



Health economic analysis of a cluster-randomised trial (OptiBIRTH) designed to increase rates of vaginal birth after caesarean section

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Abstract:	<p>Objective To perform a health economic analysis of an intervention designed to increase rates of vaginal birth after caesarean compared to usual care.</p> <p>Design Economic analysis alongside the cluster randomised OptiBIRTH trial (Optimising childbirth by increasing vaginal birth after caesarean section through enhanced women-centred care).</p> <p>Setting Fifteen maternity units in three European countries: Germany (5), Ireland (5) and Italy (5) with relatively low VBAC rates.</p> <p>Population Pregnant women with a history of one previous lower segment caesarean section; sites were randomised (3:2) intervention or control.</p> <p>Methods A cost-utility analysis from societal and health services perspective using a decision tree.</p> <p>Main outcome measures Costs and resource use per woman and infant were compared between the control and intervention group by country, from pregnancy recognition until 3 months postpartum. Based on the caesarean section rates, and maternal and neonatal morbidities and mortality, the incremental cost-utility ratios were calculated per country.</p> <p>Results The mean difference in costs per Quality Adjusted Life Years (QALYs) gained from societal perspective between the intervention and control group, using a probabilistic sensitivity analysis, was: €263</p>

	<p>(95%CI €258-268) and 0.008 QALYs (95%CI 0.008-0.009) for Germany, €456 (95%CI €448-464) and 0.052QALYs (95%CI 0.051-0.053) for Ireland and €1174 (95%CI €1170-1178) and 0.006 (95%CI 0.005-0.007) QALYs for Italy. The incremental cost-utility ratios were €33,741/QALY for Germany, €8,785/QALY for Ireland and €214,318/QALY for Italy with a 51% probability of being cost-effective for Germany, 92% for Ireland and 15% for Italy.</p> <p>Conclusions The OptiBIRTH intervention was likely to be cost-effective in Ireland and Germany.</p>

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*“Health economic analysis of the OptiBIRTH trial”***Abstract**

Objective To perform a health economic analysis of an intervention designed to increase rates of vaginal birth after caesarean compared to usual care.

Design Economic analysis alongside the cluster randomised OptiBIRTH trial (Optimising childbirth by increasing vaginal birth after caesarean section through enhanced women-centred care).

Setting Fifteen maternity units in three European countries: Germany (5), Ireland (5) and Italy (5) with relatively low VBAC rates.

Population Pregnant women with a history of one previous lower segment caesarean section; sites were randomised (3:2) intervention or control.

Methods A cost-utility analysis from societal and health services perspective using a decision tree.

Main outcome measures Costs and resource use per woman and infant were compared between the control and intervention group by country, from pregnancy recognition until 3 months postpartum. Based on the caesarean section rates, and maternal and neonatal morbidities and mortality, the incremental cost-utility ratios were calculated per country.

Results The mean difference in costs per Quality Adjusted Life Years (QALYs) gained from societal perspective between the intervention and control group, using a probabilistic sensitivity analysis, was: €263 (95%CI €258-268) and 0.008 QALYs (95%CI 0.008-0.009) for Germany, €456 (95%CI €448-464) and 0.052QALYs (95%CI 0.051-0.053) for Ireland and €1174 (95%CI €1170-1178) and 0.006 (95%CI 0.005-0.007) QALYs for Italy. The incremental cost-utility ratios were €33,741/QALY for Germany, €8,785/QALY for Ireland and €214,318/QALY for Italy with a 51% probability of being cost-effective for Germany, 92% for Ireland and 15% for Italy.

Conclusions The OptiBIRTH intervention was likely to be cost-effective in Ireland and Germany.

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Keywords cost-effectiveness analysis; elective repeat caesarean; vaginal birth after caesarean; quality of life

*“Health economic analysis of the OptiBIRTH trial”***Tweetable abstract**

The OptiBIRTH intervention (to increase VBAC rates) is likely to be cost-effective in Germany and Ireland.

Introduction

There is global concern about the rising caesarean section rates, the decline in vaginal birth after caesarean section (VBAC) rates, and the variation in rates between and within countries¹. While a caesarean section is the safest mode of birth in some circumstances, such as placenta praevia or cephalopelvic disproportion, a large number of caesarean sections are performed in the absence of any medical indications, and the practice of performing an elective repeat caesarean section (ERCS) after one previous caesarean section has become common^{2,3}. Pregnancies after a previous lower segment caesarean section are associated with increased risks for mother and infant such as placenta accreta, placenta praevia, placental abruption and stillbirth². Attempting a VBAC is associated with higher rates of uterine ruptures, and to a very slight extent long-term neonatal morbidities such as cerebral palsy and neonatal mortality^{3,4}. VBAC results in less morbidity and mortality for women, a reduction in length of hospital stay and associated hospitalisation costs^{4,5} and, from a societal perspective, is cost-effective compared to ERCS⁵. These results emphasise the health economic value, in addition to the clinical benefits, of considering VBAC over ERCS.

