Hypertension in pregnancy: diagnosis and management (update)

Consultation on draft guideline - Stakeholder comments table
13 February 2019 – 13 March 2019

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Action on Smoking and Health	Guideline	4	11-12	ASH welcomes the inclusion of cross-reference to NICE guidance on antenatal care, which includes reference to smoking and the need to promote smoking cessation amongst pregnant people who smoke. Behavioural risk factors are responsible for 80% of all diagnoses of coronary heart disease and cerebrovascular disease.[i] Although unhealthy diet, physical inactivity and harmful use of alcohol play a role, by far the leading behavioural risk factor of cardiovascular disease (CVD) is smoking. Smoking has been attributed to account for 14% of deaths from CVD;[ii] with CVD risk being substantially reduced within two years of smoking cessation.[iii] Compared with non-smokers, smokers have a 2 to 4 times increased risk of heart disease and of stroke.[iv]	Thank you for your comment and for confirming the link between smoking and cardiovascular disease. A link to the NICE guideline on avoiding smoking has been added to recommendations about reducing the risk of cardiovascular disease.
Action on Smoking and Health	Guideline	32	7-8	ASH welcomes the maintenance of cross-reference to NICE guidance on cardiovascular disease, which includes reference to smoking and the need to promote smoking cessation amongst people who smoke. Hypertensive smokers are more likely to develop severe forms of hypertension, including malignant and renovascular hypertension,[v] and are at substantially higher risk of subarachnoid haemorrhage compared to those who neither smoke nor have been treated for hypertension.[vi] It is, therefore, vital that those diagnosed with hypertension who smoke are supported to quit smoking and that this is followed through at follow-up and when care is transferred to the community setting.	Thank you for your comment. A cross-reference to the NICE guidance on smoking cessation has now also been added to the guideline.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
British Dietetic Association	Guideline	5		Pregnant women with pre-existing diabetes (type 1 or type 2) have increased risk of pre-eclampsia & are also recommended to take 75 mg aspirin. [Weissgerber, T. L., & Mudd, L. M. (2015). Preeclampsia and diabetes. *Current diabetes reports*, *15*(3), 9.]	Thank you for your comment. We agree that women with pre-existing diabetes are at a higher risk of pre-eclampsia and should take aspirin and this is already included in in recommendation 1.1.2
British Dietetic Association	Guideline	8	12	We recommend this statement 'Offer pregnant women with chronic hypertension advice on…' should be changed to: Offer pregnant women with chronic hypertension a referral to a registered dietitian for advice on… Registered dietitians are best placed to offer effective advice regarding weight management, healthy eating and reducing the salt content of the diet.	Thank you for your comment. The committee recognise the expertise of dietitians, but this recommendation provides general advice for women with chronic hypertension in pregnancy, and the evidence for the benefit of interventions by specific practitioners has not been reviewed as part of this update. The guideline cross-refers to the Hypertension in Adults guideline, therefore the committee considered that any advice should be given in line with this guideline.
British Dietetic Association	Key recommendations for research:	35		Further research regarding the genetic impairment of the methylenetetrahydrofolate reductase enzyme (MTHFR) of folate metabolism in pregnancy is required. Epidemiological studies conducted in the non-pregnant population; show that the 677C→T polymorphism in MTHFR increases the risk of hypertension by 24–87%[2]. Randomized trials conducted in non-pregnant, hypertensive patients, pre-screened for this polymorphism; show that riboflavin (Vitamin B2) supplementation in homozygous individuals (*MTHFR* 677TT genotype) lowers blood pressure by 6 to 13 mmHg[2]. Further research is needed to determine if the effect of riboflavin supplementation in pregnant women at risk of hypertension (with the MTHFR genotype) can be duplicated. [McNulty, H., Strain, J.J., Hughes, C.F. and Ward, M., 2017. Riboflavin, MTHFR genotype and blood pressure: a	Thank you for your comment. The committee agreed that there is scope for research in this area, but as we did not search for evidence for this genetic impairment, the committee were unable to prioritise this as part of the guideline research recommendations.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				personalized approach to prevention and treatment of hypertension. *Molecular aspects of medicine*, *53*, pp.2-9.]	
British Maternal & Fetal Medicine Society	Guideline	4	11	Please can you confirm that the new NICE antenatal care guideline (due 2020) will cover advice on risk factors and symptoms of PET	Thank you for your comment. We are aware that this information is included in the current NICE guideline on antenatal care and have made the team carrying out the update aware of this cross-reference so they can take this into consideration when carrying out their update of this question.
British Maternal & Fetal Medicine Society	Guideline	4	14	The advice for pre-eclampsia prevention with aspirin does not appear to have been revised from the previous guideline (2010). I suspect this is because this point was not addressed in the scope of the update and therefore the new evidence has not been reviewed. Unfortunately, this means that the statement in the current guideline does not agree with Saving Babies Lives care bundle (NHS England, release date Mar 2019) or the RCOG SGA guidelines (currently under revision). I'm not sure how this can be addressed given that this was presumably not within the scope of the update but this is going to create inconsistency and confusion amongst care providers. Would the guideline committee consider recommending a dose range for women in whom aspirin would be recommended (see below). Again, I know beyond the scope of this update but surely the NCS or NICE should be reviewing the whole process for screening for pre-eclampsia.	Thank you for your comment. As you note, this recommendation was not revised as part of the current update. However, the committee agreed that it was unhelpful to have conflicting advice in two different national guidelines. They therefore agreed to amend the recommended dose of aspirin to give a range of 75-150 mg, as they were aware of evidence for the effectiveness of both 'low doses', 75 mg and 150 mg of aspirin. The committee were aware that screening for pre-eclampsia is currently under consideration by the National Screening Committee.
British Maternal & Fetal Medicine Society	Guideline	6	23	The guidance around repeat urine testing for quantification of proteinuria appears to contradict Table 2 where it suggests that women with confirmed pre-eclampsia should have urine dipstick testing twice per week. What is the evidence that repeated dipstick testing is	Thank you for your comment. The committee agreed that the recommendation in Table 2 about repeat dipstick testing was confusing, and have amended Table 2 to state "Only repeat if clinically indicated".

