Frameworks for modelling the potential longer-term costs and consequences of self-monitoring of blood pressure (SMBP) during pregnancy

TECHNICAL REPORT FOR WORK STREAM 5 OF NATIONAL INSTITUTE FOR HEALTH RESEARCH (NIHR) PROGRAMME GRANT FOR APPLIED RESEARCH (RP-PG-0614-20005): Optimising the monitoring and management of raised blood pressure during pregnancy: The BUMP Research Programme.

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Abstract

Aims To develop model frameworks to be able to explore the potential long-term costs and effects of future interventions that may combine self-monitoring of blood pressure (SMBP) with targeted blood pressure (BP) management policies for the prevention of hypertension-related complications during pregnancy.

Methods Two model frameworks were constructed; the first focussed upon women at risk of developing pregnancy hypertension, and the second upon women with existing pregnancy hypertension. The model structures were developed using expert clinical opinion and the published literature. Modelled pregnancy pathways included the complications of pregnancy hypertension (for example pre-eclampsia and stroke). The longer-term risks of developing chronic hypertension and cardiovascular disease following pregnancy hypertension and pre-eclampsia were simulated using a Markov model over a 10-year period. Health care costs were modelled and health outcomes were expressed as quality-adjusted life years (QALYs). Event probabilities, costs and utility scores were informed by two randomised trials conducted during the same programme of work and the published literature, and were entered as distributions to enable probabilistic sensitivity analysis. The model was run for a range of different hypothesised intervention effect sizes and implemented so as to be able to simulate results for different cohorts of women with varying risk factors.

Results We present no definitive cost-effectiveness results, instead running a series of hypothetical scenarios to illustrate the capabilities of the models. For example, simulating a hypothetical scenario in which a new SMBP-guided intervention could reduce the risk of a pregnant women developing pre-eclampsia by 10%, the modelling suggested that long-term cost-effectiveness could potentially vary between hypertensive pregnant women and women at risk of pregnancy hypertension. This is because hypertensive women face a greater likelihood of developing associated complications both during and following pregnancy, in

turn suggesting a greater absolute level of benefit from a 10% reduction in complications via the mechanism of better BP control. Such hypotheses would of course require empirical testing in practice.

The model frameworks developed permit the exploration of cost-effectiveness results for cohorts of women with different risk factors and potential interventions of varying levels of effectiveness, and can be adapted and further developed by researchers for use within their own settings.

Conclusions: Model frameworks have been developed that can be used to begin to explore the potential long-term cost-effectiveness of adding novel targeted blood pressure management policies to SMBP during pregnancy.

Background / Aims

Annually, elevated blood pressure (BP) affects 18 million pregnancies worldwide and if not identified and managed promptly, can lead to pre-eclampsia and increased risks of maternal and infant morbidity and mortality.[1, 2] For the foreseeable future, a significant number of pregnant individuals will be affected by pre-eclampsia and other hypertensive disorders as a consequence of increasing risk factors including age, body mass index, and the presence of co-morbidities.[3]

As BP can increase rapidly during pregnancy and between antenatal visits, regular BP measurement is important for individuals both 'at risk' of, and with, pregnancy hypertension. With evidence from outside the field of obstetrics showing that self-monitoring of blood pressure (SMBP) by individuals away from a clinical setting has the potential to lead to better controlled hypertension, a programme of work was designed to develop and evaluate a SMBP intervention for use in pregnancy.[4-6] The Blood Pressure Monitoring in High Risk Pregnancy to Improve the Detection and Monitoring of Hypertension (BUMP) programme was funded by a National Institute for Health Research (NIHR) Programme Grant for Applied Research (RP-PG-0614-20005) and contained five work streams (WS) with aims as outlined below:

WS1: Development

- What are the best self-monitoring interventions to use?
- How can self-monitoring of BP and urine best integrate into current antenatal care pathways?

WS2: Self-monitoring to improve the detection and management of raised blood pressure in pregnancy

- What is current practice in BP self-monitoring in pregnancy?

- Can BP self-monitoring improve the detection and management of hypertension during pregnancy?
- How is BP self-monitoring in pregnancy implemented in daily life and routine clinical practice?
- Is BP self-monitoring in pregnancy cost-effective?

WS3: BP self-monitoring during pregnancy for anti-hypertensive titration

- Is titration of antihypertensive medication during and after pregnancy using self-monitoring feasible?
- What is the participant and professional experience of such monitoring and titration?

WS4: Self-monitoring of urinary protein in hypertensive pregnancy

- Can pregnant women with hypertension accurately self-monitor for proteinuria and could this detect preeclampsia earlier than usual care?
- Is self-monitoring of urine practical and acceptable to hypertensive pregnant women, their midwives and obstetricians?

WS5: Modelling of the potential long term costs and consequences

- Is self-monitoring of blood pressure and protein in hypertensive pregnancy potentially cost-effective and what are the key parameters affecting this?

Full details of the findings from WS 1 to 4 can be found in the BUMP programme's NIHR report. In brief, a SMBP intervention was developed and found to be feasible and acceptable to women and healthcare professionals. WS2 included two linked randomised controlled trials (with integrated economic evaluations) assessing the effectiveness of the SMBP intervention in addition to usual antenatal care for two different groups of pregnant individuals.[7] The BUMP 1 trial found the SMBP intervention did not lead to the earlier detection of elevated clinic BP in individuals 'at risk' of pregnancy hypertension.[8] The BUMP 2 trial reported that the SMBP intervention did not lead to better BP control in individuals 'with' pregnancy hypertension.[9] The intervention had no impact upon health-related quality

of life and healthcare costs but was safe, with no harms or unexpected consequences observed.

This document reports the work conducted for WS5 of the BUMP programme. As initially outlined in the programme of works shown above, the aim of WS5 was to develop an early economic model to establish whether self-monitoring of blood pressure and protein during pregnancy is potentially cost-effective over the longer term and to identify the key parameters affecting this. The link between pregnancy hypertension, its complications (e.g. pre-eclampsia), and long-term cardiovascular disease risk is well established. Any intervention resulting in more timely diagnosis and better management of hypertension, thus has the potential to reduce future cardiovascular morbidity and its associated costs and health effects. With trial time horizons limited, a proper exploration of cost-effectiveness requires modelling to extrapolate the potential impact of any improved effectiveness in the short term (for example a reduction in systolic blood pressure), upon future cardiovascular disease risk, costs and health outcomes. However, with no significant difference in cost or effects in either the BUMP1 or BUMP2 trial overall or for any subgroups, the need to extrapolate the longer-term cost and outcome implications of any shorter-term effectiveness, was negated. Despite this, and for the following reasons, a decision was taken to still develop model frameworks that could be used as a vehicle for future assessments of the potential cost-effectiveness of interventions for the detection and/or management of hypertension during pregnancy:

1. Other ongoing NIHR HTA trials such as Giant Panda (comparing two different antihypertensive drugs in women with pregnancy hypertension) or SNAP2 (comparing BP self-monitoring versus usual NHS care in women in the postnatal period requiring antihypertensive treatment) could make use of the modelling to ascertain how any short-term effectiveness (i.e. reductions in systolic blood pressure) could impact longer-term prognosis (i.e. risk of cardiovascular disease), costs, and effects.

2. The BUMP programme showed that SMBP during pregnancy is safe and acceptable, has the potential to detect rises in BP before they are documented in clinic, and may still offer benefits if medical management was guided on the basis of such home BP readings. Indeed research recommendations are for future studies to explore care pathways what combine SMBP in pregnancy with interventions that can act upon raised SMBP readings (e,g, self-titration of anti-hypertensive medication). Given the relationship between pregnancy hypertension and future cardiovascular disease risk, long-term modelling would be required to fully capture the long-term costs and consequences of such care pathways.

The frameworks we have developed use generic pregnancy hypertension pathways such that they could potentially be used to explore the cost-effectiveness of any intervention to monitor for and treat hypertension in pregnancy, and will thus be beneficial to other researchers and economists working within this field.

It is important to note that these frameworks provide an illustrative approach for assessing the cost-effectiveness of interventions for women with, or at risk of developing, hypertension during pregnancy. Although we describe potential model structures and illustrate how such models can be populated, analysed and the findings presented, the cost-effectiveness results presented are not definitive in nature. If wishing to make use of the frameworks presented in the following sections, researchers are encouraged to follow good practice guidelines for decision analytic modelling when adapting the frameworks to their own settings.[10] In particular, thought should be given as to whether the proposed model structures meet project requirements (for example is a more detailed modelling of cardiovascular disease progression required) and comprehensive reviews of the literature should be conducted to identify and synthesise data to inform and propagate uncertainty around model parameter input values. Such reviews were beyond the scope of the work conducted here.

Methods

The following sections describe the development and reporting of this modelling framework, with two different frameworks proposed. The first is for the assessment of the use of SMBP readings for the earlier detection and guided treatment of new gestational hypertension in 'at risk' pregnant women so as to prevent progression of the condition and associated complications. The second framework focusses upon the evaluation of SMBP readings to guide medical management for better control of existing hypertension during pregnancy.

As the links between hypertensive disorders of pregnancy and increased risks of future maternal chronic hypertension and cardiovascular disease, are now well established, the proposed frameworks consider the impact upon costs and consequences in the longer term in addition to those arising during the pregnancy.[11-14]

Framework 1 – Self-monitoring of blood pressure (SMBP) for the earlier detection and management of gestational hypertension in 'at risk' pregnant women

To illustrate this framework, we assumed the patient population were pregnant women considered to be 'at risk' for developing hypertension during pregnancy, as per the women recruited to the BUMP1 trial. Women were randomised between 16 and 24 weeks' gestation and so the starting point used for the framework was 20 weeks' gestation. Demographic and clinical characteristics of the BUMP1 cohort are reported in detail elsewhere and briefly summarised in the section below on populating the Markov model.[8] In the intervention arm, and in addition to current practice, home BP readings are assumed to be transmitted to clinical personnel, with raised readings flagged and acted upon according to current NICE

Guidance.[15] The comparator modelled was current practice without use of SMBP for monitoring women and guiding management.

Given the need to model a combination of both the short-term pathways followed by women during pregnancy and the future risks, costs, and consequences of associated chronic diseases, a hybrid model was developed, with a decision tree to cover the remaining duration of the pregnancy (20 weeks), and a Markov model to simulate disease risks over the longer-term (10 years). The time horizon for the Markov model was limited to 10-years on account of this being the longest duration over which cardiovascular disease (CVD) risk can currently be predicted by established prediction equations.[16]

The perspective for the analysis was that of the UK National Health Service and so we included only direct medical costs associated with the pregnancy, and the management of pregnancy complications and longer term chronic diseases (chronic hypertension and cardiovascular disease). The main outcome used by the framework is maternal Quality Adjusted Life Years (QALYs). QALYs are estimated in the model by adjusting the duration of time over which women are affected by key events (e.g. pre-eclampsia, or a myocardial infarction), by the level of utility or health-related quality of life they experience during this time.

Decision tree structure

Figure 1 shows the starting structure of the decision tree, which was informed by a combination of expert clinical opinion and a previously published cost-effectiveness model of diet and physical-based interventions during pregnancy.[17] The structure is replicated for both intervention and current practice arms. During the pregnancy, woman could develop gestational hypertension (GH) with or without a diagnosis of pre-eclampsia (PE), or they could remain free from pregnancy hypertension.

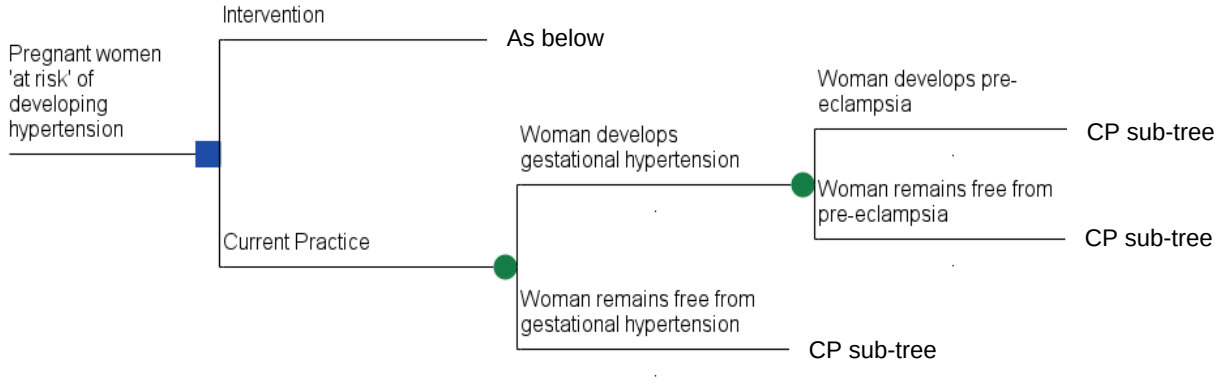


Figure 1 Starting structure of the decision tree

CP - continuing pregnancy

The continuing pregnancy sub-tree that women then follow is shown in Figure 2. The same structure was used for women with GH, women with GH with PE, and for women without pregnancy hypertension and was developed to incorporate key events known to be impacted by hypertensive disorders of pregnancy. Along the pathway, women could suffer a stillbirth or have a live birth, with the live baby delivered pre-term (<37 weeks' gestation) or term (≥ 37 weeks' gestation). Delivery could be by caesarean section, assisted delivery or normal vaginal delivery. All women face the risk of suffering a stroke during pregnancy and its associated risk of death. Women without stroke also face a pregnancy-related risk of death. Following their pregnancy, women may or may not develop new chronic hypertension. The probabilities attached to the events along this pathway varied according to whether women developed GH, GH with PE, or remained free of these disorders (see section below on populating the model structure).

