CHAPTER 6

Early cost-effectiveness analysis of screening for pre-eclampsia

ABSTRACT

Objectives: To perform an early cost-effectiveness analysis of a new screening test for pre-eclampsia from a healthcare payer perspective, in four European countries i.e. United Kingdom (UK), Ireland, the Netherlands and Sweden.

Methods: A decision tree over a 9-month time horizon was developed to explore cost-effectiveness of the new screening test for pre-eclampsia compared to the current screening strategy for healthy, nulliparous women. The screening test was applied in the first trimester of pregnancy to determine the risk of developing pre-eclampsia. Those considered at high risk would receive intensified monitoring and prophylactic aspirin, for which the effectiveness was varied based on different sources of evidence (base case and best case). The model simulated 25 plausible scenarios in which the sensitivity and specificity of the new test were varied to set a benchmark for the minimum test performance that is needed for the test to become cost-effective. The main outcome was incremental costs per pre-eclampsia case averted, expressed as an incremental cost-effectiveness ratio (ICER). Deterministic and probabilistic sensitivity analyses were conducted to assess uncertainty.

Results and Discussion: Base case results showed that the new test would be a dominant option compared to the current situation in UK. In the Netherlands, the majority of scenarios would be cost-effective from a threshold of €50,000 per pre-eclampsia case averted, while in Ireland and Sweden, the vast majority of scenarios would be considered cost-effective only when a threshold of €100,000 was used. In the best case analyses, ICERs were more favourable in all four participating countries. The new test remained dominant in UK, while in the Netherlands and Ireland, the test would be cost-effective at a lower threshold of €10,000 per pre-eclampsia case averted. In Sweden, the new test would be estimated cost-effective at a threshold of €30,000 or higher. Aspirin effectiveness, prevalence of pre-eclampsia, accuracy of the new screening test and cost of regular antenatal care were identified as driving factors for the cost-effectiveness of screening for pre-eclampsia.

Conclusion: This early cost-effectiveness analysis shows that there are several important parameters that drive the cost-effectiveness of screening for pre-eclampsia. The results also indicate that the new screening test for pre-eclampsia has potential to be cost-effective. Further studies based on proven accuracy of the test will uncover whether the new screening test can indeed be a cost-effective option as an addition to the current situation.
INTRODUCTION

Pre-eclampsia contributes significantly to the burden of maternal and perinatal morbidity and mortality worldwide\(^1,2\). In high-income regions these burdens are lower than in low and middle income countries, due to the availability of medical interventions that aim to address the known risks associated with pregnancy and childbirth\(^3\). Nevertheless, pre-eclampsia and other hypertension disorders remain responsible for approximately 13% of maternal deaths\(^2\). Early identification of pre-eclampsia is one of the important objectives of antenatal care in high-resource countries\(^4\). Effective screening, administered in the first half of pregnancy, would enable stratification of women according to their risk and thus inform the appropriate and tailored application of improved prevention, management and treatment. This stratification would also reduce the cost of misclassification and lead to efficient antenatal care in each group, resulting in potential cost-savings\(^5\).

Screening for specific clinical risk factors in the first trimester of pregnancy, followed by low-dose aspirin prophylaxis for those at increased risk is recommended by several guidelines\(^6\)–\(^8\). However, most of the anticipated risk factors are associated with other comorbidities or with previous pregnancy complications, and are thus not applicable to healthy, nulliparous pregnant women\(^4,9\). The accuracy of clinical risk prediction for pre-eclampsia in nulliparous is modest, and so (novel) biomarkers may assist in providing a personalized clinical risk profile to predict pre-eclampsia. Over the last decade, there has been considerable research into identifying potentially relevant biomarkers and their application in predicting pre-eclampsia; however, these novel biomarker-based have yet to be introduced in clinical practice\(^5,10\).

Previous economic evaluation studies show conflicting results as to the cost-effectiveness of pre-eclampsia screening; two studies suggest a cost-effective screening strategy\(^11,12\) and one study argues that screening is not the most cost-effective option\(^13\). Our previous systematic review on economic assessments of pre-eclampsia concluded that using biomarker-based tests for pre-eclampsia screening have the potential to be a cost-effective approach for clinical practice, but their accuracy is a major driver for cost-effectiveness. Routine screening for pre-eclampsia risk is potentially feasible, but only when accuracy is significantly improved\(^10\).

An early cost-effectiveness study using decision modeling could guide the predictive performance goals of a technology that is yet to be developed, or refine the specification of tests which are in the early stages of development. An ongoing project: ‘Novel metabolomics biomarkers to detect pre-eclampsia and improve outcome in nulliparous pregnant women (Improved
Pregnancy Outcomes by Early Detection or IMPROvED) targets early pregnancy to determine women’s risk for developing pre-eclampsia. Approximately 4,000 nulliparous pregnant women have been recruited to several academic medical centers across Europe i.e. Ireland, UK, The Netherlands and Sweden, in a multicenter hospital-based clinical study. To assist the implementation of a novel screening technology for pre-eclampsia, an early cost-effectiveness analysis was conducted. In this analysis, we estimate the effectiveness of the current screening strategies as well as the effectiveness the new technology might plausibly attain and analyze at what value the new technology could still be cost-effective, in a number of exploratory simulated scenarios, and thus inform the clinical performance specification for the novel test.

The aim of this study was to develop an early cost-effectiveness model to assess both costs and health outcomes of a new screening test for pre-eclampsia compared to the current screening strategy from a healthcare payer perspective in four high-income European countries, i.e. United Kingdom (UK), Ireland, the Netherlands and Sweden.

**METHODS**

**Overview of current screening and new screening test**

**Definition pre-eclampsia**

Pre-eclampsia was defined as high blood pressure (persistent blood pressure ≥140 mmHg systolic and / or diastolic ≥90 mmHg) together with proteinuria that occurred after 20 weeks of gestation.

**Current situation**

In the UK and the Republic of Ireland, healthy pregnant women with more than one moderate risk factor for developing pre-eclampsia are recommended to receive low dose aspirin prophylaxis (75 mg per day) from 12 weeks until birth and calcium supplementation for those with low calcium intake. The moderate risk factors considered are: i.e. first pregnancy, age 40 years or older, BMI of 35 kg/m² or more at first antenatal visit and family history of pre-eclampsia.

In contrast, The Netherlands and Sweden do not explicitly formulate a recommendation applicable to healthy nulliparous women, and only emphasize screening and treatment recommendations for women at increased risk i.e. pregnant women with co-morbidities such as chronic hypertension and diabetes mellitus. Thus, for the UK and Ireland we determined the maternal risk factor screening and subsequent treatment to be the current screening strategy, and we assumed no screening and treatment for pre-eclampsia in The Netherlands and Sweden.
In order to collect information about regular antenatal care in the different participating countries, an online survey on the management of healthy pregnancies, pregnancies at increased risk of pre-eclampsia and pre-eclampsia pregnancies was developed for healthcare professionals. This survey identified, beside treatment recommendations, that increased monitoring in the form of more frequent contacts with healthcare professionals was also necessary for the management of those identified as at high-risk for developing pre-eclampsia. Details on the survey are provided as Supplementary Material.