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				necessary/informative in women with a diagnosis of pre-eclampsia? I would support repeat PCR testing if there is uncertainty around the diagnosis at low levels of proteinuria but am unconvinced that there is any further merit to repeat urine dipstick testing or quantification given that absolute levels of proteinuria have not been demonstrated to have prognostic value.	
British Maternal & Fetal Medicine Society	Guideline	8	19	It is unclear if this recommendation covers pregnancy or prepregnancy. If only for those women who are pregnant (as written) could their be a recommendation regarding pre-pregnancy advice	Thank you for your comment. The recommendation your comment referred to related to women who were pregnant but the committee agreed that women may need referral as part of pre-pregnancy advice, and therefore have moved this recommendation to the start of the section on the management of chronic hypertension, to highlight that women with chronic hypertension should be cared for by a specialist prior to their pregnancy, as well as during their pregnancy.
British Maternal & Fetal Medicine Society	Guideline	9	10	Again this guidance is not in agreement with the dose of aspirin recommended in the Saving Babies Lives Care Bundle. I fully appreciative that the evidence to support aspirin as an effective preventative therapy for women with chronic hypertension (as the only risk factor) is scant and that in the trials where a CHT subgroup has been analysed a large reduction in disease has not been observed (smaller than for other risk factors). However, evidence from the recent large trial would support a higher dose of aspirin across all high risk groups and therefore the recommendation for a lower dose in the CHT group is no more or less justifiable than a higher dose. I wonder if the guideline group would therefore consider recommending a dose range (e.g. 75-150mg) given that a higher dose is	Thank you for your comment. The evidence reviewed for the treatment of chronic hypertension included evidence of some benefit with aspirin doses ranging from 50mg to 150mg a day and the committee were therefore aware there is some uncertainty about the optimal dose of aspirin. The committee were also aware that other national guidelines may recommend 150mg, and agreed that inconsistency between national guidelines is unhelpful. They therefore agreed to amend the recommended dose of aspirin to give a range of 75-150mg, as they were aware of evidence for the effectiveness of both 'low doses', 75 mg and 150 mg of aspirin.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				considered safe, is being implemented around the world and would be consistent with other UK national guidance.	
British Maternal & Fetal Medicine Society	Guideline	9	13	I don't understand why no specific advice is being given regarding frequency of BP review for women with CHT and no other risk factors. If one were to follow the current NICE guidance (as suggested) these women would only have their BP checked at 12,16, 25 (if primips), 28, 31 (if primips), 34, 36 (if primips), 38, 40 and 41. There is nothing here to state that they need to be seen weekly until BP well controlled, and then every 2-4 weeks until delivery. Previous PRECOG guidance at least stated that multips with CHT should be seen according to the primip schedule	Thank you for your comment. Although the committee had not reviewed the evidence for the frequency of antenatal appointments and BP monitoring, they agreed that this was an important point. The existing recommendation has now been amended to clarify what additional antenatal appointments might be needed, for example weekly appointments until blood pressure is controlled, and then 2 to 4 weekly appointments.
British Maternal & Fetal Medicine Society	Guideline	10	21	Who should do the review 2 weeks postnatally? In women with GH and PET it is the GP.	Thank you for your comment. We have now clarified in this recommendation (and for gestational hypertension and pre-eclampsia) that this review 2 weeks after birth can be conducted by the woman's GP or specialist.
British Maternal & Fetal Medicine Society	Guideline	12	Table 1	Why is placental growth factor-based testing missing from table 1?	Thank you for your comment. We have now amended Table 1 to include PlGF-based testing.
British Maternal & Fetal Medicine Society	Guideline	12	Table 1	NICE antenatal care does not recommend FH auscultation at every visit. Is it required for women with hypertension if the baby is moving normally?	Thank you for your comment. The committee considered that, as women with hypertension in pregnancy are a high-risk group and women find hearing their baby's heartbeat reassuring, it was appropriate to offer fetal heart auscultation at every antenatal appointment, and the guideline has been amended to state this.
British Maternal & Fetal	Guideline	13	14	There is no guidance as to which women with GH should be considered for planned delivery prior to 41+5 (ie what is recommended for otherwise normal women. Can we have	Thank you for your comment. The committee did not review the evidence for the timing of birth in gestational hypertension so were unable to make changes to these

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Medicine Society				some guidance. Eg women with other risk factors such as GDM may benefit from delivery by 38 week, consider offering delivery at 40 weeks to all women with CHT or GH	recommendations, but agreed that early birth may not be necessary or lead to benefits in these women and so this should be a decision discussed with the woman, as the recommendations already advise. The committee were aware that there is an ongoing trial comparing delivery at 38 weeks and 40 weeks in women with gestational hypertension and we will pass your comment to the NICE surveillance team which monitors guidelines to ensure that they are up to date.
British Maternal & Fetal Medicine Society	Guideline Why Recs made P 41-42 Evidence C	15	14 onwards	In my opinion, these recommendations are not fit for purpose as currently written. My points cover the inconsistencies between the models (partly because they are designed to predict different outcomes) and the lack of proven impact on clinical decision making. I fully appreciate the motivation to standardise care and encourage clinicians to risk assess every woman with pre-eclampsia – I do not however think this will be achieved with the guidance in its current form.	Thank you for your comments. We have addressed each of your 11 points separately below.
British Maternal & Fetal Medicine Society	Guideline Why Recs made P 41-42 Evidence C	15	14 onwards	1. These models contain different predictors and do generate risks which are in any way equitable (see below) – this will only create confusion and further inconsistencies in care.	Thank you for your comment. The committee agree that the risk predictor models use different predictor variables and outcome measures. However, as both models have been validated as effective to identify women at high and lower risk of complications, they considered that use of either of the models may help guide decisions about care. The recommendations relating to the use of fullPIERS and PREP-S have been amended to clarify that they should be used as an adjunct to help guide decision-making and not to replace clinical assessment and the clinical judgement of healthcare professionals. We have now moved the recommendations relating to the use of the models

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					after the list of clinical features which may warrant hospital admission, and clarified that any one (or more) of these features should be used to identify if there are any concerns for the wellbeing of the woman or baby. The suggested risk threshold of 30% has also been removed, as we agree this may cause confusion if clinical criteria and different scores from the 2 models indicate differing courses of action.
British Maternal & Fetal Medicine Society	Guideline Why Recs made P 41-42 Evidence C	15	14 onwards	2. The PIERS model is heavily weighted towards oxygen saturations and to generate a risk prediction of 30% a woman must have confirmed severe multisystem disease (abnormalities which would fit thee definition of severe pre-eclampsia in the current guidelines). Saturations of 94% or less (with chest pain/dyspnoea) or 92% or less (without) are required to drive the risk above 30%. Apart from confirming that a woman has very severe disease and therefore close surveillance and intervention in the most appropriate setting is required – I do not see how this algorithm will facilitate management at the threshold (30%) suggested. Low oxygen saturations are diagnostic of respiratory complications of pre-eclampsia, not prognostic.	**Thank you for your comment. The recommendations have been amended to clarify that these models may be used as an adjunct to help guide decision-making, rather than the main factor that determines management, and should not replace clinical assessment and the clinical judgement of healthcare professionals. We have now moved the recommendations regarding the use of the models after the list of clinical features which may warrant hospital admission, and clarified that any one (or more) of these features should be used to identify if there are any concerns for the wellbeing of the woman or baby. The suggested risk threshold of 30% has also been removed, as we agree this may cause confusion if clinical criteria and different scores from the 2 models indicate differing courses of action.**
British Maternal & Fetal Medicine Society	Guideline Why Recs made P 41-42 Evidence C	15	14 onwards	3. There is little validation of the PIERS risk prediction algorithms in UK settings especially at the lower end of the risk prediction algorithm (where calibration was poor), the vast majority of women with pre-eclampsia will generate a risk prediction of <5%.	Thank you for your comment. The committee considered that the validation of PIERS that has been conducted in datasets from Canada (BCW cohort), the Netherlands (PETRA cohort) and the UK (PREP cohort), was sufficient to indicate that the model was useful in a UK setting. The committee were aware that most women will score <5%, because the majority of

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					women are not at high risk of complications, and that the data from Ukah 2018 included over 1000 women with risk scores of <5%, and the actual prevalence of complications in these women was <5%, confirming good calibration, even at low risk levels (please see table 10 in the evidence report).
British Maternal & Fetal Medicine Society	Guideline Why Recs made P 41-42 Evidence C	15	14 onwards	4. The PIERS model includes post partum haemorrhage within the adverse maternal outcome (most common adverse event). Whilst many cases of PPH will be exacerbated severe pre-eclampsia, in many cases the PPH will not be related to the predictors in the model and will is more dependent on obstetric management. This affects the accuracy of the model.	Thank you for your comment. The committee were aware that transfusion is an outcome for both the fullPIERS and PREP-S models and that this may not reflect the most important clinical adverse consequence of pre-eclampsia. However, the committee were only able to base their assessment of the models on the validation data they reviewed, which provided evidence that the models were useful to predict adverse outcomes, and were not able to exclude the need for blood transfusion from the models or their validation.
British Maternal & Fetal Medicine Society	Guideline Why Recs made P 41-42 Evidence C	15	14 onwards	5. Both of the models generate estimates risks of complications without explicitly listing (on the online tool kits) which complications are included (these are of course included in the publications but not immediately available to a busy clinician). The severe outcomes include severe muyltisystem disease (liver and renal compromise for example) – it is not surprising that these are 'predicted' by tests which confirm renal and liver involvement.	**Thank you for your comment. The committee agree that the online calculators do not explicitly state the outcomes used in the models. However, they considered that the models may help clinicians identify women who** are **at high risk of complications, or to provide some reassurance for women at lower risk. The recommendations relating to the use of fullPIERS and PREP-S have been amended to clarify that they** may **be used as an adjunct to help guide decision-making** but do **not replace clinical assessment and the clinical judgement of healthcare professionals. We have now moved the recommendations relating to the**