The continuing increase in caesarean sections and the associated decrease in VBACs led to the development of the OptiBIRTH project which aimed to improve the organisation of maternal health service delivery and optimise childbirth through enhanced women-centred care^{6,7}. The main objective was to increase the number of VBACs, and thereby decrease the number of ERCSs, after one previous lower segment caesarean section by implementing an innovative strategy to enhance women's involvement in their care. Fifteen maternity units with low VBAC rates, less than 35%, in three European countries (Germany, Ireland and Italy) took part in the trial. This paper presents the cost-utility analysis, which was conducted alongside the cluster randomised trial to evaluate the health economic implications of the OptiBIRTH intervention.

*“Health economic analysis of the OptiBIRTH trial”***Methods*****Study design***

This health economic evaluation was conducted alongside the OptiBIRTH trial (Registration: ISRCTN10612254)⁸. The OptiBIRTH trial investigated the effects of a woman-centred intervention designed to increase VBAC rates through an unblinded cluster randomised trial in 15 maternity units in Germany, Ireland and Italy. Sample size calculations, adjusted to allow for clustering, determined that 12 sites (4 in each country) were required, each containing 120 participating women (840 women in the intervention group and 840 women in the control group). However, to allow for a loss to follow-up of 20% of women, and the possibility that one site per country would drop out of the trial, 15 sites were randomised on a 3:2 ratio, intervention to control, across the three countries⁶. Women attending intervention sites received a complex innovative programme of evidence based antenatal education classes, communities of practice and online activities to increase their empowerment, engagement and involvement in their care and decision-making. In addition, clinicians received educational sessions, and midwife and obstetrician opinion leads were appointed to support clinicians. Women attending control sites received usual care. The primary outcome of the initial analysis was the VBAC rate in the year before the trial started (2012) versus the year after trial recruitment closed (2016). Secondary outcomes and the protocol are published⁶. Ethical approval was granted for this trial (FP7-HEALTH-2012-INNOVATION-1 HEALTH.2012.3.2-1) on 27 of June 2012 by the Faculty of Health Sciences, Trinity College Dublin, Ireland and the Research Ethics Committees of all participating sites. No outcome sets were appropriate for this study.

The results of this study showed no overall significant difference in the primary outcome (relative risk (RR) 1.19 [95% confidence interval (CI) 0.88-1.62], $p=0.27$), in the one year follow-up analysis for the year 2015⁹. VBAC rates changed between 2012 and 2015, from 26% to 27% in the intervention sites, and from 18% to 20% in the control sites. However, at the country-level, results from Italy showed a significant difference in VBAC rates (from 8% to 22%, RR 2.43 [95% CI 1.84-3.22]). Secondary maternal and neonatal outcomes did not differ significantly between the IG and CG.

Economic evaluation

This health economic evaluation was a cost-utility analysis (CUA), comparing costs and outcomes of the intervention group (IG) and control group (CG) during the trial. Women were not involved in the design of this

“Health economic analysis of the OptiBIRTH trial”

health economic evaluation. The societal and health services perspective (HSP) were used. Direct medical costs (e.g. costs for labour and birth) were considered in both perspectives, other costs such as direct non-medical costs (e.g. travel costs), and indirect costs (e.g. productivity loss)¹⁰ were also considered for the societal perspective. The time horizon was from pregnancy recognition up to 3 months postpartum. Data on resource use were collected via economic diaries and health-related quality of life (HRQoL) data were collected via self-administered questionnaires at inclusion in the trial and three months postnatal. The health economic dataset comprised a subset of women who completed, at a minimum, one diary (antenatal and/or postpartum). For this subsample, mean values for costs and Quality Adjusted Life Years (QALYs) were calculated per health state for each country. These mean costs and QALYs were used to estimate the total costs and QALYs for the total study sample in each country.

Resource use

Each participant was invited to document data on resource use by completing antenatal and postpartum economic diaries. Antenatal diaries were distributed at recruitment. Entries in those diaries, included data about the number of contacts with healthcare provider(s) (HPs) prior to the enrolment in the study, the type of contact (e.g. visit, telephone, e-mail), all contacts with HPs during the study by type of contact, place of contact (hospital/local health centre/at home), duration of the visit including waiting times, diagnostic testing (blood sample, urine sample, ultrasound, etc.), travel time, and transport type (car/public transport/taxi, etc.). Data on prescribed drugs and antenatal and postpartum admissions during the study were collected also. Perinatal resource use on mode of birth, length of stay, level of care, and transfers were collected at hospital level.

