$, $\beta = 252.5824$, with a mean of £1,834.47 (95% CI: £1750.43, 2236.05). For planned CS: $\alpha = 11.1212$, $\beta = 307.0169$, with a mean of £3,411.93 (95% CI:

£2679.80, 4038.29). For emergency CS: α = 14.7329, β = 318.1354, with a mean of £4,688.27 (95% CI: £3816.15, 5443.02)

NHS reference costs do not cost vaginal breech deliveries separately. We therefore assumed these costs would have the same ratio to the costs of elective caesarean section as reported by Palencia et al. (2006).[45] The authors reported Ca$7,255 and Ca$8,440 for elective caesarean section and vaginal breech delivery, respectively, with a mean difference of Ca$1,185 (95% CI: $719, $1663). We fitted a normal distribution to this (mean = 1.1633, sd = 0.0332). The cost of vaginal breech delivery was calculated by multiplying the cost of elective CS[43] with the relative cost increase from vaginal breech.

Cost of External Cephalic Version (ECV)

External cephalic version (ECV) cost was estimated from a 2001 UK based study.[46] A low (£186.70) and high (£193.30) staff cost scenario are reported by the authors. These were converted to 2017 prices using the Hospital & Community Health Services (HCHS) inflation index,[56 57] yielding £287.20 and £297.40 for low and high staff costs. These were assumed the minimum and maximum plausible costs and a uniform distribution assigned between them.

Cost of neonatal unit admission

Neonatal critical care was divided into three levels: 'Intensive care', 'High-dependency', and 'Special care'. Intensive and high dependency care were assigned currency codes XA01Z and XA02Z from the NHS reference costs.[43] Special care was costed using a weighted average of currency codes XA03Z to XA05Z.[43] Proportions of neonates admitted to each level of care and length of stay was extracted from Alfirevic et al.:[47] 19%, 7%, and 74% percent of admitted neonates went to intensive, high dependency, and special care, with a length of stay of 2, 1.5, and 2 days, respectively. Gamma distributions were fitted to the reported mean and IQRs from NHS reference costs.

Data from the POP study[12] were reanalysed to estimate the probability of admission to neonatal care as a function of neonatal morbidity. Apgar score (5 min) was assumed a proxy for neonatal morbidity at delivery with score >7, 4-6, and 0-3 were equivalent to no, moderate and severe neonatal morbidity. Based on POP study data, 7.4% (95% CI: 6.6-8.2%) of neonates with no morbidity, and 47.4% (95% CI: 31.9-63.1%) with moderate morbidity were admitted to care. Beta distributions were fitted to these proportions. Sample sizes of neonates with severe morbidity were too small to reliably estimate proportions admitted. We therefore assumed all neonates with severe morbidity would be admitted to care. In absence of evidence of how the level of neonatal morbidity at birth affects the chance of ending up in each tier of neonatal care, we assumed that the proportions were constant, and that the level of neonatal morbidity only affected the level of overall admittance.

Cost from Respiratory morbidity

A 1995 study[27] of the incidence and length of stay at hospital for respiratory morbidity in neonates found 28% were for Respiratory Distress Syndrome (RDS) and the rest of Transient Tachypnea of the Newborn (TTN). Average length of stay in Neonatal Intensive Care Unit (NICU) was 4 days for RDS and 0.6 days for TTN. The NHS reference cost of NICU admission is £1,295 per day (IQR: £1,015-1,541).[43] Thus the average cost for a case of RDS is £5,180 (IQR: £4,060-6,164), and for TTN, £777 (IQR: 609-925). If RDS and TTN comprise 28% and 72% of respiratory morbidities respectively, the mean cost of respiratory morbidity is £2,010 (IQR: £1,575-2,392). Due to the very low mortality rate from respiratory distress among babies born at term, we assumed respiratory distress could lead to NICU admission, but would otherwise have no consequences.[59] A gamma distribution was fitted to these data, yielding alpha = 10.7125, beta = 187.6316, and a mean of £2011 (95% CI: £993, £3381).

Cost of acidosis without long-term consequences

In the absence of data, we assumed acidosis led to admission to neonatal intensive care unit (NICU) for 1-4 days, with equal probabilities. A gamma distribution was fitted to per-diem costs from NHS reference costs[43]. A gamma distribution was fitted to combined length of stay and per diem cost (alpha = 3.6143, beta = 895.6169) yielding a mean of £3,240 (95% CI: £806- 7,328).

Cost of transient and permanent BPI

Brachial Plexus Injury (BPI) costs were based on Culligan et al. (2010)[48]. Transient BPI resource use comprised specialist hospital consultation, weekly physical therapy for 4 months, and one needle electromyography (EMG) test. Permanent BPI resource use was assumed the same as transient, but with weekly physical therapy for 3 years rather than 4 months, plus one outpatient visit to a specialist, and magnetic resonance imaging (MRI) of the shoulder.[48] Cost for specialist consultations and weekly physiotherapy treatments were £199 and £87, respectively.[60] EMG and MRI costs were £269.20 and £106.59 respectively (NHS reference costs, codes AA33D and RD01C).[43] All costs were adjusted to 2016-17 prices using the HCHS index.[56] We assumed that all costs except for physiotherapy arose in the first year of life and discounted subsequent costs at 3.5%.[64] The total discounted costs from transient and permanent BPI were £2,066 and £14,133, respectively.