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					use of the models to after **the list of clinical features which may warrant hospital admission, and clarified that any one (or more) of these features should be used to identify if there are any concerns for the wellbeing of the woman or baby**. **The suggested risk threshold of 30% has also been removed, as we agree this may cause confusion if clinical criteria and** different scores from the 2 models **indicate differing courses of action.**
British Maternal & Fetal Medicine Society	Guideline Why Recs made P 41-42 Evidence C	15	14 onwards	6. There is little or no agreement between the risk prediction algorithms and their assessment of risk in the same individual. This is partly because they are designed to predict different outcomes (over different time points) and partly because they use different predictors. Nonetheless in the context of this recommendation, the option to use either or model does provide the clinician with information as to which model they should apply to which clinical situation. For example, I have tested these on two women with preterm pre-eclampsia that I have seen today (see appendix). The risk predictions vary from 1.2-45% in the same woman. The nuance of why these are different and what information they may or may not provide to support clinical decision making is not described in the recommendation and is also probably too complex to be appreciated by a busy clinician reading the guideline. In both cases illustrated, I fail to see how the algorithm would have enabled better decision making.	Thank you for your comment. The recommendations have been amended to clarify that these models may be used as an adjunct to help guide decision-making, and should not replace clinical assessment or the clinical judgement of healthcare professionals. We have now moved the recommendation relating to the use of the models below the list of features which would warrant hospital admission, and clarified that any one (or more) of these features should be used to identify if there are concerns for the wellbeing of the woman or baby. The committee agree that the models use slightly different predictor variables and outcome measures. The suggested risk threshold of 30% has been removed, as we agree this may cause confusion if clinical criteria and different scores from the 2 models indicate differing courses of action.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
British Maternal & Fetal Medicine Society	Guideline Why Recs made P 41-42 Evidence C	15	14 onwards	7. The primary publication for the PREP-S algorithm states that preterm birth (<34 weeks) is included within the primary "serious maternal complication" outcome. *We defined the primary outcome as maternal complication that included maternal death, neurological, hepatic, cardiorespiratory, renal or haematological complications, or delivery before 34 weeks (Additional file 1: Table S3a). The panel agreed that delivery before 34 weeks is often offered for medical reasons to avoid complications as per the national guidelines; thus, excluding this as an adverse outcome would underestimate the true incidence of adverse outcomes and lead to prognostic models that yield too low risk predictions of actually developing an adverse outcome"* BUT using the link provided in the guideline (https://www.evidencio.com/models/show/1038) the web tool states: *"Adverse outcomes predicted in the PREP models do not include risk of preterm delivery."* This is very confusing and I have not managed to unpick this despite reading the thorough evidence report and the primary publication. I wonder if the PREP-S model available on line has been amended in line with a second analysis (this is not referenced on the website or discussed in the evidence review as far as I can see). Inevitably predictive models which use variables – such as magnesium sulphate administration which are very	Thank you for your comment. Planned early birth at less than 34 weeks may be for maternal or fetal indications, so it is a surrogate measure for all the complications that happen in this multi-organ disease. The website referenced now states that "PREP models can be used to obtain predictions of adverse maternal outcome risk, including early preterm delivery, by 48 hours (PREP-S) and by discharge (PREP-L), in women with early onset pre-eclampsia in the context of current care." The committee reviewed evidence for the usefulness of the models as they were constructed at the time of the evidence review and found that both models have been validated as effective to identify women at high and lower risk of complications, so they considered that use of either of the models may be of benefit when assessing women, However, the recommendations have been amended to clarify that these models should be used as an adjunct to help guide decision-making, rather than the main factor that determines management, and they should not replace clinical assessment or the clinical judgement of healthcare professionals. We have now moved the recommendations relating to the use of the models to predict a high risk of complications below the list of features which would warrant hospital admission, and clarified that any one (or more) of these features should be used to identify if there are concerns for the wellbeing of the woman or baby.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				closely associated with the decision for iatrogenic preterm birth are going to be highly predictive of preterm birth, i.e there is a very significant risk of collider bias within the models which does not make them fit for purpose.	
British Maternal & Fetal Medicine Society	Guideline Why Recs made P 41-42 Evidence C	15	14 onwards	8. It is likely therefore that the PREP-S model does not predict biological progression of the disease but more likely the clinician behaviour within the dataset. For example, in my first example below (woman at 33 weeks), a risk of an adverse outcome within 2 days of 25% really means that in the dataset in which the models were developed – 1 in 4 clinicians (accepting calibration error) would have offered iatrogenic preterm birth to this woman within 2 days. It does not mean that the absolute risk of the woman developing a severe medical complication of pre-eclampsia is 25% or that the decision for preterm birth was the 'right' one.	Thank you for your comment .The committee agree that the inclusion of iatrogenic preterm birth as part of the outcome measure for PREP demonstrates clinical practice, rather than adverse outcomes as such. However, this measure was added to minimise treatment paradox. The committee found that both models have been validated as effective to identify women at high and lower risk of complications and, considered that PREP-S may be useful to help support the judgement of an individual clinician in establishing which women are at higher/lower risk of adverse outcomes. However, the recommendations have been amended to clarify that these models may be used as an adjunct to help guide decision-making, rather than the main factor that determines management, and should not replace clinical assessment or the clinical judgement of healthcare professionals. We have now moved the recommendations relating to the use of the models to predict a high risk of complications below the list of features which would warrant hospital admission, and clarified that any one (or more) of these features should be used to identify if there are concerns for the wellbeing of the woman or baby.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
British Maternal & Fetal Medicine Society	Guideline Why Recs made P 41-42 Evidence C	15	14 onwards	9. I am not convinced that a threshold risk of a serious maternal complication of 30% is helpful in clinical practice. Clearly a woman with any abnormal or deteriorating haematological or biochemical abnormalities (all markers of severe disease) in the context of preterm pre-eclampsia needs to be managed in a setting where a prompt and safe birth could be facilitated, and in my view should therefore be managed as an inpatient in an appropriate setting. Is the recommendation suggesting that a woman with a risk using the PREP-S algorithm of 25% at 25 weeks in a unit without Level 3 neonatal care should stay where she is but the woman at 29 weeks with a risk score of 60% at 29 weeks should be transferred to a tertiary unit? Most likely in both situations the PIERS model would be <5%.	Thank you for your comment. The recommendations have been amended to clarify that these models may be used as an adjunct to help guide decision-making, rather than the main factor that determines management, including the need for *in utero* transfer, and should not replace clinical assessment or the clinical judgement of healthcare professionals. We have now moved the recommendations relating to the use of the models to predict a high risk of complications below the list of features which would warrant hospital admission, and clarified that any one (or more) of these features should be used to identify if there are concerns for the wellbeing of the woman or baby. The suggested risk threshold of 30% has been removed, as we agree this may cause confusion if clinical criteria and different scores from the 2 models indicate differing courses of action.
British Maternal & Fetal Medicine Society	Guideline Why Recs made P 41-42 Evidence C	15	14 onwards	10. Until we have further evidence of what thresholds are useful, I do not think we should be recommending a specific threshold. For example, in a woman at 32 weeks with normal and stable blood tests the risk of adverse outcomes will cross the 30% threshold based on a slightly higher PCR. We know that above the threshold for diagnosis a PCR of 50mg/mmol is no more or less significant than a PCR of 250mg/mmol – but using this model it would be the difference between high and low risk. This clearly does not make sense.	Thank you for your comment. The committee agree that determining an absolute threshold to use is challenging and therefore the recommendations have been amended to clarify that these models may be used as an adjunct to help guide decision-making, rather than the main factor that determines management, and should not replace clinical assessment or the clinical judgement of healthcare professionals. We have now moved the recommendations relating to the use of the models to predict a high risk of complications to below the list of features which would warrant hospital admission, and clarified that any one (or more) of these features should be used to identify if there are concerns for the