New screening test
In the model, we defined the new screening test as a novel predictive blood test that is being developed as part of the IMPROvED project. The new test would stratify nulliparous women into risk categories based on the risks observed in second (and further) pregnancies. More specifically, nulliparous women classified as high-risk according to the new test would have a risk of about 1 in 6, which is the risk of recurrence in a multiparous woman after a first case of pre-eclampsia. Women classified as low-risk according to the new test would have a risk of about 1 in 100, which is the risk of pre-eclampsia in woman’s second pregnancy when her first pregnancy was without complications. Since not all tested women will be either ruled in to be at high-risk, or ruled out and be classified as low-risk, the remainder would be classified as intermediate-risk. The estimates for the number of pre-eclampsia cases in those not identified as high-risk or low-risk were based on sensitivity and specificity of the test. For the model, we assumed that women at high-risk would receive the same treatment as pregnant women with risk factors, including increased monitoring and treatment as recommended i.e. low dose aspirin prophylaxis. Those classified as low-risk would receive the care model pertinent to second pregnancies, i.e. a reduction in number of antenatal appointments by 30%, while women with intermediate-risk would receive similar antenatal care as in the current screening strategy.

Model structure
A decision tree, depicted in Figure 1, was constructed to explore cost, potential health outcomes and cost-effectiveness of the new screening test for pre-eclampsia and the current screening strategy for healthy, first time mothers. In the model, routine antenatal care was implemented in the first trimester of pregnancy or in the booking period (which occurred around 8-12 weeks of gestation). This was considered to be the time for the doctor or midwife to confirm the pregnancy and do a basic assessment of the pregnant...
women. The decision node (i.e. the square node in Figure 1) represents the comparison between the following two strategies:

(1) Screening all pregnant women in all participating countries using the new screening test at 15 weeks of gestation to determine their risk of developing pre-eclampsia.

The high-risk group was directed to be in the increased monitoring group, with more frequent visits to obstetrician and/or midwives and prophylactic treatment with low dose aspirin prophylaxis. Evidence from numerous randomized controlled trials and meta-analysis has confirmed that daily low-dose aspirin could reduce the overall risk for pre-eclampsia in women at increased risk of developing pre-eclampsia\textsuperscript{22–25}. Effectiveness of low dose aspirin prophylaxis was incorporated in the model with associated relative risk estimates derived from published studies\textsuperscript{13,22,26}. The estimates regarding the increases in visit frequency, and the differences in the choice of healthcare professionals who will perform the further (post-test) pregnancy monitoring (obstetrician, general practitioner, midwife, etc), were based on the results from the aforementioned survey. It was estimated that women classified as being at high-risk should have four extra visits from obstetricians and two extra ultrasound scan appointments.

In the absence of an effectiveness measure for the increased monitoring, we assumed that the effectiveness of prophylaxis treatment comprised the effect of the increased visits as well, so no additional effects were calculated for the increased monitoring \textit{per se}.

(2) The current strategy i.e. regular antenatal care in UK, Ireland, the Netherlands and Sweden. As mentioned previously, screening using maternal risk factor screening and subsequent treatment was assumed to be the current screening strategy in UK and Ireland.

The assumption was that pregnant women were screened in the booking period and stratified to be either in the high-risk or to the low-risk group. The high-risk group received the same management as those in new test strategy, while the low-risk group received the regular antenatal care. Positive predictive values (PPV) and negative predictive values (NPV) were calculated based on sensitivity and specificity reported in Wright, et al\textsuperscript{27} and the country-specific prevalence of pre-eclampsia to estimate the probability of developing pre-eclampsia in low and high-risk group with current screening in UK and Ireland.

Moreover, we assumed that for the Netherlands and Sweden, in alignment with the guidelines in these countries, there was no
official assessment, nor preventive treatment for pre-eclampsia. Pregnant women received regular antenatal care from the booking period and would be detected as having pre-eclampsia if symptoms occurred after 20 weeks of gestation.

Figure 1. A decision tree comparing the new screening test strategy with the current screening test in UK, The Netherlands, Ireland, and Sweden.

The prevalence of pre-eclampsia in the four participating countries was derived from IMPROvED data and were estimated to be 2.9% in UK, 3.2% in the Netherlands, 3.7% in Ireland and 1.7% in Sweden. The model also estimated pregnancy outcomes, i.e. term birth, premature, and stillbirth, for pregnancies with and without pre-eclampsia. Pre-eclampsia is associated with higher rates of caesarean deliveries and preterm birth, which consequently were also more likely to require hospitalizations for both mother and their offspring, as well as a higher utilization of the neonatal intensive care unit (NICU)\textsuperscript{11,27}. For UK, Ireland, and Sweden, we assumed that all deliveries occurred in hospital. For the Netherlands the situation is different, as home
birth is part of the established Dutch maternity care system for low-risk pregnant women without complications. Hence for the Netherlands, we took into account the proportion of home-births for nulliparous, low-risk pregnant women without pre-eclampsia. Furthermore, the mode of delivery, either vaginal delivery or caesarean section, as well as the probabilities for the different potential pregnancy outcomes for both pre-eclampsia and non-pre-eclampsia pregnancies in all countries were included in the estimation. Table 1 summarizes the input parameters for the model.

**Costs estimation**

The healthcare provider perspective was used for the analysis, therefore we included only direct medical costs. The country-specific costs were estimated for costs of regular antenatal care, cost of increased monitoring and preventive treatment for the high-risk group, costs of pre-eclampsia cases including hospitalization and treatment, costs of delivery, and costs of neonatal intensive care unit for preterm birth.

In the screening using new test strategy, the price for the test was set to €150 (the potential cost, as estimated by the commercial partner of the IMPROvED consortium). We assumed that, as the current screening strategy takes places within the regular antenatal care, its costs are already accounted for in the costs of regular antenatal care in UK and Ireland. Cost of increased monitoring and preventive treatment for the high-risk group comprised costs of more frequent visits to obstetrician and/or midwives, and costs for daily low dose aspirin and calcium supplementation. Pregnant women at increased risk of developing pre-eclampsia are recommended to take daily low dose aspirin from the time of the assessment until birth. We assumed comparable timing for both the new test and the current screening i.e. at 15 weeks of gestation; therefore the duration for both increased monitoring and preventive treatment was estimated to be 25 weeks. As the recommended dose of aspirin for preventive treatment was 75mg daily, the unit price of a 75mg Aspirin tablet was used for cost estimation.