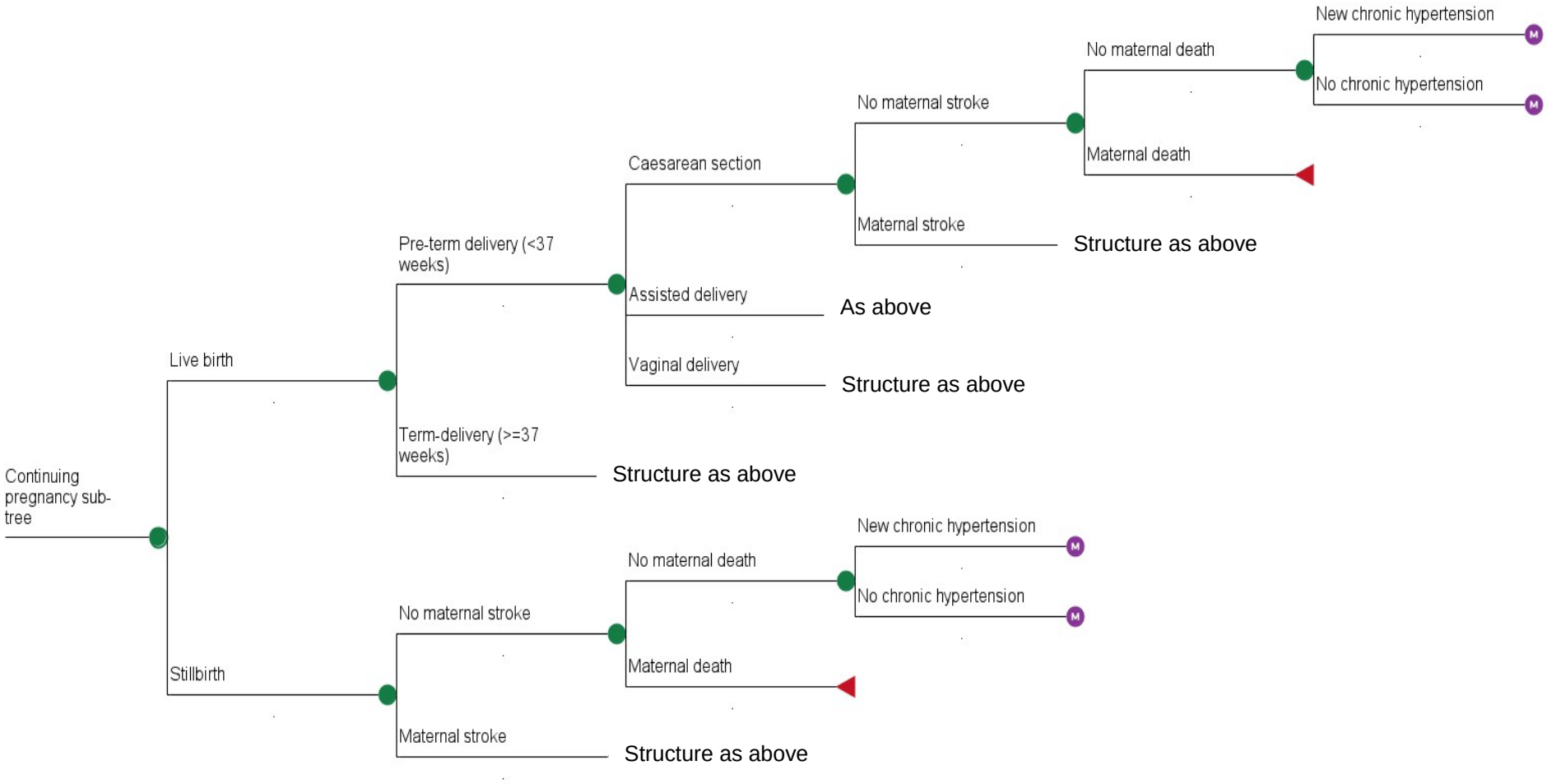


Figure 2 Continuing pregnancy sub-tree

Markov model structure

Women alive at the end of their pregnancy enter into the Markov model (denoted by the 'M' nodes in Figure 2). The Markov model was designed to simulate women's future risks of developing cardiovascular disease (CVD) and uses annual cycles over a time horizon of 10 years. Adapted from the Tasmin-SR cost-effectiveness model which evaluated SMBP for antihypertensive titration in hypertensive primary care patients, and shown in Figure 3, women first enter a 'free from cardiovascular disease' health state.[18] At the end of each cycle women in this state may develop CVD, manifesting as either stable angina, unstable angina, myocardial infarction (MI), heart failure, transient ischaemic attack (TIA), stroke, peripheral vascular disease (PVD), or a coronary heart disease death (fatal MI) or cardiovascular disease death (fatal stroke). Women experiencing non-fatal events remain in their event health state for that cycle before subsequently moving to a post-event heath state where they remain, facing an event-related annual risk of death each time the model cycles.

Populating the decision tree model

Event probabilities

Event probabilities for the decision tree component of the model are shown in Table 1 and were informed by data collected during the BUMP1 trial and reported in the published literature. So as to facilitate probabilistic sensitivity analyses (PSA), these data were entered into the model as distributions; beta distributions were used for events with binomial outcomes and Dirichlet distributions for events with multinomial outcomes.

The probability that women at risk of pregnancy hypertension would develop GH was taken from BUMP1, as was the probability that women who develop GH are also diagnosed with PE.

The probabilities of stillbirth for women with GH, women with GH with PE, and for women without pregnancy hypertension were informed by an individual patient data (IPD) meta-analysis with allied health economic model conducted by Rogozinska et al.[17] The IPD analysis combined data from 36 randomised controlled trials (12,526 women) assessing the impact of diet and physical-based interventions in pregnancy (24 studies included any BMI category and 12 included only overweight/obese women). The mean age of women in the trials was 30 years, 80% were of white ethnicity, and 42% were categorised at obese (BMI ≥ 30kg/m^2).

Data from the BUMP1 trial were used to estimate the model probabilities for pre-term birth and for the different types of delivery, in women with GH, GH with PE, and in women without pregnancy hypertension (Table 1).

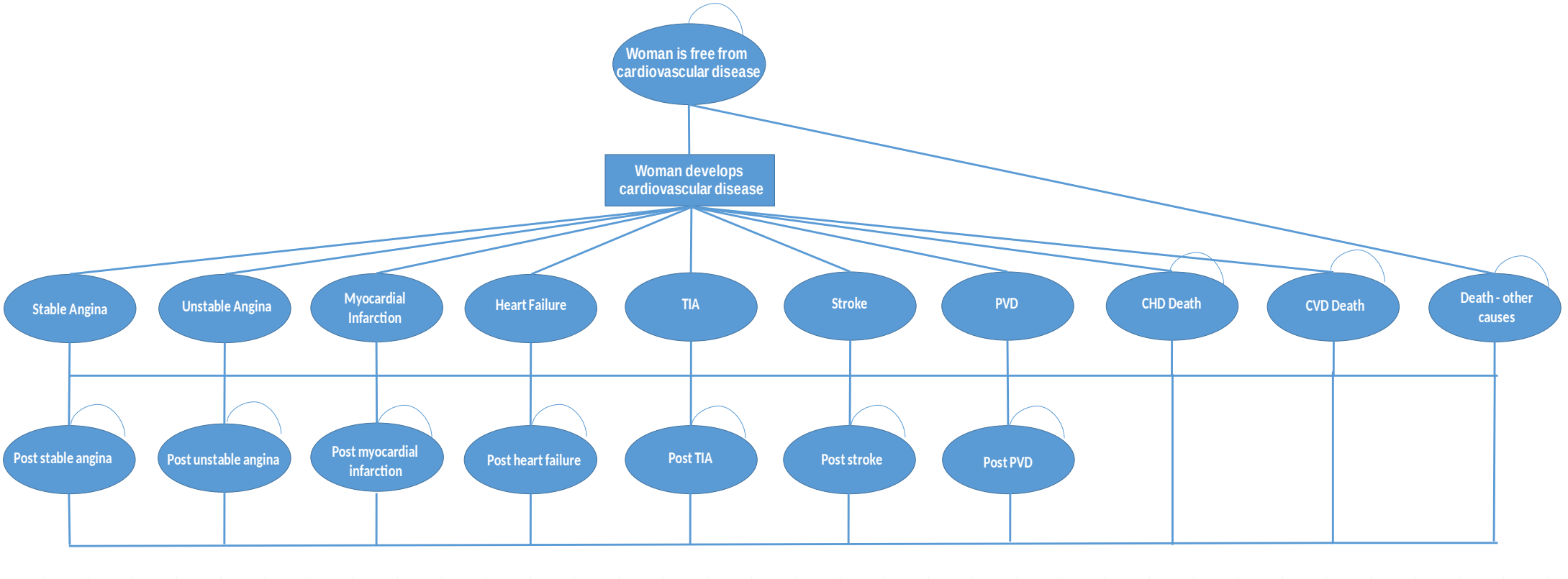


Figure 3 Markov model simulating risks and outcomes of future cardiovascular disease

TIA - transient ischaemic attack, PVD - peripheral vascular disease, CHD - coronary heart disease, CVD - cardiovascular disease

Table 1 Event probabilities used in the decision tree component of the model (Framework 1)

Parameter	Parameter Value (Distribution and moments)	Source
Hypertensive disorders		
Probability of developing GH	0.155 (Beta, α=363, β=1,983)	BUMP1 RCT [8]
Probability of woman with GH having PE	0.281 (Beta, α=102, β=261)	BUMP1 RCT [8]
Stillbirth		
Probability of stillbirth – women without pregnancy hypertension	0.002 (Beta, α=6, β=2,466)	Rogozinska et al. 2017[17]
Probability of stillbirth – women with GH	0.003 (Beta, α=1, β=332)	Rogozinska et al. 2017[17]
Probability of stillbirth – women with GH with PE	0.003 (Beta, α=1, β=358)	Rogozinska et al. 2017[17]
Pre-term birth (<37 weeks)		
Probability that live birth is pre-term – women without pregnancy hypertension	0.084 (Beta, α=167, β=1,821)	BUMP1 RCT [8]
Probability that live birth is pre-term – women with GH	0.156 (Beta, α=42, β=227)	BUMP1 RCT [8]
Probability that live birth is pre-term – women with GH with PE	0.420 (Beta, α=42, β=58)	BUMP1 RCT [8]
Delivery types for women without pregnancy hypertension		
Probability of Caesarean section delivery	0.360 (Dirichlet, 715)	BUMP1 RCT [8]
Probability of assisted delivery	0.190 (Dirichlet, 377)	BUMP1 RCT [8]
Probability of normal vaginal delivery	0.450 (Dirichlet, 892)	BUMP1 RCT [8]
Delivery types for women with GH		
Probability of Caesarean section delivery	0.398 (Dirichlet,107)	BUMP1 RCT [8]
Probability of assisted delivery	0.164 (Dirichlet, 44)	BUMP1 RCT [8]
Probability of normal vaginal delivery	0.439 (Dirichlet, 118)	BUMP1 RCT [8]
Delivery types for women with GH with PE		
Probability of Caesarean	0.66 (Dirichlet, 66)	BUMP1 RCT [8]

section delivery		
Probability of assisted delivery	0.060 (Dirichlet, 6)	BUMP1 RCT [8]
Probability of normal vaginal delivery	0.280 (Dirichlet, 28)	BUMP1 RCT [8]
Maternal stroke		
Probability of maternal stroke – women without pregnancy hypertension	0.00003 (Beta, α=61, β=1,958,142)	Scott et al. 2012 [19]
Odds ratio for increased risk of maternal stroke – women with GH	1.6 (Lognormal, mean=0.470, SE=0.188)	Liu et al. 2019 [20]
Odds ratio for increased risk of maternal stroke – women with PE	7.7 (Lognormal, mean=2.04, SE=0.96)	Scott et al. 2012 [19]
Maternal death		
Probability of maternal 'all cause' death – with causes related to stroke and PE removed	0.00008 (Beta, α=177, β=2,280,419)	Knight et al. 2019 [21]
Probability of maternal death from stroke	0.20 (Beta, α=6, β=24)	Scott et al. 2012 [19]
Probability of maternal death from PE	0.00016 (Beta, α=2.5, β=15,964)	Birth summary tables England and Wales / Leon et al. 2019 / Knight et al. 2019 [13, 21, 22]
New chronic hypertension		
Probability of developing new chronic hypertension following pregnancy – women without pregnancy hypertension	0.065 (Beta, α=1051, β=15,035)	Bellamy et al. 2007 [23]
Odds ratio for increased risk of developing new chronic hypertension following pregnancy – women with GH	2.47 (Lognormal, mean=0.904, SE=0.179)	Wilson et al. 2003 [14]
Hazard ratio for increased risk of developing new chronic hypertension following pregnancy – women with PE	4.47 (Lognormal, mean=1.497, SE=0.017)	Leon et al. 2019 [13]
Provision of neonatal intensive care		
Probability of infant being admitted to the NNU if mother is without pregnancy hypertension and delivers at term	0.063 (Beta, α=115, β=1706	BUMP1 RCT [8]
Probability of infant being	0.515 (Beta, α=86, β=81)	BUMP1 RCT [8]

admitted to the NNU if mother is without pregnancy hypertension and delivers pre-term		
Probability of infant being admitted to the NNU if mother has GH and delivers at term	0.097 (Beta, α=22, β=205)	BUMP1 RCT [8]
Probability of infant being admitted to the NNU if mother has GH and delivers pre-term	0.476 (Beta, α=20, β=22)	BUMP1 RCT [8]
Probability of infant being admitted to the NNU if mother has GH with PE and delivers at term	0.138 (Beta, α=8, β=50)	BUMP1 RCT [8]
Probability of infant being admitted to the NNU if mother has GH with PE and delivers pre-term	0.762 (Beta, α=32, β=10)	BUMP1 RCT [8]

GH gestational hypertension, PE pre-eclampsia, SE standard error, NNU neonatal unit, RCT randomised controlled trial

The underlying probability of experiencing stroke during pregnancy was taken from a United Kingdom Obstetric Surveillance System (UKOSS) report examining the incidence, risk factors, management and outcomes of stroke in pregnancy.[19] Sixty-one strokes (occurring in the antenatal and post-partum phases) were recorded across an estimated 1,958,203 women delivering between October 2007 and March 2010 (Table 1). The increased stroke risks faced by women in the model who developed GH and women who developed PE, expressed as odds ratios, were informed by population-based (nationwide) cohort studies (Table 1).[19, 20] These ratios were used in the model to adjust the underlying pregnancy stroke risk upwards.