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					wellbeing of the woman or baby. The suggested risk threshold of 30% has been removed, as we agree this may cause confusion if clinical criteria and different scores from the 2 models indicate differing courses of action. Although the level of PCR may not be used in clinical practice to identify severity of disease, it was found to be a significant predictor variable for the outcomes used in the PREP study, therefore the magnitude of the PCR will affect the risk of adverse outcomes.
British Maternal & Fetal Medicine Society	Guideline Why Recs made P 41-42 Evidence C	15	14 onwards	11. The implementation and impact on clinical decision making of neither of these models has been tested in UK clinical settings. I appreciate the desire to standardise risk assessment, inpatient/outpatient surveillance and timing of birth in women with preterm pre-eclampsia but I am unsure how these models will help given that the thresholds proposed in most cases would confirm multisystem disease which would trigger admission and close surveillance (given the guidance around features of "severe disease" later in the guidance) in any UK unit.	Thank you for your comment. The committee considered that the performance of the model has been validated in external datasets to warrant incorporation into routine clinical practice, and that use of these models may help overcome current variations in practice. The PREP-S model was specifically developed in the UK population. However, the committee agree that the models may be helpful as an adjunct to help guide decision-making but not to replace clinical assessment and the clinical judgement of healthcare professionals. The suggested risk threshold of 30% has been removed, as we agree this may cause confusion if clinical criteria and different scores from the 2 models indicate differing courses of action. The committee agree that further research may be undertaken to evaluate the impact of introducing such models into practice.
British Maternal &	Guideline	17	Table 2	Comments on PIERS and PREP-S below.	Thank you for your comment. The recommendations on the use of the fullPIERS and PREP-S models have

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Fetal Medicine Society				Using a risk threshold of 30% from PIERS would mean a woman would have pre-eclampsia with severe features as defined in rec 1.8.3 women and should probably be receiving HDU care! PREP-S has no threshold to support/guide admission. 50% risk threshold again identifies a woman with established multisystem disease who will have severe features of pre-eclampsia. As far as I can see from testing the PREP-S algorithm on a number of scenarios a risk threshold would identify women with no evidence of multisystem disease as >30% and women with abnormal blood tests (and therefore evidence of multisystem disease) being <30% - see below. Why is CTG recommended at all in women with a normal scan and normal fetal activity?	been amended to clarify that these models may be used as an adjunct to help guide decision-making, rather than the main factor that determines management, and should not replace clinical assessment or the clinical judgement of healthcare professionals. We have now moved the recommendations relating to the use of the models to predict a high risk of complications to below the list of features which would warrant hospital admission, and clarified that any one (or more) of these features should be used to identify if there are concerns for the wellbeing of the woman or baby. The suggested risk threshold of 30% has also been removed, as we agree this may cause confusion if clinical criteria and different scores from the 2 models indicate differing courses of action. The recommendations on the use of CTG have now been amended to state that CTG should be used as clinically indicated, rather than routinely.
British Maternal & Fetal Medicine Society	Guideline	17	Table 2	Why repeat dipstick daily on women with confirmed PET? In fact why repeat dipstick at all in women with confirmed PET (unless the diagnosis is in question)?	Thank you for your comment. The table has now been amended to state that repeated dipstick proteinuria testing should only be carried out if clinically indicated.
British Maternal & Fetal Medicine Society	Guideline	18	5	Most FGR guidelines and evidence from TRUFFLE would support preterm birth for a growth restricted infant (in the absence of maternal indication for birth) indicated by abnormal STV or abnormal ductus venosus Doppler. I think these should at least be mentioned here. In extreme	Thank you for the comments. A full evidence review of specific indications for planned early birth in women with pre-eclampsia was out of scope for this guideline update, therefore the evidence has not been reviewed, and so the committee were not able to review or include the TRUFFLE studies. However, to provide

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				preterm situations (<28 weeks), rEDF alone is not indicator for birth.	some more clarity on the existing recommendations, this list has been adapted and expanded based on the ISSHP criteria, but has now been clarified further to recognise that there may be other maternal or fetal indications for a planned early birth.
British Maternal & Fetal Medicine Society	Guideline	18	18	Why does a "senior obstetrician" need to be "involved" in the decision about timing of delivery in all women with PET? It is a clear indication if 38 weeks.	Thank you for your comment. The committee considered that it was good practice to discuss the timing of birth for all women with pre-eclampsia with a senior obstetrician. We agree that pre-eclampsia is a clear indication for birth at 38 weeks, and this is reflected in Table 3.
British Maternal & Fetal Medicine Society	Guideline	18	20	Why do the obstetricians need to discuss a case of PET at 38 weeks with the anaesthetic team? If her blood pressure is well controlled and her haematological and biochemistry markers normal what is going to change?	Thank you for your comment. The committee, which included an obstetric anaesthetist, considered that when working within a multidisciplinary team, it was appropriate to discuss women with potentially serious medical conditions with the anaesthetic team.
British Maternal & Fetal Medicine Society	Guideline	19	Table 3	Please change to "offer to 'initiate' birth within 24-48 hours "rather than "plan birth" within 24-48 hours. Otherwise we may have to do LSCS on women in labour at 49 hours to comply with this!	Thank you for your comment. We have now amended the wording as you suggest, to 'Initiate birth…'
British Maternal & Fetal Medicine Society	Guideline	22	4 onwards	I don't understand the fetal monitoring recommendation for GH. In women with CHT this guidance is recommending scans at 28,32 and 36. In women with PET scans are recommended 2 weekly from diagnosis to delivery. In women with GH (even early onset) a scan is recommended at diagnosis and then only repeated if "indicated". Surely these babies are at least as much risk as babies of women with CHT? Can we recommend scan	Thank you for your comment. The committee agreed with your suggested change, and have now amended the wording of the recommendations to indicate that growth scans should be carried out every 2-4 weeks for women with gestational hypertension, as clinically indicated.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				at diagnosis and then every 4 weeks (or more frequent if indicated)?	
British Maternal & Fetal Medicine Society	Guideline	22	6	This rec does not agree with Saving Babies Lives or the RCOG SGA guideline (currently being updated). No evidence to support any specific regime of ultrasound surveillance. Evidence does however support uterine artery Doppler assessment in midgestation in high risk women (including those with CHT and prior pre-eclampsia) and deferring surveillance until after 32 weeks in women with a normal assessment (Dopplers and biometry). Need for surveillance in the third trimester is clear, but exact timing not so. In light of the fact that one regime has not been tested against another and in order to avoid confusion and inconsistency this guidance could suggest 3rd trimester fetal growth assessment is necessary and should be in line with national/local recommendations (or more ideally refer to SBL).	Thank you for your comment. As fetal monitoring in chronic hypertension, including uterine artery Doppler assessment, was not included in the scope for this guideline update, the current evidence has not been assessed. We will pass your comment to the NICE surveillance team which monitors guidelines to ensure that they are up to date. Although the recommendations on scanning do not precisely align with those in Saving Babies Lives, the guideline has been updated to recognise the need for third trimester scanning - the 2010 guideline stated to carry out two scans only (at 28-30 weeks, and 32-34 weeks). The updated recommendation states to carry out these scans (at 28 and 32 weeks) as well as an additional scan during the third trimester (36 weeks).
British Maternal & Fetal Medicine Society	Guideline	22	16	Not consistent with Table 1	Thank you for your comment. The recommendation is consistent with Table 1, for women with gestational hypertension. Women with severe gestational hypertension are covered by the later recommendations (1.6.5 and 1.6.7)
British Maternal & Fetal Medicine Society	Guideline	22	25	Why CTG weekly in women with normal fetal activity?	Thank you for your comment. The wording of this has now been amended to state "unless clinically indicated"
British Maternal & Fetal	Guideline	23	7	Need to add US should be performed more frequently if abnormalities are detected following local/national guidance on monitoring of SGA/FGR.	Thank you for your comment. The wording of this recommendation has been clarified to state that "subsequent surveillance and management determined by findings of these scans", to highlight that clinical