Due to a lack of country-specific data on cost of pre-eclampsia care, we assumed that the cost would be the same in all four participating countries. The estimation was based on a recently reported estimation of pre-eclampsia care in Ireland, including hospital admissions costs (hospital admissions ante- and postpartum weighted by the average length of stay for the mothers) as well as treatment for pre-eclampsia care, and excluding cost of delivery. Moreover, we also included country-specific costs of either vaginal delivery or caesarean section and cost of hospitalization and NICU admission in case of preterm birth, for all pregnancies with or without pre-eclampsia.

The cost for neonatal hospitalization was estimated by weighing the cost with the average number of days preterm babies would spend in both NICU and...
From the survey, we derived the average of 14 – 20 hospitalization days for premature babies born between 34-37 weeks. From this estimation, 18 days of neonatal hospitalization that comprised 6 days in NICU and 12 days in neonatal ward was used for the analysis\textsuperscript{32}.

All costs were adjusted to Euro 2016 using inflation rates and official exchange rates from the World Bank annual consumer index. Details on included costs are available on Table 2.

**Analyses**

Exploratory scenario analyses were performed where we independently varied the sensitivity and specificity of the new test (at PPV 1 per 6 and NPV 1 per 100) in 25 plausible scenarios, ranging from 35\% until 75\%. The analyses were used to set a benchmark for the minimum new test performance that is needed for it to become cost-effective compared to current screening.

In the exploratory analyses, we performed base-case analyses where we used a rather modest effectiveness of aspirin prophylaxis\textsuperscript{22,23,26}. Higher effectiveness of prophylactic aspirin, based on a more recent study, was used in best-case analyses\textsuperscript{33}.

The outcome of this model was expressed as incremental cost-effectiveness ratios (ICERs) per pre-eclampsia case averted for the new screening test as compared to the current situation. The time frame for the analyses was from the booking period until discharge of the mother and child from the hospital, therefore discounting of costs and outcomes was not necessary on account of the short time period for the analysis.

Probabilistic sensitivity analyses (PSA) were performed in which incremental costs and outcome of pre-eclampsia cases were estimated in a Monte Carlo simulation with 10,000 iterations. We pre-selected five appropriate scenarios to represent lowest, highest and modest combination of sensitivity and specificity (within a 35\%-75\% range) to be assessed in the PSA i.e. scenario 1 (35\% sensitivity, 75\% specificity), scenario 3 (55\% sensitivity, 75\% specificity), scenario 13 (55\% sensitivity, 55\% specificity), scenario 21 (35\% sensitivity, 35\% specificity) and scenario 25 (75\% sensitivity, 35\% specificity). All other relevant parameters were varied simultaneously according to the reported 95\% confidence interval and from the appropriate distributions of the input parameters. Parameters involved in PSA are effectiveness of aspirin, proportion of normal delivery and caesarean section in pregnancy with and without pre-eclampsia, proportion of birth outcomes in pregnancy with and without pre-eclampsia (i.e. term birth, premature birth and stillbirth) and costs. Log normal distribution was used for aspirin effectiveness, beta distributions were used for proportion of delivery as well as proportion of birth outcomes in pregnancy, and gamma distribution was fitted for costs.
Cost-effectiveness planes and acceptability curves were generated from the Monte Carlo simulation to present the probability of the new test to be cost-effective over a range of willingness-to-pay thresholds i.e. €10,000, €30,000, €50,000 and €100,000 per pre-eclampsia case averted\textsuperscript{13}.

### Table 1. Input parameters

<table>
<thead>
<tr>
<th>Input data</th>
<th>Value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Probability of pre-eclampsia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-risk group via current screening (UK)</td>
<td>1 in 20</td>
<td>14,27</td>
</tr>
<tr>
<td>Low-risk group via current screening (UK)</td>
<td>1 in 40</td>
<td>14,27</td>
</tr>
<tr>
<td>High-risk group via current screening (Ireland)</td>
<td>1 in 16</td>
<td>14,27</td>
</tr>
<tr>
<td>Low-risk group via current screening (Ireland)</td>
<td>1 in 31</td>
<td>14,27</td>
</tr>
<tr>
<td>High-risk group via new test</td>
<td>1 in 6</td>
<td>Assumption</td>
</tr>
<tr>
<td>Low-risk group via new test</td>
<td>1 in 100</td>
<td>Assumption</td>
</tr>
<tr>
<td><strong>Effectiveness of monitor/treat for high-risk group</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RR with aspirin for high-risk women (95% CI) (base-case)</td>
<td>0.88 (0.49 – 0.97)</td>
<td>22,26</td>
</tr>
<tr>
<td>RR with aspirin for high-risk women (95% CI) (best-case)</td>
<td>0.38 (0.20 – 0.74)</td>
<td>33</td>
</tr>
<tr>
<td><strong>Frequency of increased visits (for high-risk group)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obstetrician</td>
<td>4 more visits</td>
<td>Questionnaire</td>
</tr>
<tr>
<td>Ultrasounds</td>
<td>2 more visits</td>
<td>Questionnaire</td>
</tr>
<tr>
<td>Duration of preventive treatment</td>
<td>25 weeks</td>
<td>Assumption</td>
</tr>
<tr>
<td><strong>Delivery</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Home birth proportion for low-risk women (The Netherlands)</td>
<td>7.5%</td>
<td>32</td>
</tr>
<tr>
<td>Proportion of normal delivery without pre-eclampsia</td>
<td>87%</td>
<td>Estimation\textsuperscript{b}</td>
</tr>
<tr>
<td>Proportion of C-section delivery in pregnancy without pre-eclampsia</td>
<td>13%</td>
<td>36</td>
</tr>
<tr>
<td>Proportion of normal delivery in pre-eclampsia</td>
<td>50%</td>
<td>Estimation\textsuperscript{b}</td>
</tr>
<tr>
<td>Proportion of C-section delivery in pre-eclampsia</td>
<td>41%</td>
<td>36</td>
</tr>
<tr>
<td><strong>Birth outcomes in pregnancy without pre-eclampsia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proportion of term birth</td>
<td>95.27%</td>
<td>Estimation\textsuperscript{**}</td>
</tr>
<tr>
<td>Proportion of premature birth</td>
<td>4.47%</td>
<td>37</td>
</tr>
<tr>
<td>Proportion of stillbirth</td>
<td>0.27%</td>
<td>38</td>
</tr>
<tr>
<td><strong>Birth outcomes in pregnancy with pre-eclampsia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proportion of term birth</td>
<td>71.84%</td>
<td>Estimation\textsuperscript{**}</td>
</tr>
<tr>
<td>Proportion of premature birth</td>
<td>22.49%</td>
<td>37</td>
</tr>
<tr>
<td>Proportion of stillbirth</td>
<td>5.67%</td>
<td>26</td>
</tr>
<tr>
<td><strong>Delivery outcome (for offspring)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of hospitalization for preterm babies</td>
<td>18 days (6 days in NICU and 12 days in neonatal ward)</td>
<td>Questionnaire and 32</td>
</tr>
</tbody>
</table>

\textsuperscript{a}In the model, delivery was assumed to be only categorized as normal and c-section, therefore the proportion of normal delivery was assumed to be the remaining proportion of c-section delivery.