Unit costs

Unit cost estimates for direct medical costs were collected from national standardised public tariffs lists. Ambulatory costs (consultation fees, fees for diagnostic testing), were obtained from country-specific ambulatory tariff lists¹¹⁻¹⁵ (Table S1). Intramural costs were based on country-specific Diagnostic Related Groups (DRG)^{13,16,17}. Costs were considered for both mother and infants, and specified per birth method and health outcome. Medication prices were obtained by consulting national pharmaceutical price lists¹⁸⁻²⁰, and indirect costs were calculated as productivity loss, estimated and based on the time spent per contact with HPs (including travel and waiting times) using the national cost per working hour²¹. Transportation costs were calculated based on the type of transportation used. Intervention costs were included in the analysis as an average cost per woman in the IG. To calculate these costs, the average

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hours of clinicians' time (education of clinicians, preparation time, giving the classes to women) and women's time (attendance at classes) were multiplied with the respective unit costs. All unit costs (Table S1) were expressed in 2016 Euros using the Harmonized Indices of Consumer Prices – health²². Discounting was not necessary because all costs occurred within one year (pregnancy recognition until 3 months postpartum).

Health outcomes

Postpartum quality of life was assessed three months postpartum using the Short-Form 6-Dimension (SF-6D) for deriving utilities²³. For the purposes of this analysis, data on HRQoL were assessed by study group (IG versus CG) and for each endnode of the decision tree (see below). Postpartum utility data were controlled for antenatal utility imbalances by using multiple regression based adjustment²⁴.

Cost-utility analysis

A decision tree has been developed in the context of OptiBIRTH (Figure 1)²⁵. The algorithm of the decision tree was similar for all three countries, and consisted of two main arms: intervention and control. Women in both arms were eligible for a spontaneous vaginal birth, instrumental vaginal birth, ERCS or emergency caesarean section (with or without labour). Independent of mode of birth, at the endnode of the decision tree, women could be alive, suffer a morbidity or die. Maternal morbidities included in the decision tree were: peripartum hysterectomy, uterine rupture, endometritis, blood transfusion, thrombotic events, operative injury and wound complications. Neonatal outcomes were linked to the maternal outcomes, and included mortality and the following morbidities; hypoxic ischemic encephalopathy, sepsis and respiratory conditions including transient tachypnoea of the newborn and respiratory distress syndrome.

Costs were calculated by linking resource use to their respective unit costs, and an average total cost and utility value was calculated for each endnode. The incremental cost-utility ratio (ICUR) was estimated by dividing the incremental costs (ΔC) by the incremental utility (ΔU): $ICUR = \Delta C / \Delta U$.

A country-specific cost-effectiveness threshold was used: €37,719/QALY for Germany, €45,000/QALY for Ireland and €27,219/QALY Italy²⁶. The cost-effectiveness threshold for Ireland was set historically at €45,000/QALY²⁷, and the gross domestic product per capita was used for Germany and Italy because national cost-effectiveness thresholds did not exist.

*“Health economic analysis of the OptiBIRTH trial”**Sensitivity analysis*

The uncertainty and robustness around the input parameters were evaluated by performing sensitivity analyses. One-way and probabilistic sensitivity analyses were conducted on the costs, probabilities (mode of birth, maternal and neonatal mortality and morbidities) and HRQoL data were included in the model. Parameters were varied by 20% of their base case value when performing the one-way sensitivity analyses. Tornado diagrams were used to measure the impact of different components on the ICUR result. For the probabilistic sensitivity analysis, Monte Carlo simulations with 5000 iterations were performed. The differences in mean costs and utilities between the IG and CG were estimated, and 95% CIs around the means were calculated. The results of the probabilistic sensitivity analysis were graphically presented on cost-effectiveness planes and cost-acceptability curves. Additionally, the Incremental Net Monetary Benefit (INMB) approach was used to assess the cost-effectiveness of the intervention using the respective threshold commonly used in each country^{26,27}. If for a given country the respective $INMB > 0$, the intervention was considered to be cost-effective. All analyses were performed using IBM SPSS Statistics version 24 and Microsoft Excel[®] version 2013.

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Results*Sample*

The health economic dataset comprised a subset of women who completed a minimum of one diary (antenatal and/or postpartum). In total, 964 (50%) women were included: 166 IG and 121 CG in Germany; 79 IC and 90 CG in Ireland; 303 IG and 205 CG in Italy. Data on resource use and costs were provided by 734 (38%) women for the antenatal period, 964 (50%) women for the perinatal period, and 856 (44%) postpartum women and infants, and data on HRQoL were available for 864 (44%) women. Clinical and demographic characteristics of women who did and those who did not respond to the health economic questionnaires are presented in Table S2.