Culligan et al.[48] assumed costs would vary between 50-200% of their point estimate. Directly incorporating this into our model (after adjusting for cost differences) with a uniform distribution was considered inappropriate as it would substantially overestimate costs. We therefore interpreted the plausible range as a 95% confidence interval (CI) for total costs, fitting a log-normal distribution to the appropriate mean and CI range. For transient BPI, the resulting distribution had a logged standard error of 0.3536, and mean cost £2,066 (95% CI: £1033 – 4132). For permanent BPI the logged standard error was 0.3536, with a mean of £14,133 (95% CI: £7067-28264).

Cost of perinatal death

The cost of stillbirth was assumed a proxy for the cost of perinatal death. Mistry et al.[49] estimated a cost of between £1,242 (core investigation and counselling only) and £1,804 depending on the clinical scenario surrounding the stillbirth and what tests were needed. We adjusted these estimates to 2016-17 prices [56], and assigned a uniform distribution between them.

Cost of special educational needs (SEN)

Barrett et al.[50] estimated an additional cost of SEN of £6,315 (95% CI: £3798, 8832) per annum in 2007-08 prices. Inflated to 2016-17 prices[56] resulted in an additional cost of £7,428 (95% CI: £4467, 10389). This was applied annually for years 6-17 of life (the typical school years) and discounted at 3.5%.[64]

The cost of severe neurological morbidity

Cerebral palsy (CP) was assumed a proxy for severe neurological morbidity. In the absence of relevant UK data, annual cost was based on Australian data[51]. We extracted total per capita cost for the health system, including program services, aids, and home modifications, but omitted productivity losses, dead weight losses from financial transactions, and costs for informal carers. The annual average cost in 2005 was 5,362 AUD. Adjusted to GPB using the exchange rate at 31st Dec 2005 and inflated to 2016/17 prices[56] yielded an annual mean cost of £2,929.60. In the absence of relevant data, we assumed a 95% CI around the mean at 50% and 200% of the mean (£1465, £5859), to which a log-normal distribution was fitted.

Derivation of input values for QALYs

Baseline long-term Quality-Adjusted Life Years

Lifetime quality-adjusted life years (QALYs) were calculated using survival and Quality of Life (QoL) weights for the general UK population,[53 61] discounted at 3.5%.[64] Stillbirth was assumed to accrue zero QALYs.

Quality of life for brachial plexus injury (BPI)

Culligan et al.[48] used an expert panel to estimate a plausible range of health state utilities for BPI by severity, to which was assigned a uniform distribution. Our model definition of long-term BPI was assumed equivalent to Culligan et al.'s state of either 'Permanent brachial plexus injury (mild to moderate)', or 'Permanent brachial plexus injury (severe) and uncomplicated delivery'. This yielded a uniform distribution between 0.30 (the lower boundary for severe BPI) and 0.70 (the upper boundary for mild to moderate BPI).

Long-term health outcomes following severe neurological morbidity

We assumed cerebral palsy was a proxy for all severe neurological morbidity. Analogous to Leigh et al.,[54] we divided cerebral palsy into the five levels of the Gross Motor Function Classification System (GMFCS), which focuses on ambulatory functionality of people with CP.[62] GMFCS-specific quality of life (QoL) was assigned a gamma distribution from values provided by Leigh et al. [54], subtracting these values from 1 (highest possible QoL) to provide utility weights. QoL was assumed to decrease over time at the same rate as Leigh et al. This effectively assumes that ageing has no greater effect on QoL for those with CP than otherwise healthy members of the UK.

GMFCS-specific survival rates were extracted from Leigh et al. by age band (0-10 years, 11-20 years, and 21-30 years). In the absence of evidence on GMFCS-specific mortality rates beyond 30 years of life, we made the conservative assumption that the mortality rate for those born with severe neurological morbidity who had survived to age 30 would mimic the general population in the UK after this age.

Young et al.[52] report the distribution of GMFCS states to which we assigned a Dirichlet distribution.

Combining QoL with survival, and the distribution of GMFCS states, we obtained expected lifetime QALYs accrued for neonates born with severe neurological morbidity. QALYs accrued after year 1 were discounted at 3.5%.[64]

Beneficial population

Value of information analyses require an estimate of the population who can benefit from the information yielded from research. The target population is all singleton births to nulliparous women in England, excluding those opting for elective CS for reasons other than breech presentation.

There were 636,401 births in England in FY2016-17.[63] Of these, 91.8% were at ≥37 weeks' gestational age, out of which 33.6% were to nulliparous mothers.[63] The statistics do not disaggregate by reason for elective CS (specifically, whether because of suspected breech position or not). Therefore, this means there were:

$$636{,}401 * 0.918 * \ 0.336 = 196{,}297$$

deliveries in England annually meeting our population definition.

Assuming a 10 year time horizon for the value of information analysis (a proxy for the length of time for which the decision question remains relevant before technological development changes it), no meaningful change in the number of deliveries per annum over that period and a discount rate of 3.5% yields a beneficial population of 1,689,663.