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Medicine Society					judgement should be used, and frequency of monitoring increased if necessary.
British Maternal & Fetal Medicine Society	Guideline	23	19	Again it would avoid confusion amongst clinicians if this rec could agree with other guidance using uterine artery doppler and deferring growth scanning in those with a normal assessment (fetal biometry and Dopplers) to after 32 weeks. This is justified by the fact that the prevalence of EARLY FGR in women with a normal scan at 20-24 weeks is extremely low.	Thank you for your comment. As fetal monitoring, including uterine artery Doppler assessment, in women who may need additional monitoring was not included in the scope for this guideline update, the current evidence has not been assessed and the committee did not therefore amend these recommendations. We will pass your comment to the NICE surveillance team which monitors guidelines to ensure that they are up to date.
British Maternal & Fetal Medicine Society	Guideline	24	3	NICE CG 190 recommendation 1.10.4 states that CTG should be considered if there is raised blood pressure (between contractions) at initial assessment in labour or proteinuria >1+. Thus a woman with well controlled CHT or GH would not require CTG if this were followed. Is this the intention? Neither guideline specifically states that women with PET or those on treatment for hypertension should be offered CTG in labour	Thank you for your comment. The committee agreed that treated hypertension may be an equivalent risk to untreated hypertension, and therefore warrant continuous monitoring in labour. The cross-reference to NICE CG190 has been amended to indicate that women with treated hypertension should be treated similarly to those with hypertension identified during labour. We will pass your comment to the NICE surveillance team which monitors guidelines to ensure that they are up to date.
British Maternal & Fetal Medicine Society	Guideline	25	13	I am unclear as to the reason why "failure of fetal growth" (how is this defined?) or abnormal Dopplers are now being considered as features of severe pre-eclampsia? In isolation these features would not prompt most clinicians to consider commencing MgSO4 treatment? I think this is a wording issue and I wonder if this rec could be revised to read more clearly. I think it first needs to state for whom a clinician should be considering MgSO4 treatment.	Thank you for your comment. Medical management of severe hypertension, severe pre-eclampsia and eclampsia was not included in the scope for this update but the committee agreed that failure of fetal growth and abnormal Doppler were not indications for the use of magnesium sulfate, and have removed these from the list.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
British Maternal & Fetal Medicine Society	Guideline	26	16	This isn't usual practice despite this being an old rec? Is there really good evidence to support this principle which goes against the principle of fluid restriction? I appreciate the recommendation is consider but what would be the clinical indication. We avoid fluid bolus in all other situations?	Thank you for your comment. Medical management of severe hypertension, severe pre-eclampsia and eclampsia was not included in the scope for this update so the evidence was not reviewed. The committee were aware this may no longer be common practice, but as it is a 'consider' recommendation, and the committee agreed that it was not a safety issue, they did not change the recommendation. We will pass your comment to the NICE surveillance team which monitors guidelines to ensure that they are up to date.
British Maternal & Fetal Medicine Society	Guideline	28	7	Would it be useful to suggest in what circumstances the clinician should consider enalapril? At the mandatory low starting doses ACE inhibitors are not actually that potent as antihypertensives and dose titration is required over a period of weeks with careful renal function monitoring. Clearly a very good therapy in some women and a wealth of long term advantages perhaps but may not be suitable as first line antihypertensive therapy for the majority of women who will only need treatment for a few weeks and whose hypertension will have resolved by the time they are on an effective, tolerated dose. Obviously benefit of longer term therapy in women post PE pregnancy a topic of ongoing research. I wonder if the initial rec in this section should list the options for PN treatment (and advice re breastfeeding) and the desire for a once daily regime where possible and then go on to make specific comment about the different options and the factors (such as ethnicity) and likely longevity of treatment which should influence treatment discussions and decisions.	Thank you for your comment. The recommendations in this section have been re-ordered and amendments made to the wording to clarify that women who are not breast feeding and who are not planning to breastfeed can be treated in line with the NICE guideline on hypertension in adults (which recommends an ACE inhibitor as first line therapy), but that women who are breastfeeding or who may wish to breastfeed require advice about the use of antihypertensive drugs in breastmilk, and may require modifications to the choice of agents, different from those used in other adults, but that an ACE inhibitor should still be used first line. The committee agrees that choice of treatment should depend a woman's ethnicity, choice and preferences, and that once daily treatment is preferred, and this is included in the recommendations.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
British Maternal & Fetal Medicine Society	Guideline	30 Table 5 and 6	15 onwards	I think clinicians will find Tables 5 & 6 very useful – thank you. Recognition that further evidence on prevention strategies is needed and could be included.	Thank you. We are pleased that you find these tables useful. The committee did recognise that further evidence on prevention strategies was needed and made a research recommendation to this effect.
Diabetes UK	Guideline	General	General	Diabetes UK recommends that this guideline references the link between diabetes and gestational diabetes, and hypertension and pre-eclampsia. We recommend that this guideline is cross-referenced with guideline NG3 on *Diabetes in pregnancy.* NICE guideline - Diabetes in pregnancy: from preconception to the postnatal period	Thank you for your comment. Women with diabetes are outside the scope of this guideline, but the committee agreed that it is important to ensure that women with diabetes or gestational diabetes and hypertensive disorders of pregnancy receive appropriate treatment and therefore a link to the NICE guideline on diabetes in pregnancy has been added at the beginning of the guideline.
Homerton Hospital	Use of the word Thiazide	General	General	The document uses the word thiazide in relation to diuretic treatment. The NICE guidelines for treatment of hypertension recommend the use of *thiazide-like* diuretics in the management of hypertension eg indapamide. Please can your guidelines state whether you are warning about *thiazide like* as well as thiazide diuretics.	Thank you for your comment. We can confirm that the statements relate to thiazide-like diuretics, as well as thiazides. This has now been amended throughout the guideline.
Lactation Consultants of Great Britain and the Association of Naturopathic Practitioners	Guideline	General	General	To answer the question of what interventions for chronic hypertension in pregnancy are effective at improving outcomes for women and infants, the comments by Lactation Consultants of Great Britain and the Association of Naturopathic Practitioners examine hypertension in pregnancy from the perspective and management of Functional Medicine.	Thank you for your comments and suggestions to manage pregnancy from a Functional Medicine Perspective. We have addressed your individual suggestions and comments below, in the relevant rows of the table, but the committee agreed that hypertension in pregnancy has a different aetiology compared to hypertension in the general population, as it may involve placental dysfunction, which can lead to serious adverse consequences for the woman and her