\textsuperscript{b}it was assumed that the birth outcomes comprised only term birth, premature birth and stillbirth, therefore the estimation of term birth was derived as a remaining proportion of premature and stillbirth.
### Table 2. Estimated costs

<table>
<thead>
<tr>
<th>Costs</th>
<th>Countries</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>UK</td>
<td>The Netherlands</td>
</tr>
<tr>
<td>Cost of regular antenatal care</td>
<td>£1,220</td>
<td>£609</td>
</tr>
<tr>
<td>Cost of new screening test</td>
<td>£150</td>
<td>£150</td>
</tr>
<tr>
<td><strong>Costs of monitor/treat for high-risk group</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obstetrician</td>
<td>£149.23</td>
<td>£79.47</td>
</tr>
<tr>
<td>Midwives (per hour)</td>
<td>£87.93</td>
<td>£39.31</td>
</tr>
<tr>
<td>Ultrasounds (per visit)</td>
<td>£121.50</td>
<td>£43.58</td>
</tr>
<tr>
<td>Aspirin (25 weeks)</td>
<td>£1.54</td>
<td>£1.54</td>
</tr>
<tr>
<td>Calcium supplement (25 weeks)</td>
<td>£18.32</td>
<td>£18.32</td>
</tr>
<tr>
<td><strong>Delivery outcome costs (for mothers)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cost of pre-eclampsia care (including hospitalization, treatment)</td>
<td>£2,769</td>
<td>£2,769</td>
</tr>
<tr>
<td>Normal delivery</td>
<td>£2,688</td>
<td>£2,208</td>
</tr>
<tr>
<td>C-section delivery</td>
<td>£4,781</td>
<td>£4,215</td>
</tr>
<tr>
<td>Home birth</td>
<td>NA</td>
<td>£520</td>
</tr>
<tr>
<td><strong>Delivery outcome costs (for offspring)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cost of NICU per day</td>
<td>£1,425</td>
<td>£1,193</td>
</tr>
<tr>
<td>Cost of neonatal ward (normal care) per day</td>
<td>£511</td>
<td>£331</td>
</tr>
</tbody>
</table>
RESULTS

Scenario analyses
Table 3 depicts the results of the base case (using moderate effectiveness of aspirin prophylaxis) and best case (using the more optimistic effectiveness) analyses in exploratory scenarios.

Base case
UK base-case results showed that the new test would be cost-saving and thus be a dominant option as opposed to the current screening in all scenarios, with less total costs and more pre-eclampsia cases averted. For the Netherlands, when using a willingness to pay threshold of €10,000 per pre-eclampsia case averted, the new test would not be considered cost-effective. When using a threshold of €30,000, 28% of scenarios (7 out of 25 scenarios) were cost-effective, with minimum combinations of sensitivity and specificity of either 35% and 75% or 65% and 65%, respectively. If a threshold of €50,000 was used, the majority of scenarios (76%) would be cost-effective, with minimum combinations of sensitivity and specificity of 35% and 65%, 45% and 55% or 55% and 45%, respectively. All scenarios would be cost-effective at willingness to pay thresholds of €100,00 or more per pre-eclampsia case averted.

In Ireland, less than half (40%) out of 25 scenarios had ICERs below €50,000 per pre-eclampsia case averted, suggesting that the new test was most likely not cost-effective compared to the current screening strategy if a threshold below €50,000 was used. The minimum combinations of sensitivity and specificity for the new test to be cost-effective under willingness to pay below €50,000 were either 45% and 75% or 55% and 65% for both combinations of sensitivity and specificity. At the €100,000 threshold, 84% of scenarios would be considered cost-effective, with sensitivity above 35%.

In Sweden, a similar trend was observed, as the vast majority of scenarios were only considered cost-effective at the €100,000 threshold.

Best case
In best case analyses, where higher effectiveness of prophylactic aspirin was used to inform the model, the overall ICER in all four participating countries appeared to improve, as expected. In UK, similar to base-case results, all scenarios resulted in dominance of the new test over current screening, i.e. the new test most likely would save costs and prevent pre-eclampsia cases. In the Netherlands, the new test would result in dominance, with minimum sensitivity of 55% and specificity of 75%. Below the aforementioned combinations, 95% scenarios appeared to be cost-effective using the lowest willingness to pay threshold of €10,000. A comparable trend was observed in
Ireland, where two scenarios appeared dominant with a specificity of 75%. In addition, all scenarios were cost-effective compared to the current screening strategy at the lowest willingness to pay threshold of €10,000 per pre-eclampsia case averted.

In Sweden, all scenarios were cost-effective at a threshold of €30,000 or higher per pre-eclampsia case averted. When using a willingness to pay below €30,000, only a small number of scenarios appeared to be cost-effective.

**Probabilistic sensitivity analysis**

Figure 2 and Figure 4 show the cost-effectiveness planes of five selected scenarios i.e. scenario 1, scenario 3, scenario 13, scenario 21, and scenario 25 in base case and best case analyses, respectively. The results demonstrated that all estimates in all participating countries were scattered within the northeast or southeast quadrants, meaning that the new test was certainly more effective, although in terms of costs, the probability distribution ranged from the test scenario being less expensive than current practice to being costlier. Overall, the trend in the PSA results suggested that higher sensitivity indicated more pre-eclampsia cases averted but also higher cost. Whereas higher specificity led to fewer pre-eclampsia cases averted but more savings. Similar to deterministic results, the best-case PSA indicated improved overall ICERs in all countries, with more averted pre-eclampsia cases.

Figure 3 and 5 show the cost-effectiveness acceptability curves for the new test in a different range of willingness to pay thresholds from €10,000 - €100,000 in base-case scenario and best-scenario, respectively.
Table 3. Cost-effectiveness of new test versus current screening strategy in exploratory scenario analyses in four participating countries, i.e. UK, The Netherlands, Ireland and Sweden.