Resource use

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The number of antenatal and postpartum visits, and the main healthcare providers, differed between countries (Table S3). Overall, the highest number of antenatal visits was found in the IG in Germany and Ireland, and the CG in Italy. The median number of postpartum visits was comparable between the IG and CG for all countries. Systemic hormonal preparations were the most commonly used medications during the antenatal period, and antibiotics for both postpartum mothers and infants. The frequency and length of hospital stay as well as productivity loss varied between countries.

Costs

Mean total costs for the antenatal, perinatal and postpartum period were calculated for all endnodes (Table S4). Antenatal costs included intervention costs were calculated from both perspectives (societal perspective, HSP): €51, €40 for Germany; €120, €98 for Ireland; €63, €50 for Italy. The mean (\pm SD) antenatal costs from societal and HSP varied from: €887 (\pm €729) and 570 (\pm 567) in Italy (CG) to €4,440 (\pm €2262) and 3594 (\pm 1926) in Ireland (IG). Mean perinatal costs were lowest in the CG in Italy, €2,684 (\pm €550) and highest in the CG in Ireland, €4,481 (\pm €1572). Mean (\pm SD) total maternal postpartum costs from societal and HSP varied from €115 (\pm 316) and 79 (\pm 304) in Italy (CG) to €661 (\pm 2056) and 571 (\pm 2046) in Ireland (IG), and infant costs ranged from €143 (\pm 164) and 107 (\pm 154) in Italy (CG) to €646 (\pm 1704) 600 (\pm 1705) in Ireland (CG).

Health outcomes

Health outcomes are presented as utility scores, mean utility scores were calculated for all endnodes (Table S5). The overall utility score was highest in the IG for all three countries.

Cost-utility analysis

The OptiBIRTH intervention resulted in an increase in costs from societal and HSP for all three countries: €262 and €263 for Germany, €459 and €529 for Ireland and €1,179 and €907 for Italy. There was a QALY gain of 0.008 for Germany, 0.052 for Ireland and 0.006 for Italy (Table 1). ICUR results of the deterministic analysis (Table 1) were €35,785/QALY for Germany, €8,866/QALY for Ireland and €196,136/QALY for Italy from societal perspective and €35,841/QALY for Germany, €10,208/QALY for Ireland and €150,838/QALY for Italy from HSP. From both

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perspectives, the ICUR was below the cost-effectiveness threshold for Germany and Ireland. The results of the one-way sensitivity analysis are presented in Figure S1.

The probabilistic sensitivity analysis showed comparable results to the deterministic analysis, the mean difference in costs and QALYs gained per woman were (societal perspective, HSP): €263 (CI €258-268), €265 (CI 260-270) and 0.008 QALYs (CI 0.007-0.009) for Germany; €456 (CI €448-464), €528 (CI 521-535) and 0.052 QALYs (CI 0.051-0.053) for Ireland and €1174 (CI €1170-1178), €910 (CI 905-914) and 0.006 (CI 0.005-0.007) QALYs for Italy. The ICUR (Table 1) differed from €33,741/QALY for Germany, €8,785/QALY for Ireland and €214,318/QALY for Italy from societal perspective and €34,342/QALY for Germany, €10,173/QALY for Ireland and €127,481/QALY for Italy from HSP.

The results of the Monte Carlo simulations of the societal perspective are shown in Figure 2 as cost-effectiveness planes. Similar results were found from HSP. The simulations are mainly plotted over the 4 quadrants for Germany and Ireland. Some simulations indicate to be more expensive with more health gains (North-East quadrant), less expensive with more health gains (South-East quadrant), more expensive with fewer health gains (North-West) and less expensive with less health gains (South-West). However, the majority of simulations for Germany (62%) and Ireland (96%) are plotted in the East quadrants indicating them to be less/more expensive with health gain. For Italy, all simulations were found to be more expensive and some resulted in health gain (North-East quadrant, 56%), others in health loss (North-West quadrant, 44%), indicating that the OptiBIRTH intervention was costlier but not effective for all simulations. The cost-effectiveness acceptability curves show a probability of cost-effectiveness of 51% for Germany, 92% for Ireland and 15% for Italy at their respective thresholds (Figure S2). The INMB was cost-effective at a threshold of €35,000/QALY for Germany, €9,000 for Ireland and >€50,000 for Italy (Figure S3). Based on the probability sensitivity analysis, we can conclude there is a reasonable amount of uncertainty around the results. At current thresholds, the OptiBIRTH intervention was likely to be cost-effective for Germany and Ireland.

Discussion***Main findings***

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This was a cost-utility analysis alongside the OptiBIRTH trial. The results suggest the intervention was likely to be cost-effective from HSP and societal perspective in both Ireland and Germany, but not in Italy, with an ICUR from societal perspective of €33,741/QALY for Germany, €8,785/QALY for Ireland and €214,318/QALY for Italy and a cost-effective INMB for Germany and Ireland. For all countries, the OptiBIRTH intervention resulted in a QALY gain and an increase in costs.