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Regarding 1. *Which areas will have the biggest impact on practice and be challenging to implement? Please say for whom and why?* The suggestions and recommendations provided in the comments would have the biggest impact. They might be slightly challenging to implement, as they are from a less familiar field within the NHS; that of nutrition-based, lifestyle based, prevention-based Functional Medicine. The recommendations provided here are likely to be as easy, more effective and cheaper to do, and would have the biggest positive impact on practice. However, they might be challenging to implement, simply because they are not so familiar or what health practitioners are currently trained to do – most health professionals are trained to managed hypertension using drugs. The biggest impact of adopting the alternative to drugs suggestions given in the comments below, would be a very positive one, on the health of mothers and their unborn babies. This is because if the suggestions provided here were implemented, (as the NHS Long Term Plan's new emphasis on prevention recommends) then the multiple, co-morbid root causes of hypertension in pregnancy would be addressed. The attendant risks to pregnancy would be reduced dramatically and the well-being of both mother and foetus would be more secure. The costs to the NHS of maternal and infant morbidity and potentially mortality are likely to decrease if the recommendations suggested here were implemented.	baby. This means that studies and treatment approaches valid in the general population may not be relevant or able to be extrapolated to pregnancy.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				When the NHS has targets to reduce mortality in childbirth, with eclampsia and premature birth some of the main causes of morbidity and mortality in both mother and infant, a reduction in both would be a big achievement. Even averting one death or court case could save the NHS millions of pounds in compensation. A third benefit would be to the health care professionals who adopt a functional medicine approach. They routinely state that they have become re-enchanted with medical practice. Once they have learned the application of nutritional biochemistry and functional physiology, they have at their disposal an extensive array of tools that are satisfying to implement. (Textbook of Functional Medicine, 2010) The current draft guidelines are merely an updated repeat of the pharmaceutical-based method of treating hypertension in pregnancy, with its attendant risks and dilemmas of using drugs during pregnancy – a foetus' most sensitive period for disruption of all areas of development and function. In terms of 2. *Would implementation of any of the draft recommendations have significant cost implications?* If the current draft guidelines are implemented, costs are likely to increase, because the draft guidelines do not address the root causes of the hypertension, merely their symptom management. Any new drug development to produce fewer side effects in this most vulnerable population would take years and millions of pounds to develop. Yet there are inexpensive, side effect-free, evidence-based interventions that do not	

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				use drugs – already available. They are simply not being used in the NHS. Yet. The recommendations provided in this comment form hope to change that. Suggestions for complementary, effective, non-drug interventions are provided, with the rationale and evidence-based research behind them. These suggestions aim to provide a primary, preventive and ameliorative intervention, minimising the number, impact and cost of pharmaceutical interventions. In terms of 3. *What would help users overcome any challenges? (For example, existing practical resources or national initiatives, or examples of good practice.)* A national training initiative would need to be put in place, as recommended in the NHS Long Term Plan, integrating new protocols. The information is already available; the clinical trials done – the interventions would be straightforward to roll out. There are functional medicine specialists who could be used to provide guidance on the most difficult to manage cases. Drugs may still need to be used for some patients, especially where the problem is already acute, or the patient does not comply with the recommendations, but these should be the exception rather than the rule.	
Lactation Consultants of Great Britain and the Association	Summary of the protocol (PICO table)	Table 1	16	***Dietary Interventions:*** Hypertension is less of a number, more of a symptom of endothelial dysfunction driven by low Nitric Oxide (NO), oxidative stress and the renin-angiotensin-aldosterone system (**RAAS**). (This is a signalling pathway responsible for regulating the body's blood pressure.)	Thank you for the comment. Although women with diabetes are out of the scope of this guideline, the committee agree that the link between hypertension and diabetes is important, and have now provided a cross-reference to the diabetes in pregnancy guideline, to ensure that women with both conditions are