If our analyses are assumed generalisable to all pregnancies, then the beneficial population is 636,401 per annum, or 5,477,940 over the 10-year horizon (discounted at 3.5%).

Appendix 3: EVI code walk-through

Below is the code used to calculate the EVSI, with explanation in the righthand column. Full model code available on request from the corresponding author.

Code	Comments / Walkthrough
EVI <- function(distributions=list(c.IOL = c("N", 125.3, 794.6, 650)), n=100000, lambda=20000, screens = screening, mgt = management, popn = 636401, VoIhorizon=10, discountrate=0.035, Q=30, samplesizes = c(10, 100, 100000), paramSet = params) {	Function header including some default values. The default parameter of interest is called 'c.IOL' (cost of induction of labour). It has a normal distribution, with mean, standard error and prior sample size of 125.3, 794.6 and 650.
#Based on Heath & Baio ViH 2018 # Note code is for LN and N priors written only. # parameter - parameter name (must be same as column name in samp matrix) # n - number of PSA loops for calculating NB, EVPI and EVPPI # lambda - WTP threshold # screens & mgt - different strategies # popn - beneficial population (per year) # horizon - time horizon over which to calculate EVI # discount rate - for discounting future values of EVI # Q - number of samples from prior distribution # samplesizes - vector of samplesizes of proposed study	Comments describing input parameters for function

parameters=names(distributions)
print(paste("calculating expected net benefits with current information using",n,"simulations..."))
set.seed(seed)
inputs <- samples(n,paramSet)
CNeoMorb <- costNeonatalMorb(inputs) # calculates neonatal morbidity costs
LTCQ <- longtermCQ(discountRate,horizon,survival,inputs) #calculates pv of long term costs and QALYs
inputs <- cbind(inputs,CNeoMorb,LTCQ) #bind LT costs and QALYs to end of inputs dataframe
inputs <- checkInputsAndCalculateCompoundProbs(inputs) #adds in set of compound probabilities (i.e. P(y) where P(y) = P(x)*RR) and checks for (and solves) out of bounds samples
	Run a standard PSA analysis of the model by sampling all the inputs, ultimately storing the output as a list item called x.

rm(LTCQ,CNeoMorb)
x <- runModel(inputs, screens, mgt, BCEAOutput = F)
 	
#calculate net benefit at lambda
#extract strategy names from x$output matrix
strategies <- colnames(x$output)[seq(1,ncol(x$output),by=2)]
strategies <- substr(strategies,3,nchar(strategies))
 	
NB <- NetBenefit(x$output,lambda)
colnames(NB) <- strategies
#convert to INB vs strat1
INB <- NB - NB[, 1]
rm(NB)
 	
cat("\ Inc net benefit vs strat1 (mu.theta):")
apply(INB,2,mean)
cat("\nVar of inc net benefit (sigma.theta):")
apply(INB,2,var)
cat("\nMax expected (incremental) net benefit:")
max(apply(INB,2,mean))
 	
#calculate EVPI (should be approx the same as output from BCEA package if sufficient simulations)
cat("\nPer patient EVPI:")
EVPI <- mean(apply(INB,1,max))-max(apply(INB,2,mean))
print(paste0("£",round(EVPI,2)))
cat(paste("\nPopulation EVPI (based on",popn,"pregnancies and",VoIhorizon, "year time horizon:"))
totpop <- popn
for (i in 1:(VoIhorizon-1)) {
#print(i)
totpop <- totpop + popn*(1/((1+discountrate)^i))
#print(totpop)
}
	Calculate (prior) incremental net benefit and EVPI.
	
	INB is equivalent to column 'INB' in Heath & Baio, Table 1.
	
	Not necessary to calculate EVPI here but is done for completeness when reporting the results.

pEVPI = EVPI*totpop print(paste0("£",round(pEVPI,0))) mu.theta <- apply(INB,2,mean) sigma.theta <- apply(INB,2,var)	Record prior INB and var(INB) for each strategy (INB is all vs strategy 1) in two vectors, mu.theta and sigma.theta. These are equivalent to -4.5 and 722, final two rows of column 'INB' in Table 1, Heath & Baio.

##
#EVPPI
 	
#Using SAVI code
if(length(parameters)==1) {
  # calculate the EVPPI
  z <- calSubsetEvpi(inputs[,parameters], INB, parameters)
  EVPPI <- t(as.matrix(unlist(c(z$EVPI, z$SE))))
} else {
  # calculate EVPPI for each parameter separately
  EVPPI <- applyCalcSingleParamGam(inputs[,parameters], INB)
  # calculate EVPPI for all parameters together
  z <- calSubsetEvpi(inputs[,parameters], INB)
}
 	
EVPPI <- rbind(EVPPI,unlist(c(z$EVPI, z$SE)))
EVPPI <- rbind(EVPPI,c(EVPI, 0))
 	
# format output table 	
EVPPI <- cbind(EVPPI, EVPPI[,1]/EVPI, EVPPI[,1]*popn, EVPPI[,1]*totpop)
colnames(EVPPI) <- c("EVPPI","SE","prop of EVPI","pEVPPIpa",paste0("pEVPPI",VoIhorizon))
rownames(EVPPI) <- c(parameters,"All","EVPI")
EVPPI<-cbind(round(EVPPI[,1:3],2),round(EVPPI[,4:5],0))
	Calculate EVPPI for parameters of interest.
	