Strengths and limitations

The health economic data was prospectively collected using diaries and included detailed data on resource use by women in three EU countries. This results in a unique dataset comprising data from pregnancy recognition until three months postpartum, for both mother and infant in a large sample of 964 women. Moreover, HRQoL was assessed during the antenatal and postpartum periods and adjusted postpartum HRQoL measures to the antenatal HRQoL were implemented in the model. This is the first international cost-utility analysis using a raw dataset of international HRQoL data in maternity care. In addition, this study was performed from the broadest perspective possible, the societal perspective as well as from health services perspective.

Our study has several limitations. First, the data collection relied on women using self-completed diaries and HRQoL questionnaires. Unfortunately, trial enrolment was later in pregnancy than initially planned so, for some women, the recall time to complete the antenatal diary was several months and this can impact results. However, previous research has shown that people have a good memory of major life events, such as pregnancy, which minimises recall bias²⁸. Secondly, costs were based on national tariff lists and DRGs because of low response rates to the questions about healthcare costs and the unavailability of hospital-level costs. Previous research showed there is minimal difference in the DRG reimbursement cost and the average cost of normal birth²⁹. Third, the health economic dataset comprised a subsample of women (n=964, 50%). Mean values were calculated and linked to all endnodes. This could lead to selection bias. Lastly, the one-year follow-up analysis of the OptiBIRTH trial showed no significant effects on VBAC rates for all countries, although the intervention was shown to be safe. One could argue that, when no clinical effect is seen between intervention and control, conducting a health economic evaluation is not appropriate.

In OptiBIRTH, only the VBAC rate but also data on the HRQoL of women were collected. The difference in support between the intervention and control group of the OptiBIRTH trial resulted in higher utility scores in the intervention group, suggesting the positive impact of the OptiBIRTH intervention on HRQoL. In that context, it was a valuable

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argument to conduct a full cost-effectiveness analysis with the focus on differences in costs and utilities between control and intervention group. In addition, as suggested by Briggs et al (2001)³⁰ ‘the analytic focus should be on the estimation of the joint density of cost and effect differences, the quantification of uncertainty surrounding the incremental cost-effectiveness ratio and the presentation of such data as cost-effectiveness acceptability curves’. We therefore performed an extensive sensitivity analysis.

Using HRQoL as an outcome measure has implications on the health economic result, by means although the OptiBIRTH intervention showed no statistically significant difference in overall VBAC rates, women in the intervention sites had higher HRQoL utility scores in all countries. Therefore, the OptiBIRTH intervention was likely to be cost-effective for Germany and Ireland. Despite the clinical effectiveness of the intervention in the sites in Italy, the intervention was not cost-effective in that country. The main reason for this is a higher healthcare utilisation (Table S3) and a minimal QALY gain (0.006) in the IG, compared to the CG. When estimating the ICUR with the formula $ICUR = \Delta C / \Delta U$, the combination of higher costs in the IG and a minimal difference in QALYs between the IG and CG resulted in an unfavourable ICUR for Italy.

Interpretation

These results are difficult to compare with other studies because the main focus of previously published studies is on the difference in costs and outcomes comparing VBAC with ERCS. Contrastingly, both main arms of our decision tree consists of VBAC as well as caesarean sections. Moreover, the majority of published studies include a hypothetical cohort without data from women, do not include neonatal outcomes, use a different time horizon and are limited to one country.

Looking at these hypothetical cohort studies, two European studies were conducted comparing attempting a VBAC with ERCS^{25,27}. VBAC was found to be a dominant strategy in four EU countries (Belgium, Germany, Ireland and Italy), resulting in a cost and utility gain, over ERCS using a 6 week and lifetime time horizon. Other health economic evaluations were conducted in the United States of America^{4,31-36} and all but one included neonatal outcomes³¹. The overall results of these studies suggest that, even when considering a lifetime time horizon, attempting a VBAC is a cost-effective strategy compared to ERCS in low-risk women^{4,31-36}. The results of these published models are more favourable towards attempting a VBAC than ours. However, these models are based on a hypothetical cohort where the maximum potential of having a VBAC versus ERCS is reached. In our model, women

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in the IG as well as CG, were suitable for VBAC and ERCS, and much depended on clinicians' recommendations for mode of birth. This mixed population reduces the maximum potential effect (i.e. all eligible women have VBAC). As a result, the maximum potential in benefits is not achieved, resulting in a suboptimal ICUR.