The probability of maternal death from any cause during pregnancy was informed by the MBRRACE-UK Confidential Enquiry into maternal deaths and morbidity between 2015 and 2017 and was applied to women in the model without PE or stroke.[21] The probability of maternal death following a stroke was taken from the UKOSS study by Scott and colleagues.[19] To estimate the probability of maternal death with PE, we first used the 2018

birth summary tables for England and Wales together with an estimate of PE incidence from a large UK pregnancy cohort, to determine the annual number of live births and stillbirths likely to be affected by the disorder.[13, 22] Using MBRRACE-UK data on the number of pregnancy deaths associated with PE, an estimate was then made of risk of PE death amongst women with the condition (Table 1).[21]

The likelihood of developing new chronic hypertension following pregnancy was informed by a meta-analysis of published cohort studies conducted by Bellamy and colleagues to ascertain the increased risks of cardiovascular disease and cancer following PE during pregnancy.[23] Their analysis reported that of 16,086 women without a history of pre-eclampsia identified across 13 studies, over an average of 14.1 years, 1,051 women subsequently developed chronic hypertension.[23] The resulting proportion (0.065) was used in the decision tree to model the probability of developing chronic hypertension following a pregnancy not complicated by any hypertensive disorders (see Table 1). The increased risks of chronic hypertension attributable to GH and to PE during pregnancy were modelled by applying risk / odds ratios obtained from the published literature (Table 1).[13, 14]

As per the BUMP trials, we also included in the model the need for infant admission to the neonatal unit (NNU) following a live birth and infant days on non-NNU wards. Although not explicitly modelled along the decision tree pathways, such costs are included in the framework. Data from BUMP1 were used to estimate the proportion of women with GH, women with GH and PE, and women without pregnancy hypertension, whose babies were admitted to the NNU following term and pre-term deliveries (Table 1).

Costs

Table 2 shows the costs included in the decision tree model. Based upon current NICE guidelines for the management of hypertension during pregnancy, we costed the additional antenatal care recommended for women with GH, and for women with PE.[15]

For women with GH only, data from the BUMP1 trial showed that those who delivered their babies pre-term were diagnosed with GH at an average gestation of 32.39 (SD=4.21) weeks and delivered at 34.69 (SD=1.72) weeks. NICE guidance suggests the GH diagnosis of these women would have included a full assessment at a specialist hospital clinic (£142, Obstetrics Outpatient Code 501, National Schedule of NHS Costs 2019/2020), plus a full blood count (£2.89), liver and renal function tests (£5.34), and a urine test for proteinuria (£4.41).[24-27] An ultrasound scan of the baby was also costed (£124, Code NZ21Z, National Schedule of NHS Costs 2019/2020).[24] Following this initial assessment, and again informed by NICE guidance, women were assumed to receive the following ongoing care: to start antihypertensive treatment (200mg oral labetalol twice daily, costing £0.36 per day), to have their blood pressure and urine monitored twice a week (two ten minute appointments with a nurse costing £10.50 per visit), and to have a full blood count and a liver and renal function test once per week.[25, 27, 28] This additional ongoing care was costed for GH women in the model with a pre-term delivery for the 2.3 weeks between diagnosis and delivery. The combined diagnosis and management cost is shown in Table 2.

For women with GH only and a term delivery, BUMP1 suggested a mean gestational age at diagnosis of 36.04 weeks (SD=4.51 weeks) and delivery at 38.83 weeks (SD=1.37 weeks). For these women the GH diagnosis was costed as described above, as was ongoing management, but here for the 2.8-week duration between diagnosis and delivery (see Table 2).

For women with GH with PE who delivered pre-term, the average gestation at which GH and PE were diagnosed was 31.29 weeks (SD=3.15 weeks) with delivery at 33.76 weeks (SD=2.28 weeks). For these women we assumed a hospital admission at the time of diagnosis. The length of stay of this admission was costed based on data collected during the HYPITAT II randomised trial comparing immediate delivery with expectant monitoring of women diagnosed with hypertensive disorders between 34-37 weeks of gestation.[29] During the antepartum period in the expectant monitoring arm, women spent an average of 0.01 days in intensive care (bed day cost - £2,303, weighted average of obstetrics and gynaecology critical care codes XC02Z to XC07Z, National Schedule of NHS Costs 2019/2020), 0.67 days on a medium care ward (bed day cost - £733, Ante-Natal Complex Disorders with CC Score 2+ Code NZ18A, National Schedule of NHS Costs 2019/2020), and 3.48 days on a general ward (bed day cost £495 - Ante-Natal Major Disorders with CC Score 2+ Code NZ19A, National Schedule of NHS Costs 2019/2020). In addition and informed by NICE Guidance, at the point of diagnosis we costed a cardiotocography scan (£126, code NZ22Z National Schedule of NHS Costs 2019/2020), an ultrasound scan (£124, code NZ21Z National Schedule of NHS Costs 2019/2020), and an umbilical artery doppler velocimetry scan (£126, code NZ22Z National Schedule of NHS Costs 2019/2020).[15, 24]

Following this index admission, we costed the following recommended ongoing care for women with PE: 200mg labetalol twice daily, blood pressure monitoring every 48 hours, and two full blood counts and two liver function and kidney function tests per week (see Table 2).[15] This care was costed using the unit costs detailed in the text above and for the 2.47-week duration between PE diagnosis and pre-term delivery. The combined diagnosis and management cost is shown in Table 2.

For women with GH with PE delivering a term baby, BUMP1 suggested a mean gestational age at diagnosis of 35.37 weeks (SD=3.62 weeks). We assumed delivery for these women would have been planned within 24-48 hours of them reaching 37 weeks' gestation in line

with NICE Guidance on timing of delivery with PE. As for women with PE and a pre-term delivery, we costed the hospital admission at the time of diagnosis and the same ongoing management but now for the 1.63 weeks between diagnosis and delivery (see Table 2).

For women suffering a stillbirth, and based upon published data, we assumed this would have occurred during the antenatal period at around 36 weeks' gestation.[30] Amongst these women, we assumed those with GH and those with GH with PE, would have had their hypertensive disorders diagnosed at 35 weeks' gestation (the overall mean time of a GH diagnosis in BUMP1). The appropriate diagnosis and additional antenatal care was therefore costed for one week between diagnosis and the stillbirth (see Table 2).

The different types of delivery (vaginal, assisted, or Caesarean section) for women with GH, with PE, and without pregnancy hypertension (Table 1) were costed using the national average unit costs shown in Table 2. For women with GH we used delivery costs with a complications and co-morbidities (CC) score of 1 and for women with PE, a CC score of 2.

Data from the BUMP trials suggested mothers delivering their babies following a diagnosis of GH alone or GH with PE spend additional days in hospital at the time of birth, over and above the number of days expected for their type of delivery. Trial data showed women with PE spent an average of 0.67 (SD=2.79) additional bed days in hospital, and women with GH spent an additional 0.08 (SD=0.49) days. These bed days were costed using an excess bed day cost of £410 taken from 2019/2020 National Tariff Payment System: non-mandatory maternity prices (see Table 2).[31]

Stillbirths were costed to include the care provided to women at the time a stillbirth is suspected and confirmed and also the costs of investigations and a post-mortem performed following the stillbirth.[27, 32] A cost for delivering the stillborn baby was also included (see Table 2).[24]

Table 2 Unit Costs (2019/20 UK £) and utility scores and decrements used in the decision tree (Framework 1)

Resource Use Item	Unit Cost	Source
*Antenatal period**		
Additional maternal antenatal care for GH with PE – term birth	£2702	Various, see text for details
Additional maternal antenatal care for GH with PE – preterm birth	£2744	Various, see text for details
Additional maternal antenatal care for GH – term birth	£732	Various, see text for details
Additional maternal antenatal care for GH – preterm birth	£651	Various, see text for details
Additional maternal antenatal care for GH with PE prior to a stillbirth	£2670	Various, see text for details
Additional maternal antenatal care for GH prior to a stillbirth	£319	Various, see text for details
Delivery Period		
Vaginal delivery without complications	£2470	National Schedule of NHS Costs 2019/2020 - Weighted average of Normal delivery codes NZ30C-NZ34C (CC Score of 0)[24]
Vaginal delivery with minor complications	£2922	National Schedule of NHS Costs 2019/2020 - Weighted average of Normal delivery codes NZ30B-NZ34B (CC Score of 1)[24]
Vaginal delivery with major complications	£3443	National Schedule of NHS Costs 2019/2020 - Weighted average of Normal delivery codes NZ30A-NZ34A (CC Score of 2+)[24]
Assisted delivery without complications	£3581	National Schedule of NHS Costs 2019/2020 - Weighted average of Assisted delivery codes NZ40C-NZ44C (CC Score of 0)[24]
Assisted delivery with minor complications	£4317	National Schedule of NHS Costs 2019/2020 - Weighted average of Assisted delivery codes NZ40B-NZ44B (CC Score of 1)[24]
Assisted delivery with major complications	£4978	National Schedule of NHS Costs 2019/2020 - Weighted average of

		Assisted delivery codes NZ40A-NZ44A (CC Score of 2+)[24]
Caesarean section without complications	£4641	National Schedule of NHS Costs 2019/2020 - Weighted average of C-section delivery codes NZ50C/NZ51C (CC Score of 0-1)[24]
Caesarean section with minor complications	£5552	National Schedule of NHS Costs 2019/2020 - Weighted average of C-section delivery codes NZ50B/NZ51B/NZ50A/NZ51A (CC Score of 2+)[24]
Postnatal period		
Additional maternal post-delivery inpatient bed day	£410	2019/2020 National Tariff Payment System: non-mandatory maternity prices[31]
Stillbirths		
Confirmation of stillbirth	£228	Campbell et al. 2018 [32] / Curtis and Burns 2020 [27]
Delivery of stillborn baby	£2,470	National Schedule of NHS Costs 2019/2020 - Weighted average of Normal delivery codes NZ30C-NZ34C (CC Score of 0)[24]
Post-mortem and investigations following stillbirth	£848	Campbell et al. 2018 [32] / Curtis and Burns 2020 [27]
Infant Care		
Bed day spent in the NNU	£848	National Schedule of NHS Costs 2019/2020, average of currency codes XA01Z, XA02Z, XA03Z and XA04Z (service code CCU13).[24]
Bed day spent on a non-NNU ward	£404	National Schedule of NHS Costs 2019/2020, currency codes XA05Z (service code CCU15).[24]
Non-fatal maternal stroke		
Diagnosis with CT scan	£88	National Schedule of NHS Costs 2019/2020 – code RD20A [24]
Management of stroke	£1,612	National Schedule of NHS Costs 2019/2020 – code AA35F [24]
Maternal deaths		
Stroke death	£4,490	Alva et al. 2015 [33] / Curtis and Burns 2020 [27]
Non-stroke death	£1,000	Assumption
Event	**Utility**	**Source**
Underlying utility	Population norms	Kind et al. 1999 [34]
PE decrement	0.237 (SE=0.05)	Kind et al. 1999 [34] / Bijlenga et al. 2011 [35] / Frampton et al. 2016 [36]

GH decrement	0.065 (SE=0.01)	Kind et al.1999 [34] / BUMP2 RCT [9]
Stillbirth decrement	0.308 (SE=0.05)	Heazell et al. 2016 [37] / Sobocki et al. 2007 [38]
Stroke decrement (implemented in model as multiplier)	0.629 (SE=0.04)	Ward et al. 2007 [39]
Hypothetical intervention cost	**£8.00** **£162.40**	Cost of blood pressure monitor Additional four weeks of management due to earlier detection of GH
Hypothetical intervention effectiveness (relative risk of PE with intervention)	**0.90 (SE=0.028)**	**--**

*includes care at time of diagnosis plus ongoing monitoring and management until delivery / end of pregnancy

PE pre-eclampsia, GH gestational hypertension, CT computerised tomography, NNU neonatal unit, SE standard error

To estimate and cost the length of stay in the NNU for the proportions of babies likely to be admitted (see Table 1), we used data from the BUMP1 trial. Table 3 shows, for each hypertensive disorder (GH, and GH with PE) and for women without pregnancy hypertension, the mean (SD) length of stay for infants admitted to the NNU, by timing of delivery.