Stakeholder	Document	Page No	Line No	Comments	Developer's response
of Naturopathic Practitioners		Pages 75-76		There is biochemical evidence that to produce the vasodilator Nitric Oxide (NO) you need good insulin sensitivity. This pathway is switched off with insulin resistance. Insulin resistance causes upregulation of a different, vasoconstrictive pathway. In short, **insulin resistance** reduces vasodilation and **increases vasoconstriction.** **Recommendation:** **The aim would be to reduce insulin resistance to reduce hypertension in pregnancy** (or in any other condition). **We do not see any efforts to address insulin resistance in any detail within the draft guidelines, apart from the use of the words "Exercise and Dietary interventions" This appears to be a missed opportunity.** **Indeed, women suffering from insulin resistance or IDDM are specifically excluded from many of the studies in the intervention (p75-76). Their needs do not appear to be addressed at all in relation to hypertension.** This relationship between insulin and blood pressure is further supported by studies that show blood pressure drops when the insulin dose is decreased in obese hypertensive patients with type 2 diabetes. Additionally, blood pressure increases when insulin treatment is initiated in diabetic patients.	managed appropriately. Thank you for providing us with some references to support your comments but as these references are not specific to a population of pregnant women with hypertension they would not have met the protocol criteria for inclusion in our evidence review.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Tedde R, Sechi LA, Marigliano A, et al. Antihypertensive effect of insulin reduction in diabetic hypertensive patients. *Am J Hypertens.* 1989; 2:163-70. Randeree HA, Omar MA, Motala AA, Seedat MA. Effect of insulin therapy on blood pressure in NIDDM patients with secondary failure. *Diabetes Care.* 1992; 15:1258-63. Yu, Q. Gao, F. & Ma, X.L. (2011). 'Insulin says NO to cardiovascular disease', *Cardiovascular Research*, 89(3), pp.516–524	
Lactation Consultants of Great Britain and the Association of Naturopathic Practitioners	Summary of the protocol (PICO table)	Table 1	16	**Insulin resistance plays a key role in hypertension; as much as 50% of the hypertensive population appears to be insulin resistant.** Obesity and higher visceral adiposity worsen insulin resistance, hypertension, inflammation and endothelial dysfunction. At least a third of UK pregnant women are overweight or obese, increasing their risk of various dysfunctions and going some way to explaining the large numbers of UK women suffering from hypertension during pregnancy. **Uric acid associated with the high circulating levels of insulin in insulin resistance (hyperinsulinaemia) which appears to play a key role in endothelial dysfunction and hypertension.** The associated high blood sugar levels (hyperglycaemia) stimulates the Receptors for the Advanced Glycation End products (RAGE) pathway which increases oxidative stress (Cai et al, 2017) Uric Acid also stimulates the RAGE pathway, which disrupts vasodilation, exacerbates endothelial insulin resistance and also lowers NO. This increases	Thank you for your comment. The committee agreed that management of obesity was of importance when addressing the underlying causes of hypertension. A cross-reference to the NICE guideline on Hypertension in Adults is included, and this itself includes a link to NICE guidance on obesity. Thank you for also providing references about the role of uric acid but as these references are not specific to a population of pregnant women with hypertension they would not have met the protocol criteria for inclusion in our evidence review.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				triglycerides, increasing adiposity, adding to the insulin resistance. (Zhang et al. 2015). **Hyperinsulinemia also decreases urinary excretion of uric acid.** Cai, W. Duan, X.-M. & Liu, Y. (2017). 'Uric Acid Induces Endothelial Dysfunction by Activating the HMGB1/RAGE Signaling Pathway', BioMedResearch International,4391920. Herrmann, J. (2001). Coronary vasa vasorum neovascularization precedes epicardial endothelial dysfunction in experimental hypercholesterolemia. Cardiovascular Research, 51(4), pp.762-766. Zhang, J.X. Zhang, Y.P. Wu, Q.N. et al. (2015). 'Uric acid induces oxidative stress via an activation of the renin-angiotensin system in 3T3-L1 adipocytes. Endocrine', 48(1), pp.135-142.	
Lactation Consultants of Great Britain and the Association of Naturopathic Practitioners	Summary of the protocol (PICO table)	Table 1	16	**Recommendation:** **Addressing hyperglycaemia and hyperinsulinaemia using diet (and exercise – see below) will help to alleviate hypertension in pregnancy. This can be achieved within two weeks using dietary and exercise interventions.** Again, the only mention of any such intervention in the draft guideline is in the five words, "diet, exercise and salt restriction" - and these draft guidelines give no guidance to health professionals on what sort of diet, what sort of exercise and how much salt restriction should be recommended to achieve a significant reduction in hypertension in pregnancy.	Thank you for your comment. The committee agreed that dietary and exercise interventions were potentially of great importance in managing hypertension .These were specified as part of the review protocol for treatment of chronic hypertension. However, only a single study conducted in the pregnant population was identified, and therefore the committee were unable to make specific recommendations regarding these interventions.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Targeted interventions have been very effective. See line 5.	
Lactation Consultants of Great Britain and the Association of Naturopathic Practitioners	Summary of the protocol (PICO table)	Table 1	16	**The Diet against Stroke and Hypertension (the DASH Diet):** **Recommendation:** **The DASH Diet is an evidence based diet and lifestyle approach to reducing blood pressure, which can be used as a way to reduce the requirement for anti-hypertensive drugs in pregnant women with hypertension.** The Dietary Approaches to Stop Hypertension (DASH) dietary pattern, which emphasizes fruit, vegetables, fat-free/low-fat dairy, whole grains, nuts and legumes, and limits saturated fat, cholesterol, red and processed meats, sweets, added sugars, salt and sugar-sweetened beverages, is widely recommended by international diabetes and heart association guidelines. **The DASH diet not only significantly lowers blood pressure within two weeks of starting the plan but also reduces total cholesterol and low-density lipoprotein (LDL).** Kaiser Permanente, one of the largest insurance companies in the USA, has instructed its 17,000 physicians to advise this diet as 1st line treatment for Diabetes, Hypertension & Coronary artery disease. Chiavaroli, L., Viguiliouk, E., Nishi, S., Mejia, S., Rahelić, D., Kahleová, H., Salas-Salvadó, J., Kendall, C. and Sievenpiper, J. (2019). DASH Dietary Pattern and Cardiometabolic Outcomes: An Umbrella Review of Systematic Reviews and Meta-Analyses. Nutrients, 11(2), p.338.	Thank you for your comment. As dietary interventions were specified on the protocol for the review of treatment of chronic hypertension, we would anticipate that any studies conducted on the DASH diet in a pregnant population would have been identified by the literature review. Studies conducted in the non-pregnant population were not relevant for this protocol, therefore could not be considered by the committee when drafting their recommendations.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Endemann, H. Schiffrin, E. (2004). 'Endothelial Dysfunction', JASN, 15(8), pp.1983-1992 Gans RO, Donker AJ. Insulin and blood pressure regulation. J Intern Med Suppl. 1991;735:49-64.	
Lactation Consultants of Great Britain and the Association of Naturopathic Practitioners	Summary of the protocol (PICO table)	Table 1	16	***Exercise:*** **Recommendation:** **Encourage women to work towards more aerobic exercise, which at a minimum of 1000kcal/60min intensity, 4x per week has been shown to lower blood pressure.** Exercise increases eNOS, NO, and improves endothelial function. Regularly performed aerobic exercise increases insulin action. Dimeo, F. Pagonas, N. *et al.*(2012). 'Aerobic Exercise Reduces Blood Pressure in Resistant Hypertension', *Hypertension,* (60), pp.653-658 Pescatello LS, Franklin BA, Fagard R, et al. American College of Sports Medicine position stand. Exercise and hypertension. *Med Sci Sports Exerc*. 2004;36(3):533-53. Stewart KJ. Exercise training and the cardiovascular consequences of type 2 diabetes and hypertension. *JAMA.* 2002;288(13):1622-31.	Thank you for your comment. As exercise interventions were specified on the protocol for the review of treatment of chronic hypertension, we would anticipate that any studies conducted on exercise interventions in a pregnant population would have been identified by the literature review. A single study was identified as relevant, but the evidence was insufficient for the committee to make specific recommendations on, therefore they chose instead to cross-refer to the guidance from Hypertension in Adults. Studies conducted in the non-pregnant population were not relevant for this protocol, therefore could not be considered by the committee when drafting their recommendations.
Lactation Consultants of Great Britain and the Association of	Summary of the protocol (PICO table)	Table 1	16	**Sympathetic Nervous System activity, stress, meditation and yoga effectiveness:** Insulin appears to work through other mechanisms as well to increase sympathetic nervous system activity and thus peripheral resistance. **Recommendation:**	Thank you for your comment. The committee generated the list of interventions to be considered for this review from their experience and clinical knowledge. It was not possible to include all potentially relevant interventions in the search, and meditation and yoga were not prioritised for this review.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Naturopathic Practitioners				**Techniques such as meditation and focused movement meditation such as yoga may enhance the likelihood of maintaining a lower blood pressure in pregnancy.** S Park and K Han (2017) concluded that meditation and yoga are demonstrated to be effective alternatives to pharmacotherapy, and avoidance of pharmacotherapy in pregnancy is strongly recommended. Given that blood pressure decreased with the use of meditation and yoga, scientifically measured outcomes indicate that these practices are safe alternatives in some cases. Wu et al concluded that yoga is a viable antihypertensive lifestyle therapy that produces the greatest blood pressure benefits when breathing techniques and meditation/mental relaxation are included. Park, S. and Han, K. (2017). Blood Pressure Response to Meditation and Yoga: A Systematic Review and Meta-Analysis. The Journal of Alternative and Complementary Medicine, 23(9), pp.685-695. Wu, Y., Johnson, B., Acabchuk, R., Chen, S., Lewis, H., Livingston, J., Park, C. and Pescatello, L. (2019). Yoga as Antihypertensive Lifestyle Therapy: A Systematic Review and Meta-analysis. Mayo Clinic Proceedings.	Thank you for also providing references about the benefits of yoga but as these references are not specific to a population of pregnant women with hypertension they would not have met the protocol criteria for inclusion in our evidence review. We will pass your comment to the NICE surveillance team which monitors guidelines to ensure that they are up to date, to consider if these interventions should be included in a future update.
Lactation Consultants of Great Britain and the Association of Naturopathic Practitioners	Summary of the protocol (PICO table)	Table 1	16	**Stress and Cortisol** When an individual experiences chronic stress along with maladaptive responses or a lack of coping, cortisol levels may remain inappropriately elevated. Cortisol helps maintain blood glucose levels but (as noted above) chronic stress (or chronic administration of pharmacological cortisol preparations) causes insulin resistance, hypertension, redistribution of fat in the body, decreased protein synthesis, and decreased DNA repair	Thank you for your comment. The committee generated the list of interventions to be considered for this review from their experience and clinical knowledge. It was not possible to include all potentially relevant interventions in the search, and stress reduction was not prioritised for this review. Thank you for also providing references about the effects of stress but as these references are not specific to a population of pregnant women with