Proposal for future research

Caesarean section rates remain high and outcomes for women and neonates remain unclear in some circumstances. The results of this health economic analysis suggest that the OptiBIRTH intervention is cost-effective for Germany and Ireland, but not for Italy. For all three countries, the intervention resulted in an increase in costs and QALYs. The increase in QALYs demonstrates the positive effect of this intervention on women's HRQoL. There is still, however, some uncertainty around these health economic results, indicating that the effect of VBAC interventions should be investigated further to identify potential health and health economic outcomes.

Conclusion

This health economic evaluation of the OptiBIRTH trial indicates that the intervention results in a QALY gain for women in all three countries and is likely to be cost-effective in Ireland and Germany. These results indicate that the OptiBIRTH intervention has a positive impact on the HRQoL of women, and this should be investigated further.

*“Health economic analysis of the OptiBIRTH trial”***Acknowledgements**

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Disclosure of interests

None to be declared. Completed disclosure of interest forms are available to view online as supporting information.

Contribution to authorship

MF drafted and revised the manuscript for content, performed the analysis, handled the study coordination, and is the guarantor for the overall content. KB revised the manuscript for content. SG-B, PH, and JN assisted with trial conduct in Germany, Ireland and Italy, respectively. DDe (Ireland), MMG (Germany) and SM (Italy) were the national principal investigators for the trial and responsible for conduct and management of the trial. DD was project manager and CB principal investigator for the OptiBIRTH project. They contributed to initial planning of the study and revised the manuscript for clinical applicability. KP led the work package for the health economics strand of the trial. All authors contributed to, read and approved this paper.

Details of ethical approval

Faculty of Health Sciences Ethics Committee, Trinity College Dublin, Ireland, 27/06/2012

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References

1. EURO-PERISTAT. European Perinatal Health Report. The health and care of pregnant women and babies in Europe in 2010. [www.europeristat.com] Accessed 14 May 2018.
2. Macfarlane AJ, Blondel B, Mohangoo AD, Cuttini M, Nijhuis J, Novak Z, et al. Wide differences in mode of delivery within Europe: risk-stratified analyses of aggregated routine data from the Euro-Peristat study. *BJOG* 2016;123:559-68.
3. Guise JM, Eden K, Emeis C, Denman MA, Marshall N, Fu RR, et al. Vaginal birth after cesarean: new insights. Report Number: 1530-4396. 2010.
4. Gilbert SA, Grobman WA, Landon MB, Varner MW, Wapner RJ, Sorokin Y, et al. Lifetime cost-effectiveness of trial of labor after cesarean in the United States. *Value Health* 2013;16:953-64.
5. Rogers AJ, Rogers NG, Kilgore ML, Subramaniam A, Harper LM. Economic Evaluations Comparing a Trial of Labor with an Elective Repeat Cesarean Delivery: A Systematic Review. *Value Health* 2017;20:163-73.
6. Clarke M, Savage G, Smith V, Daly D, Devane D, Gross MM, et al. Improving the organisation of maternal health service delivery and optimising childbirth by increasing vaginal birth after caesarean section through enhanced women-centred care (OptiBIRTH trial): study protocol for a randomised controlled trial (ISRCTN10612254). *Trials* 2015;16:542.
7. Cheng YW, Eden KB, Marshall N, Pereira L, Caughey AB, Guise JM. Delivery after prior cesarean: maternal morbidity and mortality. *Clin Perinatol* 2011;38:297-309.
8. ISRCTN registry. Improving the organisation of maternal health service delivery, and optimising childbirth, by increasing vaginal birth after caesarean section (VBAC) through enhanced women-centred care: ISRCTN10612254. [http://www.isrctn.com/ISRCTN10612254]. Accessed 15 May 2018.

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9. European Commission. Final Report Summary - OPTIBIRTH (Improving the organisation of maternal health service delivery, and optimising childbirth, by increasing vaginal birth after caesarean section (VBAC) through enhanced women-centred care). 2017. [https://cordis.europa.eu/result/rcn/201548_en.html] Accessed 17 February.
10. Drummond MF SM, Torrance GW, O'Brien BJ, Stoddart GL. Methods for the evaluation of health care programmes. 3th edition. United States: Oxford University Press; 2005.
11. Health Service Executive. Statutory Instruments Health Professionals (reduction of payments to general practitioners) Regulations 2013. Report Number. 2013.
12. Health Services Executive (Galway University Hospital). Unit costs Ireland. E-mail communication To: Fobelets M.; 4 September 2014
13. InEK – Institut für das Entgeltsystem im Krankenhaus. Fallpauschalen-Katalog G-DRG-Version 2015 2015. http://www.g-drg.de/cms/inek_site_de/layout/set/einspaltig/G-DRG-System_2015/Fallpauschalen-Katalog/Fallpauschalen-Katalog_2015. Accessed 4 August 2015.
14. Kassenärztliche Bundesvereinigung Köperschaft des öffentlichen Rechts. Einheitlicher Bewertungsmaßstab. Stand: 4. Quartal 2015.
15. Ministero della Salute. Prestazioni di Assistenza Specialistica Ambulatoriale. Gazzetta Ufficiale 2013.
16. Health Service Executive. Ready reckoner of acute hospital inpatient and daycase activity & costs (summarised by DRG) relating to 2011 costs and activity. Report Number: (01) 626 3447. 2013.
17. Ministero della Salute. Supplementario ordinario n. 8 alle gazzetta ufficiale. 28 January 2013.
18. Health Services Executive. Reimbursable Items 2016. <http://www.hse.ie/eng/staff/PCRS/items/>. Accessed 24 November.
19. Ministero della Salute. Medication Costs. E-mail communication To: Fobelets M.; 7 June 2016.
20. GKV-Spitzenverband. Zuzahlungsbefreite Arzneimittel [https://www.gkv-spitzenverband.de/media/dokumente/service_1/zuzahlung_und_befreiung/zuzahlungsbefreite_arzneimittel_nach_name/Zuzahlungsbefreit_sort_Name_160215.pdf.2016] Accessed 15 May 2018.