Table 3, Mean (SD) NNU length of stay for admitted babies born to mothers in BUMP1

Hypertensive disorder and timing of delivery	Babies admitted to NNU in BUMP1* (n)	Mean (SD) length of stay of babies admitted to the NNU
Women without hypertension, pre-term delivery	102	22.1 (24.0)
Women without hypertension, term delivery	124	4.9 (6.8)
Women with GH, pre-term delivery	4	13.3 (18.3)
Women with GH, term delivery	11	4.1 (5.2)
Women with GH with PE, pre-term delivery	31	19.6 (22.6)
Women with GH with PE, term delivery	7	7.7 (10.2)

*with length of stay data available
GH gestational hypertension, PE pre-eclampsia, SD standard error, NNU neonatal unit

Data were not available from the BUMP1 trial on the level of care received by babies whilst in the NNU. We therefore costed the mean length of stay on the unit for each of the above groups using a weighted average of the per diem costs of neonatal intensive care, high dependency care, and special care taken from the NHS National Cost Collection (Table 2).

Data from the BUMP1 trial was also used to estimate non-NNU post-delivery hospital length of stay for all babies. Analyses showed length of stay varied only by the timing of the delivery, with pre-term babies spending an average of 2.6 days (SD=3.4 days) on non-NNU wards and term babies 1.8 days (SD=2.2 days). These days were costed using the maternity ward bed day cost shown in Table 2.

Women suffering a non-fatal stroke were assumed to undergo a CT scan at the time of diagnosis and were also assigned an initial stroke management cost (Table 2). The costs incurred when women suffered a fatal stroke or a non-stroke related death are shown in Table 2.

Utility

Age and sex adjusted population norm utility scores were used to reflect women's underlying levels of health-related quality of life during pregnancy.[34] For those women who did not develop pregnancy hypertension, who had a live birth, and who did not suffer a stroke or die, underlying utility levels remained unchanged for the 20-week duration of the decision tree.

When strokes occurred, we assumed onset was around the time of delivery. For women without pregnancy hypertension, delivering at term (in BUMP1 this was 39.3 (SD=1.30) weeks' gestation) and suffering a non-fatal stroke, underlying levels of utility were decremented using the stroke utility decrement (Table 2) for the remaining 0.7 weeks in the decision tree and for the first year of the Markov model. For non-hypertensive women delivering pre-term and suffering a non-fatal stroke, onset was assumed to be at 34.0 (SD=2.91) weeks' gestation (mean time of delivery for these women in BUMP1) and underlying levels of utility were reduced using the utility decrement in Table 2 for the final six weeks of the decision tree and the first year of the Markov model. Utility levels were set to zero for women who died during pregnancy, from stroke, PE, or other causes.

When women without hypertension suffered a stillbirth, in line with published evidence, we assumed this would most likely have been an antepartum stillbirth and assumed occurrence at 36 weeks' gestation.[30] Underlying utility levels in the decision tree at this point were reduced using the utility decrement shown in Table 2. To reflect the longer-term devastating maternal impact of a stillbirth, utility levels also remained decremented for the first year within the Markov model.

For women without hypertension and not suffering a stillbirth, stroke or death, we assumed that their utility from the point of delivery onwards would be determined by whether or not their baby required admission to the NNU. For the NNU admission proportions shown in Table 1 for babies born term and pre-term to women without hypertension, we decremented maternal utility using the following assumptions: we assumed around 20% of mothers of infants admitted to NNU would suffer moderate to severe levels of anxiety and depression, with the remaining 80% suffering milder symptoms.[40] Using these percentages, we calculated a weighted average utility decrement, using decrements estimated separately for moderate (mean=0.355, SE=0.033) and mild (mean=0.25, SE=0.028) anxiety / depression from the EQ-5D utility levels reported by a cohort of Swedish individuals with depression during a six-month course of treatment in a primary care setting.[38] We held these decrements in place for a woman's remaining time in the decision tree model.

For women diagnosed with GH only, the utility impacts of stillbirth, stroke, and death were modelled as for non-hypertensive women, *albeit* using the GH-specific term and pre-term delivery gestations detailed previously. In addition, we reduced women's underlying utility using the GH utility decrement in Table 2. We assumed women would likely have experienced some symptoms, in the week prior to their diagnosis and applied the decrement from this point until the pregnancy ended (either with a live delivery or a stillbirth).

For GH only women not suffering a stillbirth, stroke or death, we assumed that their utility from the point of delivery onwards would be determined by whether or not their baby required admission to the NNU. For the NNU admission proportions shown in Table 1 for babies born term and pre-term to women with GH, the utility impact for these women was estimated as described above for women without pregnancy hypertension. We held these decrements in place for a woman's remaining time in the decision tree model.

For women diagnosed with GH with PE, the utility impacts of stillbirth, stroke, and death were modelled as for non-hypertensive women, *albeit* using the PE-specific delivery gestations detailed previously. We also reduced women's underlying utility using the PE utility decrement in Table 2, and as for women with GH, we assumed women would have become symptomatic in the week prior to diagnosis. The PE utility decrement was therefore applied from this point until the end of the pregnancy. Thereafter we assumed the utility of women with PE would be determined by whether their baby had required admission to the NNU (proportions detailed in Table 1). The utility impact for these women was estimated as described above for women without pregnancy hypertension.

Populating the Markov model

Event probabilities

Table 4 shows the event probabilities used in the Markov model. After women enter into the 'Free from CVD' health state of the Markov model, each year they face the probability of developing CVD, the underlying 10-year risk of which is predicted using the Framingham risk equation published by D'Agostino and colleagues.[16] Predictions for the initial run of the model were generated for a cohort of women with the same characteristics as those in the BUMP 1 trial: age 33 years, a BMI 28.1kg/m^2, a systolic blood pressure of 113.5, and non-smokers, without type 2 diabetes (see Table 4). Ten-year CVD risk predictions were converted to annual probabilities assuming a constant hazard. When new chronic

hypertension developed following pregnancy, 10-year CVD risk predictions were made after increasing systolic blood pressure in the Framingham equation to 140.0. For women who had developed GH during their pregnancy, the 10-year CVD risk prediction was further adjusted upwards using the odds ratio in Table 4.[11] For women who had suffered PE the relative risk in Table 4 was used to adjust 10-year CVD risk.[12]

Following the prediction of a first CVD event, women were distributed across the various CVD event health states in the model according to the probabilities shown in Table 4. These probabilities were estimated in part using data on new CVD presentations amongst women aged 45-54 years of age during 2017, from the British Heart Foundation's Heart and Circulatory Disease Statistics 2020.[41] Data from a previously published economic model assessing the cost-effectiveness of statins for the prevention of coronary events, were further used to ascertain the proportion of first angina events that would have been stable / unstable, the proportion of first CVD events that would have been a TIA / stroke, and the proportion of first MI and stroke events likely to have been fatal.[39]

Table 4 Base-case event probabilities used in the Markov model (Framework 1 and 2)

Event	Parameter Value (Distribution and moments)	Source
10-year CVD risk, no pregnancy hypertension, no new chronic hypertension*	0.0120 (NA)	D'agostino et al. 2008 [16]
10-year CVD risk, no pregnancy hypertension, new chronic hypertension†	0.0215 (NA)	D'agostino et al. 2008 [16]
Odds ratio for CVD with a history of GH	1.220 (Lognormal, Mean=0.199, SE=0.029)	Bhattacharya et al. 2012 [11]
Relative risk for CVD with a history of PE	1.850 (Lognormal, Mean=0.615, SE=0.428)	Wu et al. 2017 [12]
Probability first CVD event is		
- Angina	0.187 (Dirichlet, 2396)	British Heart Foundation Statistics. Heart and Circulatory Disease Statistics 2020 - Chapter 2a - Morbidity - Incidence (Admissions, Episodes, New Cases)[41]
- MI	0.193 (Dirichlet, 2481)	
- HF	0.118 (Dirichlet, 1515)	
- PVD	0.006 (Dirichlet, 844)	
- TIA/Stroke	0.436 (Dirichlet, 5604)	
First angina event is unstable angina	0.265 (NA)	Ward et al. 2007 [39]
First TIA/Stroke event is stroke	0.589 (NA)	Ward et al. 2007 [39]
First MI is fatal	0.317 (Beta, α=21715, 46707)	Ward et al. 2007 [39]
First stroke is fatal	0.191 (NA)	Ward et al. 2007[39]
Annual probability of death from any cause (CVD related deaths removed)	Age and sex adjusted life table data	National Life Tables - Office for National Statistics / Nomis - Mortality statistics, underlying cause, sex and age[42, 43]
SMR for stable angina	1.78 (Normal, Mean=1.78 SE=0.40)	Sekhri et al. 2007 [44]
SMR for unstable angina	11.06 (Lognormal, Mean=2.40 SE=1.08)	Assumption - SMR for MI adjusted based on ratio of SMRs for unstable angina and MI reported in Monahan et al. 2019 [18]
SMR for MI	13.53 (Lognormal, Mean=2.60 SE=1.08)	Nielsen et al. 2013 [45]
SMR for HF	31.66 (Lognormal, Mean=3.45 SE=0.18)	de Giulia et al. 2005 [46]
SMR for PVD	1.79 (Normal, Mean=1.79 SE=0.143)	van Kruijsdijk et al. 2016 [47]
SMR for TIA	6.7 (Lognormal, Mean=1.90 SE=0.90)	Rutten-Jacobs et al. 2013 [48]
SMR for stroke	12.12 (Lognormal,	Giang KW et al. 2013 [49]

	Mean=2.49 SE=0.31)	

NA not available, SMR standardised mortality ratio, GH gestational hypertension, PE pre-eclampsia, CVD cardiovascular disease, MI myocardial infarction, HF heart failure, PVD peripheral vascular disease, TIA transient ischaemic attack, SE standard error

*Women are aged 30 years, with a BMI 28.1kg/m^2, a systolic blood pressure of 113.5 and are non-smokers, without type 2 diabetes

†Women are aged 30 years, with a BMI 28.1kg/m^2, a systolic blood pressure of 140.0 and are non-smokers, without type 2 diabetes

Women experiencing a non-fatal CVD event in the model moved to the post-event health state for their CVD event type during the following cycle (see Figure 3). They remained here and each subsequent year faced an annual probability of death, which was determined by applying the appropriate standardised mortality ratios in Table 4 to population age and sex adjusted mortality risks with CVD deaths removed so as to avoid double counting.

Women who remained in the 'Free from CVD' health state each year faced aged and sex adjusted general population mortality risks.

Costs

A published Health Technology Assessment Report by Ara and colleagues containing a systematic review and economic evaluation of early high dose lipid-lowering therapy to avoid cardiac events provided relevant resource use estimates for the model's stable angina, unstable angina, and MI health states.[50] Resource use included initial hospitalisations and revascularisations (for MI and unstable angina), imaging, outpatient clinic visits, GP visits and medications, and were costed here using national average unit costs from established sources (see Table 5).[24, 27, 28] Ara and colleagues also reported resource use estimates for the year following a coronary event (one hospital outpatient clinic, three GP visits and medications) which we costed and assumed would reflect treatment provided in the post-stable angina, post-unstable angina, and post-MI health states.

A study by Murphy and colleagues in Ireland recorded and costed all healthcare consumed over a 12-month period by 1292 individuals presenting to hospital with a primary diagnosis of

heart failure.[51] After removing unrelated admissions (non-CVD) from the total cost estimate reported, the figure was converted into UK£ Sterling using Purchasing Power Parities (PPPs) and inflated to 2019/20 prices (see Table 5).[52] This cost was assigned to women in the model entering the heart failure state. Murphy reported costs for the index hospital admission separately from other management costs incurred during the year. These other management costs (again less non-CVD admissions) were assumed to reflect the ongoing care required by heart failure patients after an initial presentation and were converted to UK£ Sterling, inflated, and assigned to women in the post-heart failure health state (see Table 5).

The cost of a year spent in the PVD health state was taken from a published UK cost-effectiveness model evaluating a home-use negative pressure chamber system to increase blood flow, reduce pain and improve wound healing for patients with peripheral artery disease.[53] The Markov model in that study included health states for mild, progressive, and severe PVD and used a three-month cycle. We used the cost estimate for the mild PVD health state, multiplied by 4 and inflated to 2019/20 prices, to cost a year in both the PVD and post-PVD health states.

Cost estimates for the TIA, post-TIA, stroke, and post-stroke health states were taken from a patient-level costing study conducted by Luengo-Fernandez et al.[54] In that study, hospital-based contacts (Accident and Emergency visits, outpatient clinic attendances, emergency transport, day case admissions, and inpatient admissions) for 729 individuals suffering a stroke, and 485 patients suffering a TIA were identified out to five years and costed. All patients were part of the Oxford Vascular Study, which collected information on individuals from across 9 GP practices in Oxfordshire, who were suspected of having a stroke or a TIA.

Luengo-Fernandez et al. reported costs for each type of event (TIA and stroke) and for each of the five years following the event. For this model we converted their costs (expressed in 2008/09 US $) into UK £ using Purchasing Power Parities (PPPs) and inflated these to the

2019/20 price year using the Hospital and Community Health Services (HCHS) Inflation Index.[27, 55] Table 5 below shows these inflated costs. As annual costs reported in years 2 to 5 following an event were not dissimilar, we averaged across these years when generating a cost estimate for the post-TIA and post-stroke health states.

The published paper by Alva et al. reported costs for a fatal MI and for a fatal stroke, which were attached to the CHD death and CVD death health states in the model.[33] Estimates, were inflated to 2019/20 prices and are shown in Table 5.[27] We assumed a cost of £1000 for a non-CVD death.

Finally and for women in the model who were diagnosed with new chronic hypertension following their pregnancy, we assumed an annual management cost of £208.81 per year based on an assumption of receiving 200mg labetalol twice daily and requiring three GP visits per year.