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>UK</th>
<th>The Netherlands</th>
<th>Ireland</th>
<th>Sweden</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Base-case</td>
<td>Best-case</td>
<td>Base-case</td>
<td>Best-case</td>
</tr>
<tr>
<td>Scenario 1</td>
<td>35%</td>
<td>75%</td>
<td>Dominant</td>
<td>Dominant</td>
<td>£26,840</td>
<td>£789</td>
</tr>
<tr>
<td>Scenario 2</td>
<td>45%</td>
<td>75%</td>
<td>Dominant</td>
<td>Dominant</td>
<td>£24,179</td>
<td>£274</td>
</tr>
<tr>
<td>Scenario 3</td>
<td>55%</td>
<td>75%</td>
<td>Dominant</td>
<td>Dominant</td>
<td>£22,486</td>
<td>Dominant</td>
</tr>
<tr>
<td>Scenario 4</td>
<td>65%</td>
<td>75%</td>
<td>Dominant</td>
<td>Dominant</td>
<td>£21,314</td>
<td>£3,152</td>
</tr>
<tr>
<td>Scenario 5</td>
<td>75%</td>
<td>75%</td>
<td>NA</td>
<td>NA</td>
<td>£20,454</td>
<td>£497</td>
</tr>
<tr>
<td>Scenario 6</td>
<td>55%</td>
<td>65%</td>
<td>Dominant</td>
<td>Dominant</td>
<td>£40,124</td>
<td>£3,360</td>
</tr>
<tr>
<td>Scenario 7</td>
<td>45%</td>
<td>65%</td>
<td>Dominant</td>
<td>Dominant</td>
<td>£34,511</td>
<td>£2,274</td>
</tr>
<tr>
<td>Scenario 8</td>
<td>55%</td>
<td>65%</td>
<td>Dominant</td>
<td>Dominant</td>
<td>£30,940</td>
<td>£1,582</td>
</tr>
<tr>
<td>Scenario 9</td>
<td>65%</td>
<td>65%</td>
<td>Dominant</td>
<td>Dominant</td>
<td>£28,467</td>
<td>£1,104</td>
</tr>
<tr>
<td>Scenario 10</td>
<td>75%</td>
<td>65%</td>
<td>Dominant</td>
<td>Dominant</td>
<td>£26,653</td>
<td>£753</td>
</tr>
<tr>
<td>Scenario 11</td>
<td>35%</td>
<td>55%</td>
<td>Dominant</td>
<td>Dominant</td>
<td>£53,409</td>
<td>£5,931</td>
</tr>
<tr>
<td>Scenario 12</td>
<td>45%</td>
<td>55%</td>
<td>Dominant</td>
<td>Dominant</td>
<td>£44,844</td>
<td>£4,273</td>
</tr>
<tr>
<td>Scenario 13</td>
<td>55%</td>
<td>55%</td>
<td>Dominant</td>
<td>Dominant</td>
<td>£39,393</td>
<td>£3,218</td>
</tr>
<tr>
<td>Scenario 14</td>
<td>65%</td>
<td>55%</td>
<td>Dominant</td>
<td>Dominant</td>
<td>£35,620</td>
<td>£2,488</td>
</tr>
<tr>
<td>Scenario 15</td>
<td>75%</td>
<td>55%</td>
<td>Dominant</td>
<td>Dominant</td>
<td>£32,853</td>
<td>£1,953</td>
</tr>
<tr>
<td>Scenario 16</td>
<td>35%</td>
<td>45%</td>
<td>Dominant</td>
<td>Dominant</td>
<td>£66,693</td>
<td>£8,502</td>
</tr>
<tr>
<td>Scenario 18</td>
<td>55%</td>
<td>45%</td>
<td>Dominant</td>
<td>Dominant</td>
<td>£47,847</td>
<td>£4,855</td>
</tr>
<tr>
<td>Scenario 19</td>
<td>65%</td>
<td>45%</td>
<td>Dominant</td>
<td>Dominant</td>
<td>£42,773</td>
<td>£3,873</td>
</tr>
<tr>
<td>Scenario 20</td>
<td>75%</td>
<td>45%</td>
<td>Dominant</td>
<td>Dominant</td>
<td>£39,052</td>
<td>£3,152</td>
</tr>
<tr>
<td>Scenario 21</td>
<td>35%</td>
<td>35%</td>
<td>Dominant</td>
<td>Dominant</td>
<td>£79,978</td>
<td>£11,074</td>
</tr>
<tr>
<td>Scenario 22</td>
<td>45%</td>
<td>35%</td>
<td>Dominant</td>
<td>Dominant</td>
<td>£65,509</td>
<td>£8,273</td>
</tr>
<tr>
<td>Scenario 23</td>
<td>55%</td>
<td>35%</td>
<td>Dominant</td>
<td>Dominant</td>
<td>£66,301</td>
<td>£6,491</td>
</tr>
<tr>
<td>Scenario 24</td>
<td>65%</td>
<td>35%</td>
<td>Dominant</td>
<td>Dominant</td>
<td>£49,926</td>
<td>£5,257</td>
</tr>
<tr>
<td>Scenario 25</td>
<td>75%</td>
<td>35%</td>
<td>Dominant</td>
<td>Dominant</td>
<td>£45,232</td>
<td>£4,352</td>
</tr>
</tbody>
</table>

ICER: Incremental cost-effectiveness ratio, UK: United Kingdom, NA: not applicable
Dominant new test is more effective (better health outcomes) with lower cost compared to current screening.
NA indicates that the combination of sensitivity and specificity is not applicable due to low prevalence.
Figure 2. Cost-effectiveness planes of the new screening test for pre-eclampsia versus current screening strategy in base-case scenario analyses in four participating countries

PE: Pre-eclampsia, UK: United Kingdom, NL: the Netherlands, IR: Ireland, SW: Sweden
UK: United Kingdom, NL: the Netherlands, IR: Ireland, SW: Sweden

**Figure 3.** Cost-effectiveness acceptability curves for the new screening test in base-case scenario analyses in a different willingness to pay thresholds ranging from €10,000 - €100,000 per pre-eclampsia cases averted, in four participating countries.
Figure 4. Cost-effectiveness planes of the new screening test for pre-eclampsia versus current screening strategy in best-case scenario analyses in four participating countries.

PE: Pre-eclampsia, UK: United Kingdom, NL: the Netherlands, IR: Ireland, SW: Sweden
Early cost-effectiveness analysis of screening for pre-eclampsia

Figure 5. Cost-effectiveness acceptability curves for the new screening test in best-case scenario analyses in a different willingness to pay thresholds ranging from €10,000 - €100,000 per pre-eclampsia cases averted, in four participating countries.

UK: United Kingdom, NL: the Netherlands, IR: Ireland, SW: Sweden
DISCUSSION

Our exploratory scenario results indicate that there are several significant driving factors for cost-effectiveness of screening for pre-eclampsia i.e. aspirin effectiveness, prevalence of pre-eclampsia, accuracy of the new screening test and cost of regular antenatal care.

The analyses using the more optimistic effectiveness of prophylactic aspirin resulted in an improved overall ICER in the four participating countries compared to the ICERs obtained in the analyses using moderate effectiveness. However, these two effectiveness estimates are somehow difficult to compare, as the moderate effectiveness estimate is based on a population of women at moderate risk as assessed according to maternal risk factors only, such as nulliparity, obesity, or a family history of pre-eclampsia\textsuperscript{26}, while the optimistic effectiveness estimate is based on a population considered to be at high-risk according to a combination of maternal factors, mean arterial pressure and biomarkers, i.e. pregnancy-associated plasma protein A (PAPP-A) and placental growth factor (PIGF)\textsuperscript{33}. In addition, the moderate effectiveness with relative risk 0.88 is generated from a meta-analysis which pooled results of studies applying various doses ranging from 60 – 150 mg daily\textsuperscript{22,23,26}, and the more optimistic effectiveness with relative risk 0.38 was derived from a recent randomized controlled trial at a dose of 150 mg per day\textsuperscript{33}. The National Institute for Clinical Excellence (NICE) guideline for hypertension in pregnancy, advises women at high risk of pre-eclampsia to take 75 mg of aspirin daily from the first trimester of pregnancy until the delivery of the baby. Therefore, the dose of 150 mg daily as recommended by the recent trial may be challenging to implement in the participating countries, as it is double the dose of what is used in current situation\textsuperscript{7}.