	Functions here are SAVI functions, downloaded from https://github.com/Sheffield-Accelerated-VoI/SAVI. Code was modified to return g.hat from the functions rather than deleting it.
	
	Output of calSubsetEvpi() is stored as a list called z.
	
	Format EVPPI output nicely then print to console

EVPPI
 	
g.hat <- matrix(unlist(z$g.hat[-1]), ncol = length(z$g.hat)-1, byrow = FALSE)
g.hat <- cbind(rep(0,nrow(g.hat)),g.hat)
colnames(g.hat) <- strategies
rm(z)
 	
# save the fitted values and the var/covar matrix 	
fitted.phi <- g.hat
sigma.phi <- var(g.hat) #note this spits out var/covar matrix by default
	Extract g.hat from the output of the EVPPI calculations (SAVI just deletes this – code edited to remove these respective lines. See functions gpFunc() and gamFunc() in SAVI source code). G.hat is the conditional expected net benefit as per Strong et al. 2014 (DOI: 10.1177/0272989X13505910).
	
	Save g.hat as fitted.phi and sigma.phi. Fitted.phi is the column 'INB-phi' in Table 1, Heath & Baio.
	
	To check code is correct, confirm apply(fitted.phi,2,mean) yields approximately the same means as mu.theta. The diagonals of sigma.phi are all less than sigma.theta

##
#EVSI
#sampling possible values of x Q times
 	
x.possMeans <- apply(as.matrix(x$inputs[,parameters]),2,quantile,probs=1:Q/(Q+1),type=4) #need to specify as.matrix in case of 1 parameter (returns as vector)
 	
x.samp <- NULL
p.x.prepost <- array(data=NA, dim=c(Q,2,length(parameters)), dimnames=list(NULL,c("mean","SE"),parameters))
 	
# Si is 'S' in Heath's toy example 	
Si <- matrix(data=NA, ncol=length(strategies),nrow=Q,dimnames=list(NULL,strategies))
	Now calculate the EVSI of a study of sample size n.
	
	Set up results matrix 'x.possMeans', and find the values of prior distribution of c.IOL at the 1/Qth quantile.
	
	Set up matrices to hold preposterior mean and SE at each Q, and various outputs

INB.scale <- matrix(data=NA, ncol=length(strategies),nrow=n,dimnames=list(NULL,strategies)) EVSI <- matrix(data=c(samplesizes,rep(0,length(samplesizes))),nrow=length(samplesizes), ncol=2, dimnames=list(NULL,c("sample size","EVSI")))	

for (samplesize in samplesizes) {
for (i in 1:Q) {
cat(paste("\nCalculating EVSI for a sample size of",samplesize,"Q:",i,"of",Q,"\n"))
#x.samp is equiv of X1, X2 and X3 in the toy example
 	
for (param in parameters) {
	Loop round for each sample size
	Loop for each Q
	
	Loop for each parameter

if(distributions[eval(param)][[1]][1] == "LN") {
 	
x.samp <- rnorm(1,log(x.possMeans[i,match(param,
parameters)]),as.numeric(distributions[eval(param)][[1]][3]))
 	
prepostmean <- (as.numeric (distributions[eval(param)][[1]][2]) * as.numeric(distributions[eval(param)][[1]][4]) + x.samp * samplesize) / (as.numeric(distributions[eval(param)][[1]][4])+samplesize)
SD <- as.numeric(distributions[eval(param)][[1]][3]) * sqrt(as.numeric(distributions[eval(param)][[1]][4]))
prepostSE <- SD/sqrt(as.numeric(distributions[eval(param)][[1]][4]) + samplesize)
 	
p.x.prepost[i,,param] <- c(prepostmean, prepostSE)
rm(x.samp,prepostmean,SD,prepostSE)
}
	For a LN distributed parameter:
	
	Sample one possible trial sample mean, conditional on the prior mean being the first value of Q, and SE as specified in the prior distribution. Store this as x.samp.
	
	Calculate preposterior mean and standard error – mean is weighted av of prior and sampled mean, SE is SD * 1/root(prior n + samplesize)

if(distributions[eval(param)][[1]][1] == "N") {	Same code, but for Normal parameter.

x.samp <- rnorm(1,x.possMeans[i,match(param, parameters)],as.numeric(distributions[eval(param)][[1]][3])) prepostmean <- (as.numeric(distributions[eval(param)][[1]][2])*as.numeric(distributions[eval(param)][[1]][4])+x.samp*samplesize)/(as.numeric(distributions[eval(param)][[1]][4])+samplesize) SD <- as.numeric(distributions[eval(param)][[1]][3])*sqrt(as.numeric(distributions[eval(param)][[1]][4])) prepostSE <- SD/sqrt(as.numeric(distributions[eval(param)][[1]][4])+samplesize) p.x.prepost[i,,param] <- c(prepostmean, prepostSE) rm(x.samp,prepostmean,SD,prepostSE) }	
}	Loop is repeated for every parameter