Table 5 Unit costs (2019/20 UK £) and utilities used in the Markov model (Frameworks 1 and 2)

Resource Use Item	Unit Cost	Source
Year in 'stable angina' health state	£595	Ara et al. 2009 [50] / Curtis and Burns 2020 [27]
Year in 'post-stable angina' health state	£342	Ara et al. 2009 [50] / Curtis and Burns 2020 [27]
Year in 'unstable angina' health state	£3,695	Ara et al. 2009 [50] / Curtis and Burns 2020 [27]
Year in 'post-unstable angina' health state	£342	As for stable angina
Year in 'MI' health state	£4,514	Ara et al. 2009 [50] / Curtis and Burns 2020 [27]
Year in 'post-MI' health state	£342	As for stable angina
Year in 'HF' health state	£9,995	Murphy et al. 2016 [51] / Curtis and Burns 2020 [27]
Year in 'post-HF' health state	£2,972	Murphy et al. 2016 [51] / Curtis and Burns 2020 [27]
Year in 'PVD' health state	£598	Ezeofor et al. 2021 [53] / Curtis and Burns 2020 [27]
Year in 'post-PVD' health state	£598	Ezeofor et al. 2021 [53] / Curtis and Burns 2020 [27]
Year in 'TIA' health state	£5,913	Luengo-Fernandez et al. 2012 [54] / Curtis and Burns 2020 [27]
Year in 'post-TIA' health state	£2,300	Luengo-Fernandez et al. 2012 [54] / Curtis and Burns 2020 [27]
Year in 'stroke' health state	£11,027	Luengo-Fernandez et al 2012 [54] / Curtis and Burns 2020 [27]
Year in 'post-stroke' health state	£1,931	Luengo-Fernandez et al. 2012 [54] / Curtis and Burns 2020 [27]
CHD Death	£1,727	Alva et al. 2015 [33] / Curtis and Burns 2020 [27]
CVD Death	£4,490	Alva et al. 2015 [33] / Curtis and Burns 2020 [27]
Non-CVD Death	£1,000	Assumption
Year managing chronic hypertension	£209	Assumption
Health State	**Utility**	**Source**
Disease Free – underlying utility	Age and sex adjusted population norms	Kind et al. 1999 [34]
Utility decrements		
New chronic hypertension	0.065 (SE=0.012)	Kind et al. 1999 [34] / BUMP2 RCT [9]
Stable angina*	0.808 (SE=0.03)	Ward et al. 2007 [39]
Unstable angina*	0.770 (SE=0.04)	Ward et al. 2007 [3939](39)
MI*	0.760 (SE=0.02)	Ward et al. 2007[39]
HF*	0.690 (SE=0.03)	Dyer et al. 2010 [56]
PVD*	0.683 (SE=0.02)	Petersohn et al. 2019 [57]
TIA*	0.900 (SE=0.05)	Assumption
Stroke*	0.629 (SE=0.04)	Ward et al. 2007 [39]

PE pre-eclampsia, GH gestational hypertension, Pop population, MI myocardial infarction, TIA transient ischaemic attack, HF heart failure, PVD peripheral vascular disease, CVD cardiovascular disease, CHD coronary heart disease, SE standard error

*Used as multipliers to decrement underlying utility levels (e.g. utility in a women with stable angina is assumed to be 80.8% that of a woman without stable angina)

Utility

As per the decision tree, women's underlying health-related quality of life was assumed to be reflected by age and sex adjusted population norm values.[34] We assumed a utility decrement for women with new chronic hypertension based on the EQ-5D scores of women with chronic hypertension in the BUMP2 RCT (see Table 5). When women in the model experienced a CVD event, we reduced their utility according to the type of event experienced. This was done using the utility multipliers shown in Table 5 to decrement underlying utility levels. Such decrements then remained in place for a woman's remaining time in the model (10 years or death).

Hypothetical intervention

As detailed at the start of the section, the intervention for framework 1 assumed women's home BP readings would be transmitted to clinical personnel with raised readings flagged and acted upon according to current NICE Guidance.[15] We assumed that this would allow the earlier detection of GH and though the initiation of antihypertensive medication, would reduce the proportion of women diagnosed with PE. In a base-case analysis, we simulated a 10% (hypothesised relative risk of 0.90 SE=0.028) reduction in diagnoses of PE. We assumed the cost of such a policy to include the cost of home BP monitoring (£8.00 as in the BUMP1 trial) plus for women developing GH, additional weeks of monitoring and management on account of earlier detection. Data from BUMP1 suggested the potential for home BP readings to be raised in women with GH approximately one month prior to a clinic diagnosis. Thus, we included the costs of an additional four weeks of medical management and monitoring at a cost of £40.60 per week (see Table 2).

Running the model

The hybrid model was run over a time horizon of the pregnancy (20 weeks) plus 10 years, with estimated costs and maternal QALYs discounted using the recommended rate of 3.5%.

Joint parameter uncertainty was assessed using probabilistic sensitivity analysis, with the model run 5000 times, each time sampling a set of parameter values from the distributions shown in tables 1 to 4.

Reporting of results

Table 6 shows for the base case analysis, how the estimated number of pregnancy-related events for each arm of the model for a cohort of 10,000 women at risk of developing pregnancy hypertension, could be reported. For example, a 10% reduction in PE diagnoses was estimated to reduce the number of cases of PE from 435 (4.35% of the cohort) to 392 (3.92% of the cohort). Table 6 shows the impact upon subsequent events along the pregnancy pathway is small; amongst 10,000 women, one might expect 0.014 fewer strokes, six fewer women to develop chronic hypertension, and 0.006 fewer pregnancy-related deaths. These findings are explained by the fact that although PE is known to significantly increase the risks of pregnancy stroke, death, and new chronic hypertension (see Table 1) these events are already rare, such that a doubling or tripling of the underling rates as a result of PE leads to small absolute increases in event numbers.

Extending the framework to include the 10-year outcomes generated by the Markov model, produces the cost and QALY figures shown in the first rows of Table 7. Mean cost and QALY differences are also plotted on the cost-effectiveness plane in Figure 4 (panel a), which shows a funnel-shaped cloud spanning the North East and South West quadrants, close to the origin. Small mean cost savings and QALY gains are explained by the fact that intervening to produce a 10% reduction in the risk of developing PE would potentially improve outcomes for 0.4% of an overall cohort of women at risk of developing GH during pregnancy; Table 6 shows that in a cohort of 10,000 women, an estimated 43 fewer women would develop PE. For these women, without intervention, the 10-year predicted risk of subsequently developing CVD with PE is around 2.7% (approximately 29% would have

developed new chronic hypertension and faced an estimated 10-year CVD risk of 4.0% and 71% without new chronic hypertension would face a risk of 2.2%). With intervention and the prevention of PE, their 10-year risk of developing CVD reduces to an average of 1.7% (approximately 15% would have developed new chronic hypertension and faced a 10-year CVD risk of 2.6% and 85% without new chronic hypertension would face a risk of 1.5%). Thus, across the cohort as a whole 0.4% of women receive a 1% reduction in their 10-year risk of developing CVD.

On the costing side, the additional costs of providing women with a home blood pressure monitor are low, as are the costs of providing monitoring and antihypertensive medication for women with GH for an additional period of time as a result of earlier detection. On average, such costs appear outweighed by savings from preventing high cost CVD events in small numbers of women.

Scaling up the mean per woman cost and QALY estimates in Table 7 for a cohort of 10,000 ‘at risk’ pregnant women suggests total cost savings of around £40,000 and the generation of 5 additional QALYs.

Figure 5 (panel a) shows the cost-effectiveness acceptability curve for this base-case analysis and illustrates how the probability of SMBP being cost-effective changes as the maximum willingness to pay for a maternal QALY increases.

Table 6 Predicted outcomes to the end of the pregnancy period for a cohort of 10,000 pregnant women at risk of developing pregnancy hypertension*

	Number of events in 10,000 at risk women				
Events	**Control arm**	**Base-case†: Intervention reduces PE by 10%**	**Difference (95% CI) Base-case v control**	**Scenario 1: Intervention reduces PE by 15%**	**Scenario 2: Intervention reduces PE by 20%**
GH without PE	1113	1157	44 (20 to 68)	1178	1200
GH with PE	434	391	-43 (-68 to -20)	369	347
Maternal stroke (pregnancy related)	0.484	0.469	-0.014 (-0.07 to 0.0007)	0.462	0.456
New chronic hypertension	844	838	-6 (-11 to -2.6)	835	832
Maternal deaths (pregnancy related)	0.906	0.900	0.006 (-0.02 to 0.001)	0.896	0.893

*Women are aged 33 years, with a BMI 28.1kg/m^2, and are non-smokers, without type 2 diabetes.
†Base-case analysis assumes earlier detection and medical management of GH reduces the underlying risk of PE by 10% (relative risk 0.90)
PE pre-eclampsia, GH gestational hypertension, CI confidence interval

Table 7 Expected discounted mean 10-year costs and QALYs per pregnant woman at risk of developing pregnancy hypertension*

	Intervention arm	Control arm	Difference
Base-case†: intervention reduces risk of PE by 10%			
Mean total cost per woman	£6,075	£6,079	-£4
Mean total QALYs per woman	8.148	8.147	0.0005
Scenario 1: intervention reduces risk of PE by 15%			
Mean total cost per woman	£6,057	£6,079	-£22
Mean total QALYs per woman	8.148	8.147	0.0007
Scenario 2: intervention reduces risk of PE by 20%			
Mean total cost per woman	£6,038	£6,079	-£41
Mean total QALYs per woman	8.148	8.147	0.0010

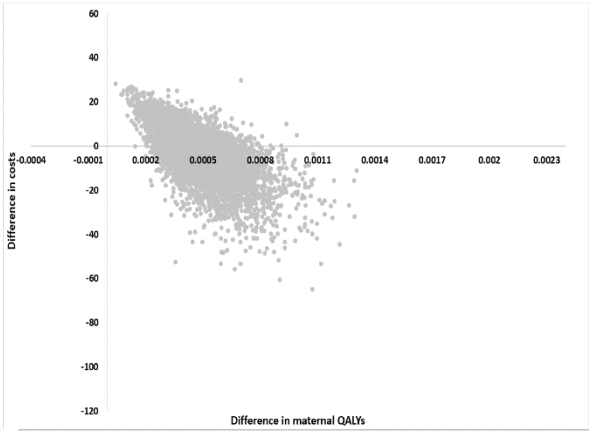
*Women are aged 33 years, with a BMI 28.1kg/m^2, and are non-smokers, without type 2 diabetes.
†Base-case analysis assumes an intervention reduces the underlying risk of PE by 10% (relative risk 0.90)
PE pre-eclampsia, QALY quality adjusted life year

The framework detailed above can also be used to illustrate the impact upon cost-effectiveness results of alternative study parameter values, reflective perhaps of different modes of intervention or for different subgroups of women. To illustrate, two scenarios are presented in which the effectiveness of the intervention is modified and the results re-calculated. In scenario 1 for example, the size of the treatment effect of a hypothetical intervention on reducing the risk of progression from GH to PE was increased from 10% to 15% and in scenario 2 from 10% to 20%. The impact of these changes upon events during pregnancy and 10-year cost-effectiveness results is shown in Tables 6 and 7 and Figures 4 and 5 (panels b and c).

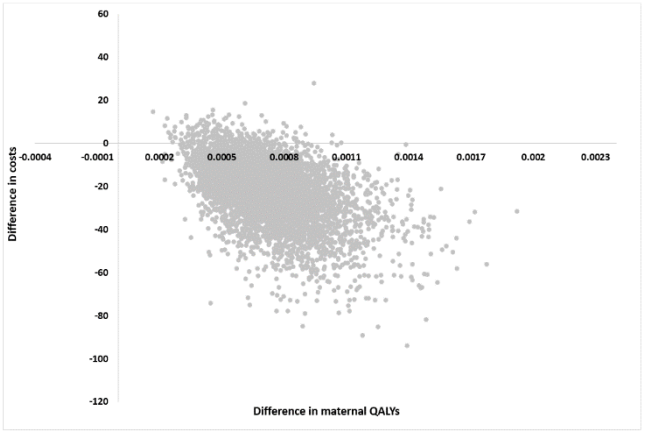
The framework was also used to explore the cost-effectiveness implications of intervening for certain groups of women who may be at higher risks of developing CVD and for whom preventing PE may result in larger absolute CVD risk reductions. Table 8 shows model results for women with the same characteristics as the base-case cohort, other than that they are smokers and have a diagnosis of Type 2 diabetes (Scenario 3). Women with these characteristics who develop PE have an estimated average 10-year risk of CVD of 10.7%, which would fall by 4.3% to 6.4% if PE is prevented. In comparison with the base-case cohort of women, Table 8 shows that intervening for a cohort of 'at risk' pregnant women who are smokers and have Type 2 diabetes gives an overall mean QALY gain that is over one third greater (0.00067 versus 0.00049).

In scenario 4, the age of women in scenario 3 is increased to 40. Women with these characteristics who develop PE are at a greater risk of developing CVD, and thus the absolute benefit of preventing this disorder is greater. Table 8 shows a mean QALY gain across all women that is around 15% greater than that observed for younger women in Scenario 3.