Prevalence of pre-eclampsia also had a sizeable impact on cost-effectiveness results, in the sense that the lower the prevalence (e.g. Sweden), the less cost-effective universal screening would be. In this study, we used prevalence of pre-eclampsia based on IMPROvED data. The real-world prevalence might be higher than prevalence observed in IMPROvED, as the trial population may not be fully representative of the general population with respect to risk factors for pre-eclampsia.

Another driving factor for the cost-effectiveness is, obviously, the accuracy of the new screening test. When the accuracy of the new test increases, the number of low-risk women who may receive a reduced number of antenatal appointments would increase, and those who may receive unnecessary increased monitoring would decrease, which essentially escalates the likelihood of the new screening test becoming cost-effective.

Cost of regular antenatal care is also an important driving factor for cost-
Early cost-effectiveness analysis of screening for pre-eclampsia

...effectiveness result. The higher these costs are, the higher the probability that screening is cost-effective because expensive regular care would leave more room for cost saving in those at low risk. This was reflected in the UK analysis, where the cost of regular antenatal care was the highest of the four participating countries. For the UK, dominance of the new test was observed in all scenarios even in the base-case scenarios where modest effectiveness of prophylactic aspirin was used. In contrast, for Ireland, which was the country with the lowest cost of regular antenatal care, ICERs were unfavorable at a willingness to pay threshold below €50,000, which was all the more striking since the prevalence estimate of pre-eclampsia for Ireland was higher than for the UK.

To date, there have been very limited studies on cost-effectiveness of screening for pre-eclampsia. Based on our previous systematic review\textsuperscript{10}, there were only three published CEA studies on screening and diagnosis of pre-eclampsia\textsuperscript{11–13}, and only two of them were directed specifically towards screening\textsuperscript{11,13}. The results from previous studies suggest different results due to distinctive screening interventions. A study by Meads, et al\textsuperscript{13} shows that screening is not cost-effective. However, the interventions assessed in this study left out potential novel biomarkers with improved accuracy\textsuperscript{13}. Another study\textsuperscript{11} indicates that screening for pre-eclampsia with biomarkers might be cost-effective, although it would decidedly depend on some particular important parameters, such as the prevalence of pre-eclampsia, the effectiveness of prevention strategies and screening accuracy. Thus, in light of these previous findings the results of the present study are quite confirmative.

The current early analysis can contribute to estimating the cost-effectiveness of the new test and provide valuable insights on the potential parameters that drive the cost-effectiveness, before the implementation of the new technology in clinical practice. This can be important in guiding product development as well as future research when more detailed parameters are readily available\textsuperscript{34,35}.

In addition, the multi-country design with disparities in terms of prevalence of pre-eclampsia, costs of antenatal care and in terms of the current screening situation, allow us to generate a more comprehensive analysis on both costs and health consequences of the intervention in diverse settings. We also are able to highlight the driving factors of the analysis that are applicable in the various settings.

Inevitably, this study has some limitations. In common with other early cost-effectiveness analysis (CEA) studies, data for several input parameters were incomplete. In our study, data regarding current care and the new test was lacking, therefore we synthesized some of the input parameter and costs data for current antenatal care from multiple data sources and also made
assumptions, supported by expert opinion, regarding the probability of developing pre-eclampsia in the new screening test strategy. In addition, based on the data available to us, pricing of antenatal care was found to be very heterogeneous, resulting in substantial cost differences for antenatal care between countries, even when resource use was more or less comparable. Although we incorporated the uncertainty of all cost estimates in the PSA, this has probably only partly addressed the structural issue of different pricing approaches between countries.

Another potential limitation of our study might be the issue of implementation of the downgraded care pathway for low-risk pregnancies. In the model, we stratified nulliparous women into risk groups comparable to the risks as found in women in second or further pregnancies. Consequently, we assumed that those identified as low-risk would receive a 30% reduction in the number of antenatal appointments\textsuperscript{21}, i.e. a number comparable to second pregnancies with a similar risk. In reality, the reduced number of antenatal appointments for low-risk nulliparous women would be challenging to implement in certain countries, as it would require quite a significant change in the system by which midwives and clinicians are used to manage pregnancies.

For the present study we did not undertake a headroom analysis for maximum additional cost of the new test to be considered cost-effective under certain willingness to pay thresholds\textsuperscript{34,35}. This might be an interesting option for future research as it could provide insight for the test developers regarding the further development of the test\textsuperscript{34}. However, in our case, due to uncertainties both in test accuracy as well as willingness to pay threshold, it was not found instructive to perform a headroom analysis at this moment. Nevertheless, in order to account for these uncertainties, the current study design employed exploratory scenario analysis, based on plausible ranges of sensitivity and specificity provided by expert opinion, and focuses on exploring the accuracy of the new test and assess at which incremental cost the new screening test could still be cost-effective, using a fixed price. Due to limited previous research exploring the cost-effectiveness of pre-eclampsia screening, we did not have any reference threshold as to the ICER per pre-eclampsia case averted that would be regarded as cost-effective. Therefore we used various willingness to pay thresholds as applied in a previous study\textsuperscript{13}, to explore the range of plausible thresholds for all four participating countries.

In conclusion, in this assessment of cost-effectiveness of early screening for pre-eclampsia, we have shown that there were some general important parameters that drive the cost-effectiveness. Further economic evaluation studies and long-term follow up based on proven accuracy of the test that take into account these parameters will reveal whether the new screening test for pre-eclampsia can be a cost-effective option compared to the current situation.
Early cost-effectiveness analysis of screening for pre-eclampsia

REFERENCES


SUPPLEMENTARY MATERIAL

IMPROvED questionnaire for healthcare providers

Part I. Usual care in normal pregnancy

1. Could you indicate, in percentages, in what way pregnant women (nulliparous, healthy, no risk factors) are managed in your country?
   Options are obstetrician (either or not in collaboration with for instance a midwife), clinical midwife, and community based midwife or GP.
   Please enter percentage as a whole number ranging between 0 and 100 and make sure the different percentages add up to 100 *
   - Percentage managed by an obstetrician (with or without other health care workers):
   - Percentage managed by a clinical midwife:
   - Percentage managed by a community midwife or GP:

2. What is the average pregnancy duration/gestational age (in weeks) at which women come in for the booking visit?
   - Obstetrician (with/without other healthcare workers):
   - Clinical midwife:
   - Community midwife or GP:

3. What is the frequency of check-ups during (normal) first pregnancies? There is room for 4 different frequencies, if you only need three, for instance, you can start with the initial frequency, then use one of the middle frequencies, and finally fill out the ultimate frequency. Please also mention the gestational age up to which the frequency applies.