#now calculate INB.X1, INB.X2 and INB.X3 (preposterior INB)
# (calls samples() to generate inputs then replaces target parameters with preposterior samples) 	
samp <- samples(n, paramSet)
CNeoMorb <- costNeonatalMorb(samp) # calculates neonatal morbidity costs
LTCQ <- longtermCQ(discountRate,horizon,survival,samp) #calculates pv of long term costs and QALYs
samp <- cbind(samp,CNeoMorb,LTCQ) #bind LT costs and QALYs to end of inputs dataframe
samp <- checkInputsAndCalculateCompoundProbs(samp) #adds in set of compound probabilities (i.e. P(y) where P(y) = P(x)*RR) and checks for (and solves) out of bounds samples
	Calculation of preposterior INB
	
	Sample from the prior distribution of every parameter

for (param in parameters) {
if(distributions[eval(param)][[1]][1] == "LN") {
samp[,param] <- exp(rnorm(n, p.x.prepost[i,1,param], p.x.prepost[i,2,param]))
}
if(distributions[eval(param)][[1]][1] == "N") {
samp[,param] <- rnorm(n, p.x.prepost[i,1,param], p.x.prepost[i,2,param])
	Replace sampled values of parameters of interest with samples from the pre-posterior distributions.
	
	(Note it was more expedient to code the model to sample all parameters using the prior

} }	distributions, then replace with the preposteriors rather than changing the distributions sent to the samples() function)

output <- runModel(samp, screens, mgt, BCEAOutput = F)$output
cat(paste("Calculating preposterior NB with",n," loops.\n"))
NB <- NetBenefit(output,lambda)
colnames(NB) <- strategies
#convert to INB rel to strat 1 (as used in SAVI code)
INB <- NB - NB[, 1]
 	
cat("storing variances of preposterior net benefit\n")
Si[i,] <- apply(INB,2,var)
	Run the model with the sampled PSA values and calculate preposterior INB
	
	Save preposterior variance of INB for each strategy

}	Repeat process for all Q
sigma.X <- apply(Si,2,mean)	Calculate mean preposterior variance of INB for each strategy across all Q.

INB.scale[,1] = 0
for (i in 2:ncol(Si)) {
INB.scale[,i] <- (fitted.phi[,i]-mu.theta[i])/sqrt(sigma.phi[i,i])*sqrt(max(0,sigma.theta[i]-sigma.X[i]))+ mu.theta[i]
}
	Rescaled INB as per Heath & Baio.
	
	Note the requirement for the max(0,sigma.theta[i]-sigma.X[i]). For some parameters, the estimated preposterior variance is greater than prior. This occurs where the prior for, eg a probability between two long term outcomes is very vague and one of the outcomes is very certain and the other is highly uncertain (eg death vs a highly uncertain future prognosis). Methodological work exploring this is ongoing.

#EVSI EVSI[match(samplesize,EVSI),2] <- mean(apply(INB.scale,1,max))-max(mu.theta)	Calculate EVSI
}	Repeat for every sample size

EVSI <- cbind(EVSI,EVSI[,2]*popn,EVSI[,2]*totpop) colnames(EVSI)[3:4] = c("pEVSIpa","pEVSI10") # EVSI[,2] <-round(EVSI[,2],4) EVSI[,3:4] <-round(EVSI[,3:4],0) list(EVPPI = EVPPI, EVSI = EVSI) }	Tidy up EVSI results table and return EVPPI and EVSI

Appendix 4: Stability testing

Stability testing was conducted to quantify (and thence minimise) Monte Carlo error as a function of the number of simulations. The model was run 30 times with a given number of simulations. The coefficient of variation of the estimates of mean and standard error of mean cost and QALYs for each comparator were calculated. The mean of all of these was used as a summary measure of the Monte Carlo error. We used an arbitrary 2% cut-off to declare the results stable.

Our analyses showed that we were able to achieve extremely stable results (coefficient of variation of <0.01%) with 100,000 simulations, at a 'reasonable' run time of around 30 seconds. We therefore run our cost-effectiveness analyses with 100,000 simulations. However, due to the need for repeated loops, the EVSI calculations are based on 10,000 simulations. This still generates stable results with a coefficient of variation of only 0.56%.