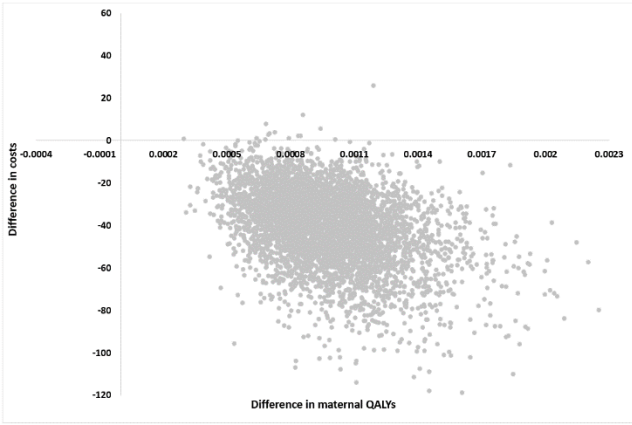
Figure 4 Mean estimated and discounted 10-year cost and QALY differences plotted on the cost-effectiveness plane (Framework 1 – women at risk of developing pregnancy hypertension)



Panel (a)



Panel (b)



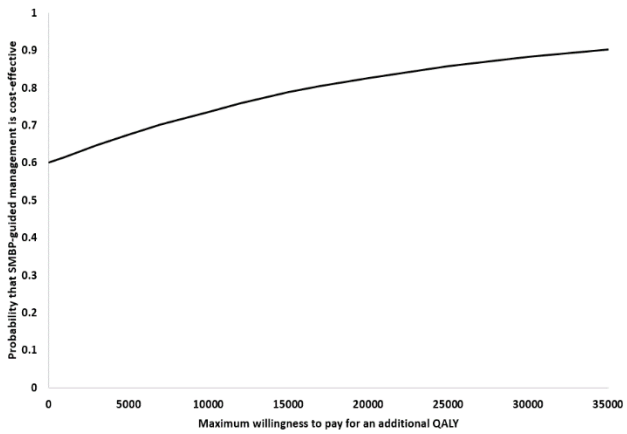
Panel (c)

Panel (a) Intervention is assumed to reduce the risk of PE by 10%

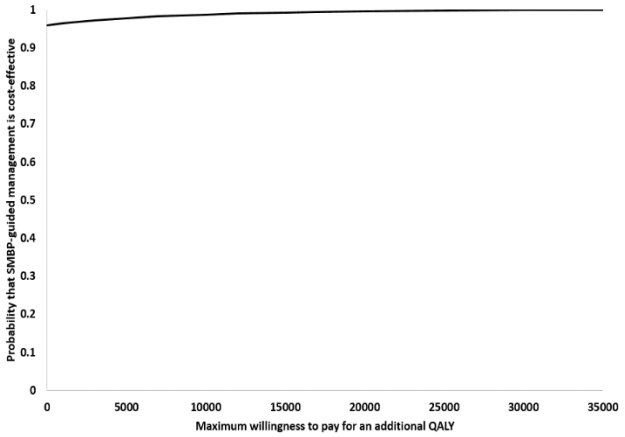
Panel (b) Intervention is assumed to reduce the risk of PE by 15%

Panel (c) Intervention is assumed to reduce the risk of PE by 20%

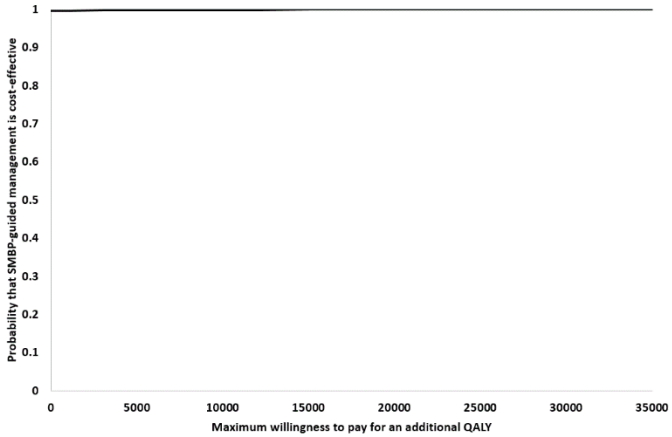
Figure 5 Cost-effectiveness acceptability curves (Framework 1 – women at risk of developing pregnancy hypertension)



Panel (a)



Panel (b)



Panel (c)

Panel (a) Intervention is assumed to reduce the risk of PE by 10%

Panel (b) Intervention is assumed to reduce the risk of PE by 15%

Panel (c) Intervention is assumed to reduce the risk of PE by 20%

Table 8 Expected discounted mean 10-year costs and QALYs per pregnant woman at risk of developing pregnancy hypertension – results for women with different characteristics*

	Intervention arm	Control arm	Difference
Scenario 3: As for base-case except women are smokers with Type 2 diabetes			
Mean total cost per woman	£6,413	£6,418	-£5
Mean total QALYs per woman	8.102	8.102	0.0007
Scenario 4: As for base-case except women are aged 40, smokers and with Type 2 diabetes			
Mean total cost per woman	£6,708	£6,715	-£6
Mean total QALYs per woman	8.063	8.062	0.0008

*Base-case analysis assumes an intervention reduces the underlying risk of a woman developing PE (pre-eclampsia) by 10% (relative risk 0.90)
QALY quality adjusted life year

Framework 2 – Self-monitoring of blood pressure (SMBP)-guided intervention for management of hypertension during pregnancy

To illustrate this framework we focussed upon pregnant women with chronic hypertension (CH), but the framework is easily amendable for the evaluation of SMBP-guided management in women with gestational hypertension.

Following the BUMP2 trial protocol, the starting point for framework 2 was 20 weeks' gestation. The comparator modelled was current practice without SMBP and guided intervention. As for framework 1, a hybrid model is proposed to facilitate modelling of both the short-term pathways followed by women during pregnancy and the future risks, costs, and consequences of associated chronic disease. A decision tree was constructed to cover the remaining duration of the pregnancy (20 weeks), and a Markov model to simulate disease risks over the longer-term (10 years). We used the same analysis perspective and costs and health outcomes (maternal QALYs) as described above for framework 1.

Decision tree structure

Figure 6 shows the starting structure of the decision tree and is replicated for both intervention and current practice arms. During the pregnancy, woman with CH could develop pre-eclampsia (PE), or they could remain free from this disorder. The continuing pregnancy (CP) tree is as shown in Figure 2 for framework 1 with the exception that the final set of branches indicating whether women develop new chronic hypertension are not relevant for this cohort of women.

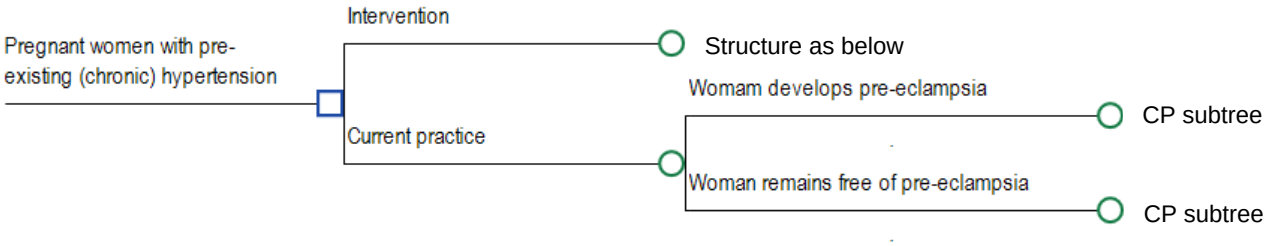


Figure 6 Starting structure of the decision tree for framework 2 (shown for women with CH)

CP - continuing pregnancy

Markov model structure

Women who are alive at the end of their pregnancy enter into a Markov model using the same structure as described for framework 1 and illustrated in Figure 3. The model again simulates women's future risks of developing cardiovascular disease (CVD) and uses annual cycles and a time horizon of 10 years.

Populating the decision tree model

Event probabilities

Event probabilities for the decision tree component of the model are shown in Table 9 and were informed by data collected on women with CH recruited to the BUMP2 trial, and the published literature. As illustrated by the baseline demographic tables presented for women in the BUMP1 and BUMP2 trials, women with CH tend to be older (mean age 36 years v 33 years), with a higher BMI (31kg/m^2 versus 28kg/m^2), more comorbidities, and are less likely to be of white ethnicity (49% versus 75%) than women without pre-existing hypertension.[8, 9] The risks of adverse pregnancy outcomes for CH women are therefore greater than observed for women 'at risk' of developing pregnancy hypertensive disorders who were the focus of framework 1.

The probability that pregnant women with CH would develop PE was informed by combining data from both arms of the BUMP2 trial (Table 9). At, 17%, this figure was not dissimilar to estimates reported by other studies.[58, 59] The probability of suffering a foetal loss or stillbirth with CH alone and following the development of PE were obtained from a *post hoc* analysis of adverse pregnancy outcomes in 822 women with CH who had previously been recruited to a randomised controlled trial of vitamin use for the prevention of PE during pregnancy.[58] Amongst the women who did not develop PE, 2% (n=12/642) suffered an antenatal loss. For women with PE, the corresponding percentage was 3% (n=5/180).

Parameter estimates for the timing of live births were informed by the BUMP2 trial, where available data on deliveries showed 11.1% of women (n=39/350) with CH alone had a live pre-term birth (<37 weeks' gestation). For women with CH developing PE, the corresponding figure was 66.7% (n=50/75). BUMP2 also provided data on the different types of delivery for women with CH alone and for women with CH and PE (see Table 9).

Table 9 Event probabilities used in the decision tree component of the model (Framework 2)

Parameter	Parameter Value (Distribution and moments)	Source
Hypertensive disorders		
Probability of women with CH developing PE	0.17 (Beta, α=77, β=377)	BUMP2 RCT [9]
Stillbirth		
Probability of stillbirth – women with CH alone	0.018 (Beta, α=12, β=650)	Chappell et al. 2008 [58]
Probability of stillbirth – women with CH who subsequently develop PE	0.028 (Beta, α=5, β=175)	Chappell et al. 2008 [58]
Pre-term birth (<37 weeks)		
Probability that live birth is pre-term – women with CH	0.111 (Beta, α=39, β=311)	BUMP2 RCT [9]
Probability that live birth is pre-term - women with CH and PE	0.667 (Beta, α=50, β=25)	BUMP2 RCT [9]
Delivery types for women with CH		
Probability of Caesarean section delivery	0.566 (Dirichlet)	BUMP2 RCT [9]
Probability of assisted delivery	0.091 (Dirichlet)	BUMP2 RCT [9]
Probability of normal vaginal delivery	0.343 (Dirichlet)	BUMP2 RCT [9]
Delivery types for women with CH and PE		
Probability of Caesarean section delivery	0.895 (Dirichlet)	BUMP2 RCT [9]
Probability of assisted delivery	0.039 (Dirichlet)	BUMP2 RCT [9]
Probability of normal vaginal delivery	0.066 (Dirichlet)	BUMP2 RCT [9]
Maternal stroke		
Probability of maternal stroke – women without pregnancy hypertension	0.00003 (Beta, α=61, β=1,958,142)	Scott et al. 2012 [19]
Odds ratio for increased risk of maternal stroke – women with CH	2.61 (Lognormal, mean=0.959, SE=0.339)	Bateman et al. 2006 [60]
Odds ratio for increased risk of maternal stroke – women	9.23 (Lognormal, mean=2.22,	Bateman et al. 2006 [60]

with CH and PE	SE=0.287)	
Maternal Death		
Probability of maternal 'all cause' death – with causes related to stroke and PE removed	0.00008 (Beta, α=177, β=2,280,419)	Knight et al. 2019 [21]
Probability of maternal death from stroke	0.20 (Beta, α=6, β=24)	Scott et al. 2012 [19]
Probability of maternal death with CH and PE	0.00016 (Beta, α=2.5, β=15,964)	Birth summary tables England and Wales / Leon et al. 2019 / Knight et al. 2019 [13, 21, 22]
Provision of neonatal unit care		
Probability of infant being admitted to NNU if mother has CH and delivers at term	0.058 (Beta, α=18, β=292)	BUMP2 RCT [9]
Probability of infant being admitted to NNU if mother has CH and delivers pre-term	0.667 (Beta, α=26, β=13)	BUMP2 RCT [9]
Probability of infant being admitted to NNU if mother has CH and PE and delivers at term	0.192 (Beta, α=5, β=21)	BUMP2 RCT [9]
Probability of infant being admitted to NNU if mother has CH and PE and delivers pre-term	0.776 (Beta, α=38, β=11)	BUMP2 RCT [9]

CH chronic hypertension, PE pre-eclampsia, RCT randomised controlled trial, SE standard error, NNU neonatal unit

For the underlying risk of stroke during pregnancy, we again used the UKOSS study by Scott and colleagues.[19] The increased stroke risks faced by women with CH and by women with CH and PE were then modelled by applying the relevant odds ratios for stroke risk reported by Bateman et al. in their analysis of 10 years of data from the US Nationwide Inpatient Sample database (Table 9).[60]

To model the risk of maternal death for CH women both with and without PE, we used the same data as used in framework 1. Maternal death following stroke was again informed by

the study by Scott et al., with the case fatality rate of 20% similar to that reported by Bateman et al.[19, 60]

As per the BUMP trials, we also included in the framework the need for neonatal unit (NNU) care and non-NNU care following a live birth. Although not explicitly modelled along the decision tree pathways, such costs are included in the analysis. The BUMP2 trial provided data on the proportion of babies requiring such care at the end of pregnancies delivered pre-term and term, and complicated by CH and by CH and PE together (see Table 9).