“Health economic analysis of the OptiBIRTH trial”

21. Eurostat. Annual net earnings 2014. [[http://ec.europa.eu/eurostat/statistics-explained/index.php/File:Annual_net_earnings,_2014_\(EUR\)_YB15.png](http://ec.europa.eu/eurostat/statistics-explained/index.php/File:Annual_net_earnings,_2014_(EUR)_YB15.png)] Accessed 15 May 2018.
22. Eurostat. HICP - health 2016. [<http://ec.europa.eu/eurostat/en/web/products-datasets/-/TEICP060>] Accessed 15 May 2018.
23. Brazier J, Roberts J, Deverill M. The estimation of a preference-based measure of health from the SF-36. *J Health Econ* 2002;21:271-92.
24. Manca A, Hawkins N, Sculpher MJ. Estimating mean QALYs in trial-based cost-effectiveness analysis: the importance of controlling for baseline utility. *Health Econ* 2005;14:487-96.
25. Fobelets M, Beeckman, K., Faron, G., Daly, D., Begley, C., Putman, K. Vaginal birth after caesarean versus elective repeat caesarean delivery after one previous caesarean section: a cost-effectiveness analysis in four European countries. *BMC Pregnancy Childbirth* 2018;18.
26. International Monetary Fund. Gross domestic product per capita, current prices 2016. [<https://www.imf.org/external/pubs/ft/weo/2016/01/weodata/weorept.aspx?sy=2016&ey=2016&scsm=1&ssd=1&sor=country&ds=.&br=1&pr1.x=80&pr1.y=9&c=124%2C134%2C178%2C136&s=NGDPPC&grp=0&a=>] Accessed 15 May 2018.
27. Fawsitt CG, Bourke J, Greene RA, Everard CM, Murphy A, Lutomski JE. At what price? A cost-effectiveness analysis comparing trial of labour after previous caesarean versus elective repeat caesarean delivery. *PLoS One* 2013;8:e58577.
28. Roberts RO, Bergstralh EJ, Schmidt L, Jacobsen SJ. Comparison of self-reported and medical record health care utilization measures. *J Clin Epidemiol* 1996;49:989-95.
29. Bellanger MM, Or Z. What can we learn from a cross-country comparison of the costs of child delivery? *Health Econ* 2008;17:S47-57.
30. Briggs AH O'Brien BJ. The death of cost-minimization analysis? *Health economics* 2001;10:179-84.
31. Chuang JH, Jenders RA. Trial of labor versus elective repeat cesarean section for the women with a previous cesarean section: a decision analysis. *Proc AMIA Symp* 1999:226-30.

“Health economic analysis of the OptiBIRTH trial”

32. Chung A, Macario A, El-Sayed YY, Riley ET, Duncan B, Druzin ML. Cost-effectiveness of a trial of labor after previous cesarean. *Obstet Gynecol* 2001;97:932-41.
33. Gilbert SA, Grobman WA, Landon MB, Spong CY, Rouse DJ, Leveno KJ, et al. Cost-effectiveness of trial of labor after previous cesarean in a minimally biased cohort. *Am J Perinatol* 2013;30:11-20.
34. Grobman WA, Peaceman AM, Socol ML. Cost-effectiveness of elective cesarean delivery after one prior low transverse cesarean. *Obstet Gynecol* 2000;95:745-51.
35. Wymer KM, Shih YC, Plunkett BA. The cost-effectiveness of a trial of labor accrues with multiple subsequent vaginal deliveries. *Am J Obstet Gynecol* 2014;211:56 e1- e12.
36. Rogers AJ, Rogers NG, Kilgore ML, Subramaniam A, Harper LM. Economic Evaluations Comparing a Trial of Labor with an Elective Repeat Cesarean Delivery: A Systematic Review. *Value Health* 2017;20:163-73.