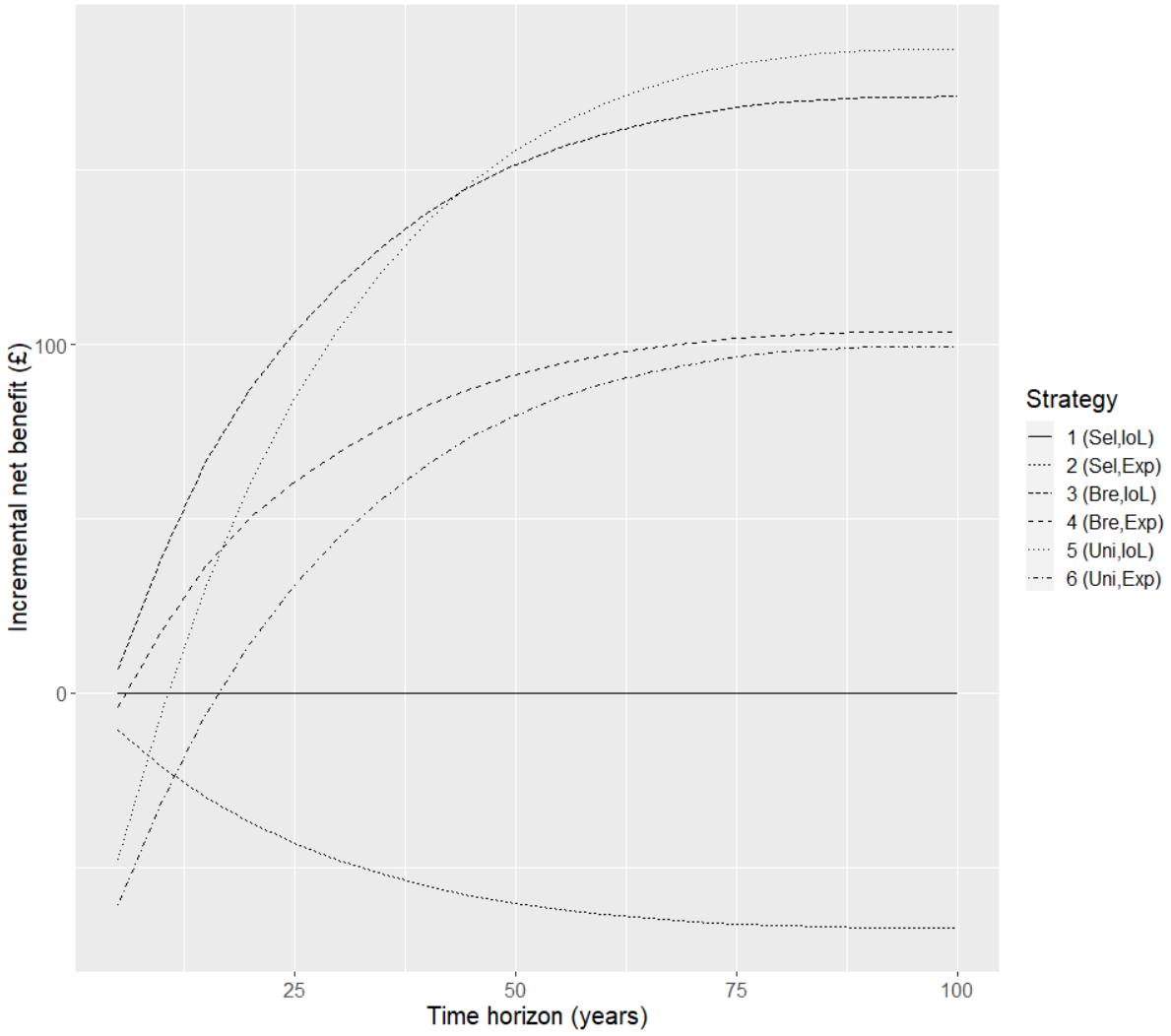
Figure A3.1. Stability testing

Simulations	Computation time (seconds)	Mean Coefficient of Variation (%)
10	0.10	24.68
100	0.09	7.73
1000	0.33	2.53
10000	2.75	0.56
100000	29.56	<0.01