Costs

Table 10 shows the costs included in the decision tree model. Amongst women with CH who did not develop PE, data from the BUMP 2 trial showed that in the 11.1% delivering a live baby pre-term (<37 weeks' gestation), mean gestational age at delivery was 33 weeks (SD=3.02). Based upon current NICE Guidelines for the management of CH during pregnancy, we costed the additional recommended antenatal care for these women between the start of the analysis at 20 weeks' gestation up to the point of delivery (a period of 13 weeks). We assumed women would take 200mg oral labetalol twice daily, costing £0.36 per day, and would also be prescribed 150mg Aspirin daily (costing £0.08 per day).[28] Given the need for pre-term delivery in these women, we assumed their CH would have been poorly controlled and as such they would have needed weekly antenatal appointments with an obstetrician (each costing £142.00 - Obstetrics Outpatient Code 501, National Schedule of NHS Costs 2019/2020). Also costed (in line with NICE Guidance) were an ultrasound scan (£124, code NZ21Z National Schedule of NHS Costs 2019/2020), and an umbilical artery doppler velocimetry scan (£126, code NZ22Z National Schedule of NHS Costs 2019/2020) at 28 weeks' gestation and again at 32 weeks' gestation.[15, 24]

In women with CH who delivered a live baby at term, the mean gestation at delivery was 38 weeks (SD=1.09). We costed the additional antenatal care for these women, as for women

with CH and a live pre-term delivery, with the following adjustments: we assumed antenatal appointments every 2-4 weeks as opposed to weekly (assuming better controlled hypertension), and costed management from the start of the analysis at 20 weeks' gestation, up to delivery at 38 weeks. Also in line with current NICE Guidance, we included the costs of an extra ultrasound scan and an extra umbilical artery doppler velocimetry scan at 36 weeks' gestation.[15]

Table 10 Unit Costs (2019/20 UK £) and utility scores and decrements used in the decision tree (Framework 2)

Resource Use Item	Unit Cost	Source
Antenatal period		
Additional antenatal care with CH – term birth	£1,657	Various, see text for details
Additional antenatal care with CH – preterm birth	£2,386	Various, see text for details
Additional antenatal care with CH and PE – term birth	£4,171	Various, see text for details
Additional antenatal care with CH and PE – preterm birth	£5,072	Various, see text for details
Additional antenatal care prior to a stillbirth	£1,557	Various, see text for details
Delivery Period		
Delivery types	See Table 2	See Table 2
Postnatal period		
Additional maternal post-delivery inpatient bed day	£410	2019/2020 National Tariff Payment System: non-mandatory maternity prices [31]
Diagnosis, management and investigation of stillbirth	See Table 2	See Table 2
Infant Care		
Bed day spent in the NNU	£848	National Schedule of NHS Costs 2019/2020, average of currency codes XA01Z, XA02Z, XA03Z and XA04Z (service code CCU13). [24]
Bed day spent on a non-NNU ward	£404	National Schedule of NHS Costs, currency codes XA05Z (service code CCU15) [24]
Non-fatal maternal stroke		
Diagnosis and management	See Table 2	See Table 2
Maternal deaths		
Stroke death	See Table 2	See Table 2
Non-stroke death	See Table 2	See Table 2
Event	**Utility**	**Source**
Underlying utility	Population norms	Kind et al. 1999 [34]
CH decrement	0.065 (SE=0.012)	Kind et al.1999 [34] / BUMP2 RCT [9]
PE decrement	0.237 (SE=0.05)	Kind et al. 1999 [34] / Bijlenga et al. 2011 [35] / Frampton et al. 2016 [36]
Stillbirth decrement	0.308 (SE=0.05)	Heazell et al. 2016 [37] / Sobocki et al. 2007 [38]
Stroke decrement (implemented in model as multiplier)*	0.629 (SE=0.04)	Ward et al. 2007 [39]

Hypothetical intervention cost	**£7.00** **£71.00**	Cost of blood pressure monitoring Contact with obstetrician to review raised BP readings and adjust medication in 50% of women
Hypothetical intervention effectiveness (relative risk of PE with intervention)	**0.90 (SE=0.028)**	**--**

CH chronic hypertension, PE pre-eclampsia, NNU neonatal unit, SE standard error, RCT randomised controlled trial
*Used as a multiplier to decrement underlying utility levels (e.g. utility in a women who has suffered a stroke is assumed to be 62.9% that of a woman without a stroke)

Amongst women with CH who developed PE and delivered a live pre-term baby (66.7%), the BUMP2 trial showed a mean gestational age at delivery of 33 weeks (SD=3.03). We assumed that for these women, PE would have been severe enough to warrant pre-term delivery.[61] Accordingly, we included the costs of additional antenatal care described above for women with CH, between 20 and 33 weeks' gestation, at which point we costed a hospital admission during which we assumed PE would have been diagnosed and the woman would have received a course of intravenous corticosteroids for foetal lung maturation (with 24mg of dexamethasone, costing £7.14) before delivering 24-hours later.[28] We assumed the woman would have been monitored in intensive care for these 24 hours (at a cost of £2,303 – weighted average of obstetrics and gynaecology critical care codes XC02Z to XC07Z, National Schedule of NHS Costs 2019/2020).[24] In addition and informed by NICE Guidance, at the point of diagnosis we costed a cardiotocography scan (£126, code NZ22Z National Schedule of NHS Costs 2019/2020), an ultrasound scan (£124, code NZ21Z National Schedule of NHS Costs 2019/2020), and an umbilical artery doppler velocimetry scan (£126, code NZ22Z National Schedule of NHS Costs 2019/2020). The sum of these antenatal care costs is shown in Table 10.

For women with CH in the BUMP2 trial who developed PE and had a live term birth (33.3%), mean gestation at delivery was 37 weeks (SD=0.49). We again assumed that PE would have been diagnosed during a hospital admission but that the disorder would have been less severe in nature, allowing women to be managed with expectant monitoring up until delivery

at 37 weeks as recommended by NICE Guidance. Based upon data reported from the HYPITAT II trial comparing immediate delivery with expectant monitoring of women diagnosed with hypertensive disorders between 34-37 weeks of gestation (60% of whom had PE or superimposed PE) we assumed women would have had their PE diagnosed and monitored for approximately one week prior to delivery at 37 weeks' gestation.[29]

For these women therefore, we costed the additional weekly antenatal care described above for women with CH and a term delivery, for the period between 20 and 36 weeks' gestation. We then costed a diagnostic hospital admission at 36 weeks, the length of stay for which was informed by the HYPITAT II trial. During the antepartum period in the expectant monitoring arm, women in HYPITAT II spent an average of 0.01 days in intensive care (bed day cost - £2,303, weighted average of obstetrics and gynaecology critical care codes XC02Z to XC07Z, National Schedule of NHS Costs 2019/2020), 0.67 days on a medium care ward (bed day cost - £655, Ante-Natal Complex Disorders with CC Score 0-1 Code NZ18B, National Schedule of NHS Costs 2019/2020), and 3.48 days on a general ward (bed day cost £440 - Ante-Natal Major Disorders with CC Score 0-1 Code NZ19B, National Schedule of NHS Costs 2019/2020).[24] As for women with CH and PE who had a pre-term delivery, also included at the point of diagnosis were costs for a cardiotocography scan (£126, code NZ22Z National Schedule of NHS Costs 2019/2020), an ultrasound scan (£124, code NZ21Z National Schedule of NHS Costs 2019/2020), and an umbilical artery doppler velocimetry scan (£126, code NZ22Z National Schedule of NHS Costs 2019/2020).[24]

For women suffering a stillbirth, and based upon published data, we assumed this would have occurred during the antenatal period at around 36 weeks' gestation.[30] For these women, additional antenatal care was costed up to this time point.

The different types of delivery (vaginal, assisted, or Caesarean section) observed during the BUMP2 trial for women with CH, and with CH and PE (Table 9) were costed using the same

national average delivery unit costs used for framework 1 and shown in Table 2. For women with CH alone we used delivery costs with a complications and co-morbidities (CC) score of 1 and for women with CH and PE, a CC score of 2.

Data from the BUMP2 trial suggested some mothers with CH, and with CH and PE spend additional days in hospital at the time of birth, over and above the number of days expected for their type of delivery. Trial data showed women with CH and PE spent an average of 0.27 (SD=0.69) additional bed days in hospital, and women with CH spent an additional 0.09 (SD=0.78) days. These bed days were costed using an excess bed day cost of £410 taken from 2019/2020 National Tariff Payment System: non-mandatory maternity prices (see Table 10). Stillbirths were costed with the same unit costs as used for framework 1 (see Table 2).

To estimate and cost the length of stay in the NNU for the proportions of babies likely to be admitted (see Table 9), we used data from the BUMP2 trial. For women with CH, and women with CH and PE, we estimated NNU length of stay separately following pre-term and term deliveries. For women with CH who delivered pre-term and whose baby was admitted to the NNU (n=26), average NNU length of stay was 33.7 days (SD=39.9 days). In contrast, and for women with CH, a term delivery, and a baby admission to NNU (n=18), NNU length of stay was shorter at 3.5 days (SD=3.03 days). For women with CH and PE who delivered pre-term and whose baby was admitted to NNU (n=37), length of stay was 33.5 days (SD=34.1 days) and for women with CH and PE, a term delivery, and a baby admission to NNU (n=5), length of stay was 6.0 days (SD=4.5 days).

Data were not available from the BUMP2 trial on the level of care received by babies whilst in the NNU. We therefore costed the mean length of stay on the unit for each of the above groups using a weighted average of the per diem costs of neonatal intensive care, high dependency care, and special care taken from the NHS National Cost Collection (£848 -

National Schedule of NHS Costs, currency codes XA01Z, XA02Z, XA03Z and XA04Z (service code CCU13))[27, 62]

Data from the BUMP2 trial were also used to estimate non-NNU post-delivery hospital length of stay for all babies. Pre-term babies born to mothers with CH spent an average of 3.4 days (SD=8.4 days) on non-NNU wards, and term babies, 2.3 days (SD=2.0 days). Pre-term babies born to mothers with both CH and PE spent an average of 2.0 days (SD=4.6 days) on non-NNU wards and term babies 3.0 days (SD=2.2 days). These days were costed using a maternity ward bed day cost (£404, National Schedule of NHS Costs, currency codes XA05Z (service code CCU15)).[24]

Women suffering and surviving a stroke were assumed to undergo a CT scan at the time of diagnosis and were also assigned an initial stroke management cost (costs shown in Table 2 for Framework 1). For stroke and non-stroke related maternal deaths, we used the same costs as used in Framework 1 (£4,490 and £1,000 respectively as shown in Table 2).

Utility

Age and sex adjusted population norm utility scores were used to reflect women's underlying levels of health-related quality of life during pregnancy (Table 10).[34] The baseline EQ-5D score averaged across both trial arms in BUMP2 was 0.845 (SE=0.008), which is 0.065 (SE=0.012) units below the age and sex matched population norm value of 0.910 (SE=0.009). This decrement was assigned to all women in the model to reflect the negative implications of CH upon HRQoL during pregnancy and beyond.

For women suffering a stillbirth, this would most likely have been an antepartum stillbirth and we assumed occurrence at 36 weeks' gestation.[30] Utility levels in the decision tree at this point were reduced further using the stillbirth utility decrement shown in Table 10. To reflect

the longer-term maternal impact of a stillbirth, utility levels also remained decremented for the first year within the Markov model.

For women with CH alone delivering a live baby but then suffering a stroke and surviving, we assumed stroke occurred around the time of delivery and decremented utility levels further using the stroke utility multiplier shown in Table 10. The decrement was held in place for a woman's remaining duration in the decision tree (from delivery to 40 weeks' gestation) and during her first year spent in the Markov model.

For women with CH who did not suffer a stroke or a CH-related death, we assumed that their utility from the point of delivery onwards would be determined by whether or not their baby required admission to the NNU. For the NNU admission proportions shown in Table 9 for babies born to women with CH, we decremented maternal utility using the following assumptions: we assumed around 20% of mothers of infants admitted to NNU would suffer moderate to severe levels of anxiety and depression, with the remaining 80% suffering milder symptoms.[40] Using these percentages, we calculated a weighted average utility decrement, using utility decrements calculated separately for moderate (mean=0.355, SE=0.033) and mild (mean=0.25, SE=0.028) anxiety / depression from the EQ-5D utility levels reported by a cohort of Swedish individuals with depression during a six-month course of treatment in a primary care setting.[38] We held these decrements in place for a woman's remaining time in the decision tree model.

For women with CH who developed PE, we modelled the CH decrement described previously (0.065) up to 1 week prior to PE diagnosis (assumed to be 33 weeks' gestation for pre-term births and 36 weeks' gestation for term births). At this point, we assumed women would develop symptoms of PE and so utility was decremented further using the PE utility decrement shown in Table 10. For women with CH and PE suffering a stroke around the time of delivery and surviving, the PE decrement was maintained until delivery at which

point it was replaced with the stroke utility multiplier for a woman's remaining time in the decision tree model (and the first year of the Markov model). For women with CH and PE who did not suffer a stroke or a PE-related death, we assumed that their utility from the point of delivery onwards would be determined by whether or not their baby was admitted to the NNU. Decrements were modelled using the approach described above for women with CH alone.

Populating the Markov model

The risk of developing CVD and the associated costs and QALYs over the following ten years were simulated using the same Markov modelling approach implemented for framework 1 with a small number of changes. Firstly, the patient characteristics entered into the Framingham equation to predict 10-year CVD risk were amended to better reflect those of women with CH during pregnancy. Informed by the BUMP2 trial, we entered age as 36 years, BMI as 31.2kg/m^2, a systolic blood pressure of 133 maintained with antihypertensive treatment, and assumed women were non-smokers, without type 2 diabetes. The resulting 10-year CVD risk prediction for women with CH was 0.03532. To predict 10-year CVD risk for women with CH who developed PE during their pregnancy, we applied the same CVD relative risk estimate for women with a history of PE as used in Framework 1 (see Table 3).

The second amendment made to the Markov model used in framework 1 was that utility for all women remaining in the well and free from CVD health state each year was decremented for the impact of CH using the decrement (0.065) shown in Table 10.