*“Health economic analysis of the OptiBIRTH trial”***Figure legends*****Figure 1***

Decision-tree of the OptiBIRTH trial.

Figure 2

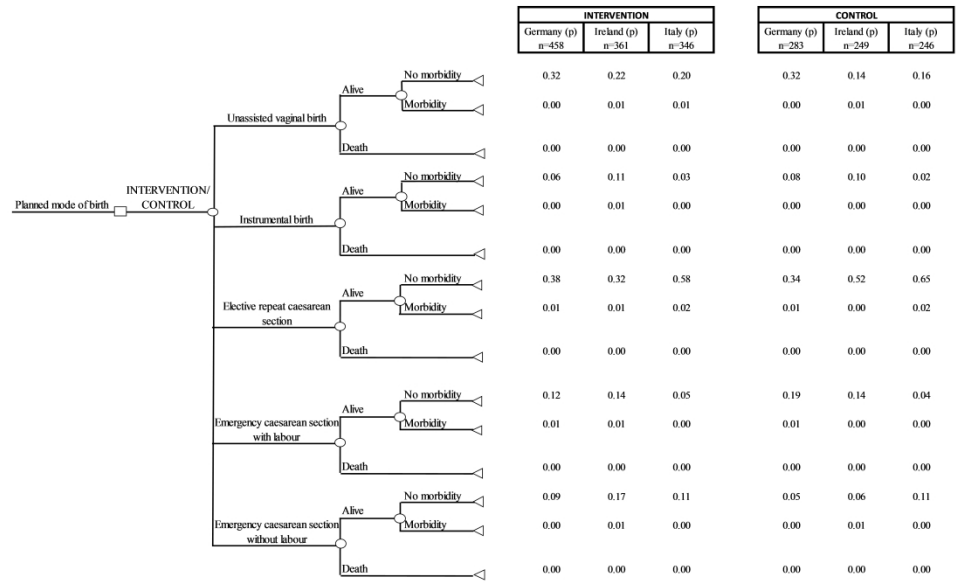
Cost-effectiveness planes: distribution of incremental costs and outcomes in intervention versus control group for Germany, Ireland and Italy. 5000 Monte-Carlo simulations were conducted for each country.

For Review Only

Table 1. Cost-utility results of the OptiBIRTH trial, per woman, €

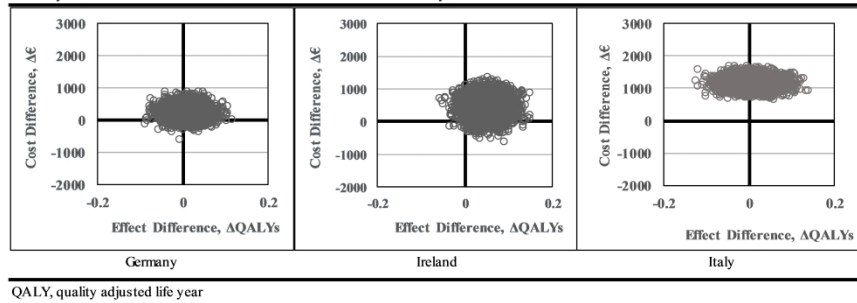
Model	Intervention		Control		ICUR (€/QALY)
	Cost (€)	Utility (QALY)	Cost (€)	Utility (QALY)	
<i>Societal perspective</i>					
Germany					
Deterministic	6,021	0.77	5,759	0.76	35,785
Probabilistic (mean)	6,024	0.77	5,761	0.76	33,741
Ireland					
Deterministic	9,930	0.82	9,471	0.77	8,866
Probabilistic (mean)	9,928	0.82	9,472	0.77	8,785
Italy					
Deterministic	4,983	0.78	3,804	0.78	196,136
Probabilistic (mean)	4,980	0.78	3,806	0.78	214,318
<i>Health services perspective</i>					
Germany					
Deterministic	5,017	0.77	4,754	0.76	35,841
Probabilistic (mean)	5,019	0.77	4,754	0.76	34,342
Ireland					
Deterministic	8,958	0.82	8,429	0.77	10,208
Probabilistic (mean)	8,959	0.82	8,431	0.77	10,173
Italy					
Deterministic	4,332	0.78	3,425	0.78	150,838
Probabilistic (mean)	4,333	0.78	3,423	0.78	127,481

QALY, quality adjusted life year; ICUR, incremental cost-utility ratio



1574x942mm (96 x 96 DPI)

Figure 2. Cost-effectiveness planes: distribution of incremental costs and outcomes in intervention versus control group for Germany, Ireland and Italy. 5000 Monte Carlo simulations were conducted for each country.



1481x570mm (96 x 96 DPI)