Appendix 5: One-way sensitivity analyses

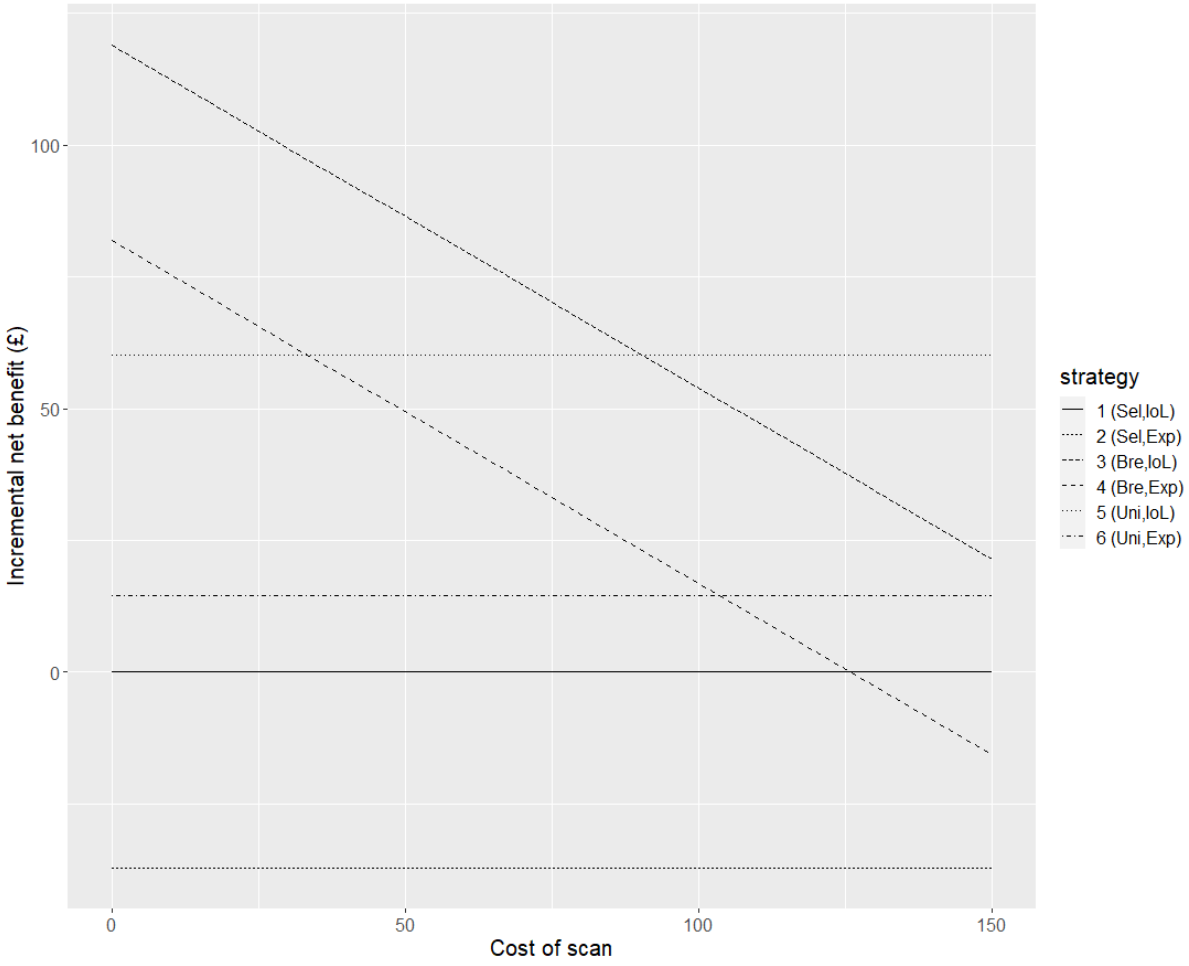
The following figures show the relationship between the parameter of interest and (expected) net benefit of each strategy (net benefit shown as incremental net benefit compared with strategy 1, assumed to represent status quo). The option with the highest net benefit (or equivalently, the highest incremental net benefit versus strategy 1) is the most cost-effective, on average. Net benefit calculated at £20,000 per QALY gained.

Figure A4.1. One-way sensitivity analysis on model time horizon, showing expected incremental net benefit relative to status quo.



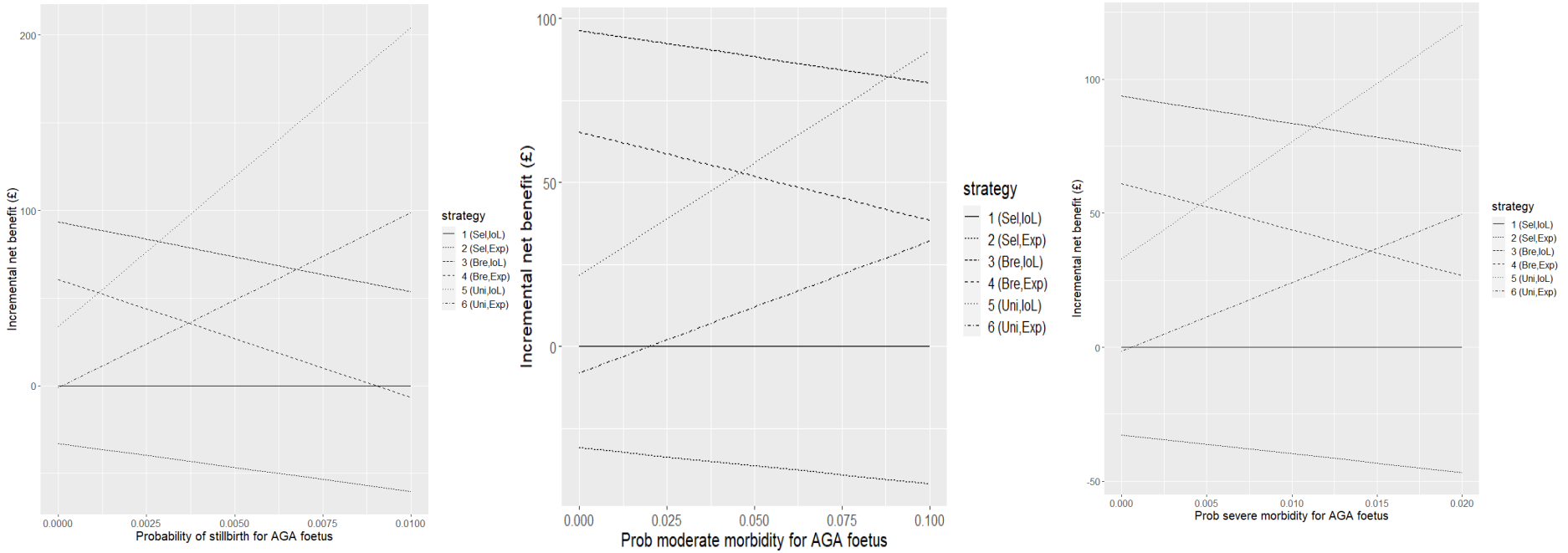
Sel = selective scanning; Bre = Universal presentation-only scan; Uni = Universal scan of foetal biometry and presentation; IoL = Induction of labour if LGA suspected; Exp = Expectant management if LGA suspected.