Hypothetical intervention

For framework 2 we assumed that a hypothetical intervention might consist of the transmission and clinical review of raised home BP readings so as to facilitate earlier up-titration of antihypertensive medication. This in turn may then reduce the proportion of

women developing PE. To illustrate the potential impact of such an intervention, we assumed a 10% reduction in the proportion of women developing PE (hypothesised relative risk of 0.90 SE=0.028). The cost of providing the intervention, we assumed to comprise of the cost of home BP monitoring (£7.00 as per in the BUMP2 trial) plus the cost of clinician time required to review a raised home blood pressure reading and to consult the woman about changes to her medication. We assumed that 50% of women would need a raised home BP reading reviewed and a consultation with an obstetrician (0.5* £142.00 (Obstetrics Outpatient Code 501, National Schedule of NHS Costs 2019/2020)).

Running the model

The hybrid model was run over a time horizon of the pregnancy (20 weeks) plus 10 years, with estimated costs and maternal QALYs discounted using the recommended rate of 3.5%. Joint parameter uncertainty was assessed using probabilistic sensitivity analysis, with the model run 5000 times and each time sampling a set of parameter values from the distributions shown in tables 5, 9 and 10.

Reporting of results

Table 11 shows for the base case analysis, the estimated number of pregnancy-related adverse events for each arm of the model for a cohort of 10,000 women with pre-existing CH. A hypothetical intervention generating a 10% reduction in the risk of developing PE reduces the number of women diagnosed with PE from 1696 (17.0% of the cohort) to 1528 (15.3% of the cohort). As for framework 1, Table 11 shows the impact upon subsequent events along the pregnancy pathway is small; amongst 10,000 women, one might expect 0.03 fewer strokes and 0.02 fewer pregnancy-related deaths. These findings are explained by the fact that although PE is known to significantly increase the risks of pregnancy stroke and death, these events continue to be rare, such that a doubling or tripling of the underling rates as a result of PE leads to small absolute increases in event numbers.

Table 11 Predicted outcomes to the end of the pregnancy period for a cohort of 10,000 pregnant women with chronic (pre-existing) hypertension*†

	Number of events in 10,000 at risk women				
Events	**Control arm**	**Base-case: Intervention reduces risk of PE by 10%**	**Difference (95% CI) Base-case intervention versus control**	**Scenario 1: Intervention reduces risk of PE by 15%**	**Scenario 2: Intervention reduces risk of PE by 20%**
Development of PE	1696	1528	-168 (-270 to -71)	1443	1358
Maternal stroke (pregnancy related)	1.22	1.19	-0.03 (-0.09 to -0.007	1.17	1.15
Maternal deaths (pregnancy related)	1.15	1.13	-0.02 (-0.07 to 0.003)	1.12	1.11

PE pre-eclampsia, CI confidence interval
*Women are aged 36 years, with a BMI 31.2kg/m^2, a treated systolic blood pressure of 133, and are non-smokers, without type 2 diabetes.
†Base-case analysis assumes hypothetical intervention reduces the risk of a woman developing PE by 10% (relative risk 0.90)
PE - Pre-eclampsia

Extending the framework to include the 10-year outcomes generated by the Markov model, produces the cost and QALY figures shown in the first rows of Table 12. Mean cost and QALY differences are also plotted on the cost-effectiveness plane in Figure 7 (panel a) and using the cost-effectiveness acceptability curve in Figure 8 (panel a).

The mean cost savings and QALY gains by intervening for this group of women are larger than those observed for 'at risk' women in framework 1. This is explained by the fact that for CH women, a 10% reduction in the risk of developing PE would potentially improve outcomes for 1.7% of an overall cohort (in comparison with 0.4% of 'at risk' women); Table 11 shows that in a cohort of 10,000 women with CH, an estimated 168 fewer women would develop PE.

For these 168 women, without intervention, the 10-year predicted risk of subsequently developing CVD having suffered with PE during pregnancy is around 6.5%. With intervention and the prevention of PE, their 10-year risk of developing CVD halves to an average of 3.5%. Thus, across the cohort as a whole, 1.7% of women receive a 3% reduction in their 10-year risk of developing CVD.

Table 12 Expected discounted mean 10-year costs and QALYs per pregnant woman with chronic (pre-existing) hypertension*

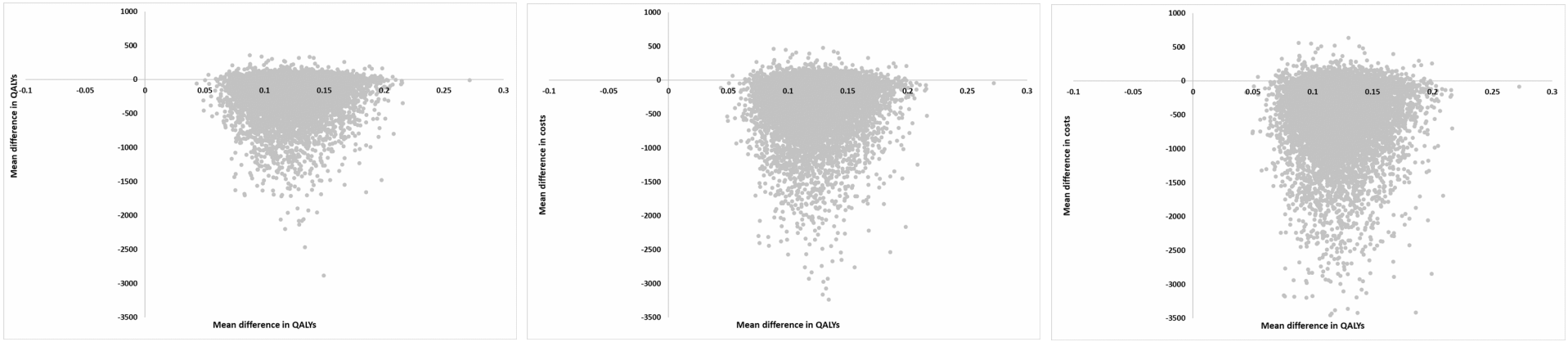
	Intervention arm	Control arm	Difference
Base-case: intervention reduces risk of women with CH developing PE by 10%			
Mean total cost per patient	£13,688	£13,893	-£205
Mean total QALYs per patient	7.341	7.220	0.121
Scenario 1: intervention reduces risk of women with CH developing PE by 15%			
Mean total cost per patient	£13,546	£13,893	-£348
Mean total QALYs per patient	7.341	7.220	0.122
Scenario 2: intervention reduces risk of women with CH developing PE by 20%			
Mean total cost per patient	£13,403	£13,893	-£490
Mean total QALYs per patient	7.342	7.220	0.122

*Women are aged 36 years, with a BMI 31.2kg/m^2, a treated systolic blood pressure of 133, and are non-smokers, without type 2 diabetes.
CH chronic hypertension, PE pre-eclampsia, QALY quality adjusted life year

As with framework 1, the model can also be used to illustrate the impact upon cost-effectiveness results of alternative study parameter values. To illustrate, we again present the same two scenarios as for framework 1 in which the effectiveness of the intervention is modified and the results re-calculated. In scenario 1 the size of the treatment effect of a hypothetical intervention on reducing the risk of developing PE was increased from 10% to

15% and in scenario 2 from 10% to 20%. The impact of these changes upon events during pregnancy and 10-year cost-effectiveness results is shown in Tables 11 and 12 and Figure 7 and 8 (panels b and c).

Figure 7 Mean estimated and discounted 10-year cost and QALY differences plotted on the cost-effectiveness plane (Framework 2 – women with chronic hypertension)



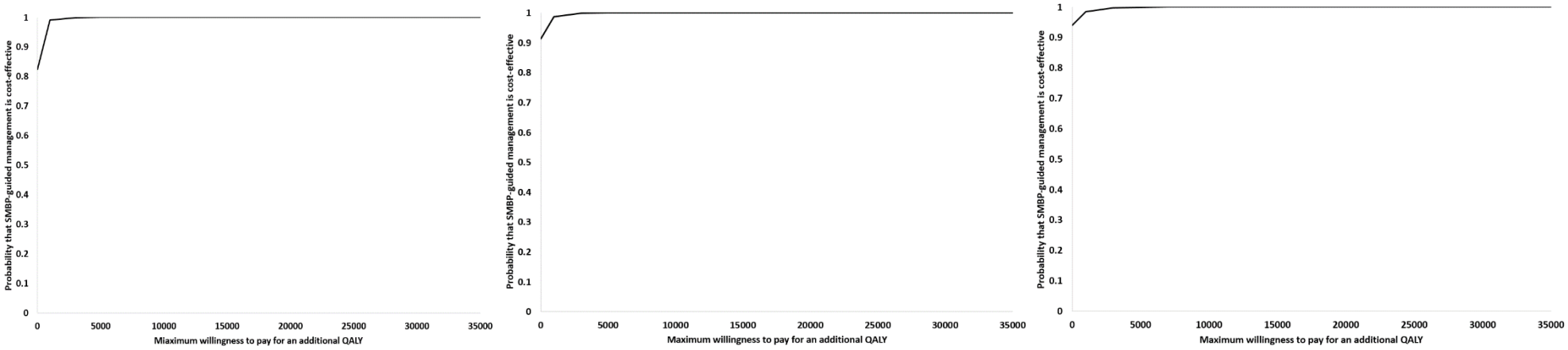
Panel (a) Panel (b) Panel (c)

Panel (a) Intervention is assumed to reduce the risk of women with CH developing PE by 10%

Panel (b) Intervention is assumed to reduce the risk of women with CH developing PE by 15%

Panel (c) Intervention is assumed to reduce the risk of women with CH developing PE by 20%

Figure 8 Cost-effectiveness acceptability curves (Framework 2 – women with chronic hypertension)



Panel (a) Panel (b) Panel (c)

Panel (a) Intervention is assumed to reduce the risk of women with CH developing PE by 10%

Panel (b) Intervention is assumed to reduce the risk of women with CH developing PE by 15%

Panel (c) Intervention is assumed to reduce the risk of women with CH developing PE by 20%

Discussion

The aim of this work stream in the BUMP programme was to understand the potential value for money of interventions to either detect raised BP in women at risk of pregnancy hypertension or to monitor BP in women diagnosed with hypertension, using an early health economic model. The report has described the development and presentation of two modelling frameworks which can be used to begin to explore the potential longer-term cost-effectiveness of SMBP-guided management for both of these groups of women and indeed other groups of pregnant women too.

The cost-effectiveness results presented here are not definitive in nature, rather they allow contemplation of the potential for SMBP-guided management to be cost-effective for different cohorts of pregnant women. In mapping out and populating the pregnancy pathways, the frameworks provide a means of quantifying the proportions of women at risk of complications associated with pregnancy hypertension, along with the magnitude of potential changes to these proportions and the likely implications for cost-effectiveness results, as a consequence of intervention. Indeed the frameworks suggest that the use of SMBP to monitor and guide therapy for women already diagnosed with hypertension during pregnancy may be a more cost-effective use of resources than SMBP use for detecting woman at risk of pregnancy hypertension. Such findings are intuitive given that the frameworks model the intervention effect through a relative reduction in the risk of pre-eclampsia, and women with existing hypertension are at greater risk of this condition.

Further, and though use of the Framingham CVD risk prediction equation, the model also permits exploration of cost-effectiveness results according to women's characteristics and thus may be helpful in identifying sub-groups of women for whom intervention may prove particularly cost-effective.

As discussed at the start of this report, analysts wishing to make use of the models presented here are encouraged to follow good practice guidelines for decision analytic modelling when adapting the frameworks to their own settings.[10] In particular, attention should be paid to whether the structure is appropriate, and to comprehensive reviews of the literature which should be conducted to identify and synthesise data to inform and appropriately propagate uncertainty around model parameter input values.

Researchers using the frameworks can also make their own amendments and further developments. For example, and with regard to the model input data, although we chose to use the Framingham risk equation developed by D'Agostino and colleagues to predict the 10-year risk of CVD, other risk prediction models such as QRISK are available, have been used previously within published cost-effectiveness models, and could easily be substituted into the frameworks presented here.[63] Further, and although the frameworks do include some costs of providing neonatal care, over the longer-term they do not currently seek to quantify the costs associated with and the health implications for babies who are born pre-term as a result of hypertensive disorders of pregnancy. Previous work by Petrou and colleagues for example has shown health impact and associated costs for pre-term infants to be substantial.[64, 65]

It may also be prudent to implement a longer time horizon for the frameworks as the risks for cardiovascular disease will extend beyond the 10-year time horizon used here. Also the costs and health outcomes of such chronic conditions will likely affect a woman over her remaining lifetime. Other noteworthy points are that it was not possible to propagate uncertainty for all model parameters. We could not, for example, enter a distribution around the Framingham 10-year CVD risk predictions on account of the variance co-variance matrix not being available. Some of the costs in the Markov model were also entered as point estimates as they were calculated using resource use estimates elicited from expert opinion or reported without measures of variability. Finally, both the costs and the levels of

effectiveness associated with the interventions modelled here are hypothetical in nature. Research is needed to determine the likely value of these parameters before any firm conclusions can be drawn about the cost-effectiveness of SMBP for pregnancy hypertension.

Conclusion

The frameworks presented here provide a means with which to explore the potential cost-effectiveness of SMBP for detecting and monitoring pregnancy hypertension. Although no definitive cost-effectiveness results are presented, the model has illustrated to potential for cost-effectiveness to vary between pregnant women at risk of hypertension and those with hypertension already diagnosed. Of course empirical work would be needed to confirm these findings in practice.

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