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Obstetrician (with/without other health care workers)</th>
<th>Clinical midwife</th>
<th>Community midwife or GP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initially every</td>
<td>Until … weeks (frequency)</td>
<td>Until … weeks</td>
<td>Until … weeks</td>
</tr>
<tr>
<td></td>
<td>(gestational age)</td>
<td>(frequency)</td>
<td>(frequency)</td>
</tr>
<tr>
<td></td>
<td>Then every … weeks (frequency)</td>
<td>Then every … weeks (frequency)</td>
<td>Then every … weeks (frequency)</td>
</tr>
<tr>
<td></td>
<td>(gestational age)</td>
<td>(frequency)</td>
<td>(frequency)</td>
</tr>
<tr>
<td></td>
<td>Ultimately every … weeks (frequency)</td>
<td>Ultimately every … weeks (frequency)</td>
<td></td>
</tr>
</tbody>
</table>

4. How long does a standard visit take, in minutes?

<table>
<thead>
<tr>
<th>Visit Type</th>
<th>Obstetrician (with/without other health care workers)</th>
<th>Clinical midwife</th>
<th>Community midwife or GP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Booking visit</td>
<td>Booking visit … minutes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow up visit</td>
<td>Follow up visit … minutes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Early cost-effectiveness analysis of screening for pre-eclampsia

5. For pregnancies managed by an obstetrician (with or without other health care workers), a regular visit consists of: (If a certain test is performed at each visit, please check ’always’, otherwise fill out the frequency in one of the other columns)

<table>
<thead>
<tr>
<th>Test</th>
<th>Always</th>
<th>First/booking visit only</th>
<th>Only every … visit</th>
<th>Only at … weeks (multiple time points possible)</th>
<th>Other frequency (please specify)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measuring blood pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weighing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fetal heart rate auscultation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood test for Hb</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood test for rubella</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood test for HIV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood test for Treponema pallidium</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood test for blood group and irregular erythrocyte</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood test for other</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine test for protein</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ultrasound</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiotocography</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

6. For pregnancies managed by a clinical midwife, a regular visit consists of: (If a certain test is performed at each visit, please check ’always’, otherwise fill out the frequency in one of the other columns)

<table>
<thead>
<tr>
<th>Test</th>
<th>Always</th>
<th>First/booking visit only</th>
<th>Only every … visit</th>
<th>Only at … weeks (multiple time points possible)</th>
<th>Other frequency (please specify)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measuring blood pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weighing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fetal heart rate auscultation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood test for Hb</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood test for rubella</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood test for HIV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood test for Treponema pallidium</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood test for blood group and irregular erythrocyte</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood test for other</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine test for protein</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ultrasound</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiotocography</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
7. For pregnancies managed by a community midwife or a GP, a regular visit consists of: (If a certain test is performed at each visit, please check 'always', otherwise fill out the frequency in one of the other columns)

<table>
<thead>
<tr>
<th>Test</th>
<th>Always</th>
<th>First/booking visit only</th>
<th>Only every ... visit</th>
<th>Only at ... weeks (multiple time points possible)</th>
<th>Other frequency (please specify)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measuring blood pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weighing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fetal heart rate auscultation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood test for Hb</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood test for rubella</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood test for HIV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood test for Treponema pallidum</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood test for blood group and irregular erythrocyte</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood test for other</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine test for protein</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine test for other</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ultrasound</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiotocography</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Part II. Usual care for pregnant women considered at high risk for pre-eclampsia

8. What is the typical/average number of weeks at which the patient is recognized to be at high risk for pre-eclampsia?
   - ..... weeks (fill out in whole weeks)
   - ..... in my country, there is no official 'high risk' status, pre-eclampsia is usually only recognized when signs are detected

9. What percentage of pregnant women considered to be at high risk for developing pre-eclampsia (either from the start, or later in pregnancy) are managed by the obstetrician, and will there be cases still managed by a midwife? Please enter percentage as a whole number ranging between 0 and 100 *
   - Percentage managed by an obstetrician (with or without other health care workers):
   - Percentage managed by a clinical midwife:
   - Percentage managed by a community midwife or GP:

10. What is the frequency of check-ups during these high-risk pregnancies? There is room for 4 different frequencies, if you only need three, for instance, you can start with the initial frequency, then use one of the middle frequencies, and finally fill out the ultimate frequency. Please also mention the gestational age up to which the frequency applies.

<table>
<thead>
<tr>
<th>Obstetrician (with/without other health care workers)</th>
<th>Initially every ... weeks (frequency)</th>
<th>Until ... weeks (gestational age)</th>
<th>Then every ... weeks (frequency)</th>
<th>Until ... weeks (gestational age)</th>
<th>Ultimately every ... weeks (frequency)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical midwife</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Community midwife or GP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
11. How long does a visit in a **high-risk** pregnancy take, in minutes? Please note that if high-risk pregnancies are only treated by an obstetrician, you do not need to fill out the other two categories.

<table>
<thead>
<tr>
<th></th>
<th>Minutes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obstetrician (with/without other health care workers)</td>
<td></td>
</tr>
<tr>
<td>Clinical midwife</td>
<td></td>
</tr>
<tr>
<td>Community midwife or GP</td>
<td></td>
</tr>
</tbody>
</table>

12. For **high-risk** pregnancies managed by an obstetrician (with or without other health care workers), a regular visit consists of: (If a certain test is performed at each visit, please check 'always', otherwise fill out the frequency in one of the other columns)

<table>
<thead>
<tr>
<th>Test</th>
<th>Always</th>
<th>First/booking visit only</th>
<th>Only every … visit</th>
<th>Only at … weeks (multiple time points possible)</th>
<th>Other frequency (please specify)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measuring blood pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weighing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fetal heart rate auscultation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood test for Hb</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood test for rubella</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood test for HIV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood test for Treponema pallidum</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood test for blood group and irregular erythrocyte</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood test for other</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine test for protein</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine test for other</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ultrasound</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiotocography</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

13. For **high-risk** pregnancies managed by a clinical midwife, a regular visit consists of: (If a certain test is performed at each visit, please check 'always', otherwise fill out the frequency in one of the other columns)

<table>
<thead>
<tr>
<th>Test</th>
<th>Always</th>
<th>First/booking visit only</th>
<th>Only every … visit</th>
<th>Only at … weeks (multiple time points possible)</th>
<th>Other frequency (please specify)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measuring blood pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weighing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fetal heart rate auscultation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood test for Hb</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood test for rubella</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood test for HIV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood test for Treponema pallidum</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood test for blood group and irregular erythrocyte</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood test for other</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine test for protein</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine test for other</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ultrasound</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiotocography</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
14. For high-risk pregnancies managed by a community midwife or GP, a regular visit consists of:
(if a certain test is performed at each visit, please check 'always', otherwise fill out the frequency in one of the other columns)