Figure A4.2. One-way sensitivity analysis on the cost of a scan for foetal presentation only, showing expected incremental net benefit relative to status quo.



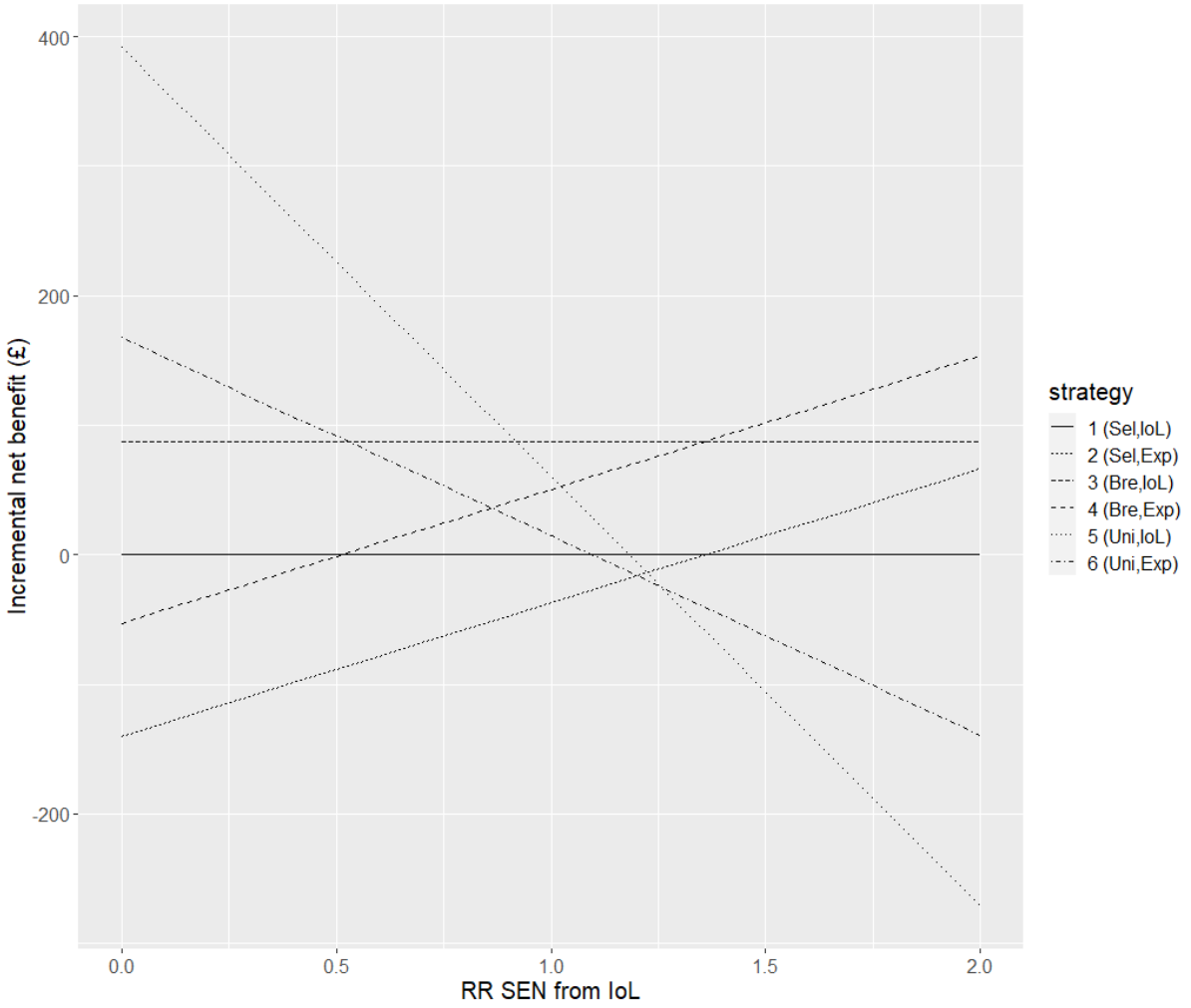
Sel = selective scanning; Bre = Universal presentation-only scan; Uni = Universal scan of foetal biometry and presentation; IoL = Induction of labour if LGA suspected; Exp = Expectant management if LGA suspected.

Figure A4.3a, A4.3b and A4.3c. One-way sensitivity analysis on baseline risk of perinatal mortality, moderate and severe morbidity respectively, showing expected incremental net benefit relative to status quo.



Sel = selective scanning; Bre = Universal presentation-only scan; Uni = Universal scan of foetal biometry and presentation; IoL = Induction of labour if LGA suspected; Exp = Expectant management if LGA suspected. AGA = average size for gestational age (i.e. not SGA or LGA)

Figure A4.4. One-way sensitivity analysis on the relative risk of special educational needs following induction of labour, showing expected incremental net benefit relative to status quo.



Sel = selective scanning; Bre = Universal presentation-only scan; Uni = Universal scan of foetal biometry and presentation; IoL = Induction of labour if LGA suspected; Exp = Expectant management if LGA suspected; SEN = Special Educational Needs; RR = relative risk.