<table>
<thead>
<tr>
<th>Test</th>
<th>Always</th>
<th>First/booking visit only</th>
<th>Only every ... visit</th>
<th>Only at ... weeks (multiple time points possible)</th>
<th>Other frequency (please specify)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measuring blood pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weighing</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fetal heart rate auscultation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood test for Hb</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood test for rubella</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood test for HIV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood test for Treponema pallidum</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood test for blood group and irregular erythrocyte</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood test for other</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine test for protein</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine test for other</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ultrasound</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiotocography</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

15. Would you prescribe any prophylactic medication in a high-risk pregnancy?
   no
   yes

   What prophylactic drugs would you prescribe?
   • acetylsalicylic acid, enter mg per day:
   • calcium, enter mg per day:
   • other, please specify:
   • enter mg per day of other drug:
   • other (2), please specify:
   • enter mg per day of other (2) drug:

16. Would you prescribe any prophylactic medication in a high-risk pregnancy?
   no
   yes

   What therapeutic drugs would you prescribe?
   • acetylsalicylic acid, enter mg per day:
   • calcium, enter mg per day:
   • other, please specify:
   • enter mg per day of other drug:
   • other (2), please specify:
   • enter mg per day of other (2) drug:

17. Is there any prophylactic or therapeutic action besides intensified monitoring or medication that you would advise or prescribe to high-risk patient?
   no
   yes, please specify:
Part III. Treatment of pre-eclampsia

18. After onset of pre-eclampsia, where are patients usually treated?
   - women diagnosed with pre-eclampsia are always admitted to hospital until after delivery
   - some of the women diagnosed with pre-eclampsia are treated as outpatients, and some are admitted

What percentage of women diagnosed with pre-eclampsia is treated as outpatient, and what percentage is treated as inpatient? (please enter a whole number ranging between 0 and 100)

<table>
<thead>
<tr>
<th>outpatient</th>
<th>inpatient</th>
</tr>
</thead>
</table>

19. During hospital admission, how are pre-eclampsia patients typically treated? Please check those items that are part of treatment and then enter the frequency per week - or check the box when something is performed every day

<table>
<thead>
<tr>
<th>Daily</th>
<th>… times per week</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure measurements</td>
<td></td>
</tr>
<tr>
<td>Urine assessment</td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td></td>
</tr>
<tr>
<td>Fetal heart rate monitoring by cardiotocography</td>
<td></td>
</tr>
<tr>
<td>Fetal heart rate monitoring by auscultation</td>
<td></td>
</tr>
<tr>
<td>Full blood count</td>
<td></td>
</tr>
<tr>
<td>Blood tests of renal function</td>
<td></td>
</tr>
<tr>
<td>Blood tests of liver function</td>
<td></td>
</tr>
<tr>
<td>Ultrasound assessment of fetal growth/wellbeing</td>
<td></td>
</tr>
<tr>
<td>MgSO4 medication</td>
<td></td>
</tr>
<tr>
<td>Antihypertensive medication</td>
<td></td>
</tr>
<tr>
<td>Other medication</td>
<td></td>
</tr>
<tr>
<td>Admission to a high-care unit</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
</tbody>
</table>

20. Please specify, following the previous question: Unless you have checked one of these options (other medication, admission to high-care unit, or other) in the previous question, you do not need to answer this
   - if you indicated any 'other' medication, please specify
   - if admission to a high-care unit, what would be the indication
   - if any 'other' diagnostic/therapeutic action, what is it

21. Could you estimate, the proportion of patients with expectant or conservative management (as opposed to those with active management or immediate delivery)? Please enter a whole number ranging between 0 and 100

22. Could you estimate, the average gestational age (in whole weeks) at which the baby is delivered in pregnancies complicated by pre-eclampsia?

23. Could you estimate, for your country, the proportion of deliveries that are preceded by induction of labour and the proportion of C-sections in normal pregnancies for various categories of gestational age?

<table>
<thead>
<tr>
<th>Gestational age</th>
<th>% induced delivery in normal pregnancies</th>
<th>% C-sections in normal pregnancies</th>
</tr>
</thead>
<tbody>
<tr>
<td>34 – 37 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>37 – 42 weeks</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
24. Could you estimate, for your country, the proportion of deliveries that are preceded by induction of labour and the proportion of C-sections in pre-eclampsia pregnancies for various categories of gestational age?

<table>
<thead>
<tr>
<th>Gestational age</th>
<th>% induced delivery in pre-eclampsia pregnancies</th>
<th>% C-sections in pre-eclampsia pregnancies</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 24 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24-28 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>28-32 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>32-34 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>34-37 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>37-42 weeks</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

25. What is the typical length of stay (in days) in hospital after a normal delivery and after a C-section, for pre-eclampsia pregnancies? Please note there are separate entries for mothers and babies as length of stay can differ between these

<table>
<thead>
<tr>
<th>Gestational age</th>
<th>Normal delivery – length of stay mother</th>
<th>Normal delivery – length of stay baby</th>
<th>C-section – length of stay mother</th>
<th>C-section – length of stay baby</th>
</tr>
</thead>
<tbody>
<tr>
<td>34-37 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>37-42 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

26. What is the typical length of stay (in days) in hospital after a normal delivery and after a C-section, for pre-eclampsia pregnancies? Please note there are separate entries for mothers and babies as length of stay can differ between these

<table>
<thead>
<tr>
<th>Gestational age</th>
<th>Normal delivery – length of stay mother</th>
<th>Normal delivery – length of stay baby</th>
<th>C-section – length of stay mother</th>
<th>C-section – length of stay baby</th>
</tr>
</thead>
<tbody>
<tr>
<td>34-37 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>37-42 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Part IV. General questions

27. What is your estimate of the prevalence of pre-eclampsia in nulliparous pregnancies in your country? (either the official number, or if that is not available, a 'best guess') please enter a whole number ranging between 0 and 100

28. What is your guess on the percentage of privately insured patients among the population in question (nulliparous pregnant women)? Please enter a whole number ranging between 0 and 100

29. Is there a (publicly available) guideline for the general management of pregnancy in your country? If so, could you fill out where to find it (if possible, a website-address)
Early cost-effectiveness analysis of screening for pre-eclampsia

30. Is there a (publicly available) guideline for the **management of pre-eclampsia and eclampsia** in your country? If so, could you fill out where to find it (if possible, a website-address)

31. I am (choose one)
   - An obstetrics nurse
   - A clinical midwife
   - A community midwife
   - GP
   - An obstetrician in a general hospital
   - An obstetrician in a teaching hospital
   - An obstetrician in a university hospital
   - other - please specify

32. I practice in
   - Germany
   - Ireland
   - Sweden
   - The Netherlands
   - United Kingdom
   - Other - please specify