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				due to persistent stimulation of the CRH-ACTH-cortisol axis. Metabolically, this can take a toll. The ongoing high concentrations of cortisol may keep blood glucose levels high for prolonged periods, cause redistribution of fat from the thighs and buttocks to the abdominal and cervical regions ("buffalo hump") due to mobilization of free fatty acids; cause insulin resistance to develop; cause fluid retention and hypertension; produce proteolysis in muscle, bone, and connective tissues; and inhibit peptide and protein hormone formation (especially by the pituitary gland). **Recommendation:** **Therefore, techniques to reduce stress and / or reduce endogenous or exogenous cortisol sources help to mitigate hypertension in pregnancy.** Orth DN, Kovac WJ. The adrenal cortex. In: Wilson JD, Foster DW, Kronenberg HM, Larsen PR, eds. Williams Textbook of Endocrinology.9th ed. Philadelphia: WB Saunders, 1998: 517-664. Munck A, Guyre PM, Holbrook NJ. Physiologic function of glucocorticoids in stress and their relation to pharmacologic actions. Endocr Rev. 1984;5(1):25-44. Pacak K. Stressor-specific activation of the hypothalamic-pituitaryadrenocortical axis. Physiol Res. 2000;49 (Suppl 1):S11-S17.	hypertension they would not have met the protocol criteria for inclusion in our evidence review. We will pass your comment to the NICE surveillance team which monitors guidelines to ensure that they are up to date, to consider if this intervention should be included in a future update.
Lactation Consultants of Great Britain and the Association	Summary of the protocol (PICO table)	Table 1	16	**Meditation/relaxation is associated with lower blood pressure:** Religion/spirituality/meditation is associated with lower blood pressure, less hypertension, better immune function (all category 2).	Thank you for your comment. The committee generated the list of interventions to be considered for this review from their experience and clinical knowledge. It was not possible to include all potentially

Stakeholder	Document	Page No	Line No	Comments	Developer's response
of Naturopathic Practitioners				Meditation/relaxation is associated with lower cholesterol, lower stress hormone levels, and differential patterns of brain activity (category 2). **Meditation is associated with less oxidative stress, and less blood** pressure and stress hormone reactivity under challenge (category 1). **Recommendation:** **Encourage meditation in women with hypertension in pregnancy.** Park, S. and Han, K. (2017). Blood Pressure Response to Meditation and Yoga: A Systematic Review and Meta-Analysis. The Journal of Alternative and Complementary Medicine, 23(9), pp.685-695.	relevant interventions in the search, and meditation/relaxation was not prioritised for this review. Thank you for also providing references about the role of meditation in blood pressure control in pregnancy. We will pass your comment to the NICE surveillance team which monitors guidelines to ensure that they are up to date, to consider if this intervention should be included in a future update.
Lactation Consultants of Great Britain and the Association of Naturopathic Practitioners	Summary of the protocol (PICO table)	Table 1	16	**C Reactive Protein (CRP), homocysteine and inflammation:** We have described how **insulin resistance, hyperglycaemia and hyperuricemia all increase inflammation** via RAGE activation and eNOS/NADPH oxidase uncoupling, leading to hypertension. Homocysteine also increases CRP and **CRP Increases Hypertension**. **Inflammation is now understood to be a central aspect of the pathophysiology of a wide range of conditions** from obesity, diabetes mellitus, atherosclerosis, and **hypertension**, to Alzheimer's and Parkinson's diseases, cancer, depression, and autism. **Recommendation:** **Dietary and lifestyle approaches to reducing insulin resistance, hyperglycaemia, hyperuricemia and the underlying inflammation, indicated by CRP markers -**	Thank you for your comment. The committee generated the list of interventions to be considered for this review from their experience and clinical knowledge. Dietary interventions were included in the search, and if evidence specific to the pregnant population was identified then this would have been included in the review. It was not possible to include all potentially relevant interventions in the search, and lifestyle approaches (other than diet and exercise) were not prioritised for this review. Thank you for also providing references about the role of C-reactive protein and homocysteine but as these references are not specific to a population of pregnant women with hypertension they would not have met the protocol criteria for inclusion in our evidence review.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				would all be preferable to pharmacological interventions, especially in pregnancy. Bawaskar, H. Bawaakar, P. *et al.*(2014). 'Homocysteine: Often Neglected but Common Culprit of Coronary Heart Diseases', *Journal of Cardiovascular Disease Research,* 5(3). Charradi, K. Sebai, H. et al.(2011). 'Grape Seed Extract Alleviates High-Fat Diet-Induced Obesity and Heart Dysfunction by Preventing Cardiac Siderosis', Cardiovascular Toxicology,11(1), pp 28-3 Hage, F.G. (2014). 'C-reactive protein and hypertension. Journal of Human Hypertension', 28(7), pp.410-415 Zampelas A, Paschos G, Rallidis L, Yiannakouris N. Linoleic acid to alpha-linolenic acid ratio. From clinical trials to inflammatory markers of coronary artery disease. World Rev Nutr Diet. 2003;92:92-108.	
Lactation Consultants of Great Britain and the Association of Naturopathic Practitioners	Summary of the protocol (PICO table)	Table 1	16	***Dietary salt reductions:*** The sodium hypothesis of hypertension attributes increased peripheral vascular resistance to elevated *intra*cellular sodium concentrations. Based on cross-cultural comparisons, this was thought to be mainly due to increased dietary intake of sodium in salt-sensitive individuals. **Intracultural studies suggest, however, that dietary salt may account for only a minor segment of increased blood pressure in the hypertensive population**. It has been proposed that **a large segment of essential hypertension is caused by enhanced renal sodium**	Thank you for your comment. The committee generated the list of interventions to be considered for this review from their experience and clinical knowledge. Dietary interventions were included in the search, and if evidence on reduction of salt intake in pregnant women was identified then this would have been included in the review. However, as no evidence was identified relating to this specific population, then the committee cross-referred to the existing guidelines on managing hypertension in adults. Thank you for also providing references about the role of salt but as these references are not specific to a population of pregnant women with hypertension they would not have met the protocol criteria for inclusion in

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				reabsorption in the distal tubule, which is promoted by hyperinsulinemia. Hyperinsulinemia may also play a role by altering internal sodium and potassium distribution in a direction that is associated with increased peripheral vascular resistance. Insulin appears to work through other mechanisms as well to increase sympathetic nervous system activity and thus peripheral resistance. This relationship between insulin and blood pressure is further supported by studies that show **blood pressure drops when the insulin dose is decreased in obese hypertensive patients with type 2 diabetes.** Additionally, blood pressure increases when insulin treatment is initiated in diabetic patients. **Recommendation:** **Sodium restriction is important for managing obesity and cardiometabolic risk.** **Research into the DASH diet found that dose dependent sodium restriction had more pronounced effects on hypertension.** Of the following three intake patterns, the lowest intakes saw the greatest improvements: 1) 3,300 mg of sodium per day (a normal amount for many); 2) 2,300 mg of sodium (a moderately restricted amount); 3) 1,500 mg of sodium (a more restricted amount, about 2/3 of a teaspoon of salt He, F.J. Li, J. & Macgregor, G.A. (2013). 'Effect of longer term modest salt reduction on blood pressure: Cochrane	our evidence review. We will pass your comment to the NICE surveillance team which monitors guidelines to ensure that they are up to date.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				systematic review and meta-analysis of randomised trials', *British Medical Journal*, 346, pp.f1325 Immumorin IG, Dong Y, Zhu H, et al. A gene-environment interaction model of stress-induced hypertension. *Cardiovasc Toxicol.* 2005;5(2):109-32. Johnson, C. Raj, T.S. Trieu, K. *et al*. (2016). 'The Science of Salt: A Systematic Review of Quality Clinical Salt Outcome Studies June 2014 to May 2015', *Journal of Clinical Hypertension,* 18(9), pp.832-839 Luft FC. Salt and hypertension at the close of the millennium. *Wien Klin Wochenschr*. 1998:110(13-14):459-66. Taylor, R.S. Ashton, K.E. Moxham, T. *et al*. (2013). 'Reduced dietary salt for the prevention of cardiovascular disease', *Cochrane Database of Systematic Reviews,* 2(9), CD009217 Zavaroni I, Coruzzi P, Bonini L, et al. Association between salt sensitivity and insulin concentrations in patients with hypertension. *Am J Hypertens*. 1995; 8:855-58.	
Lactation Consultants of Great Britain and the Association of Naturopathic Practitioners	Summary of the protocol (PICO table)	Table 1	16	**Vitamin D3, and multivitamin / multimineral supplementation to reduce pre-eclampsia:** A systematic review & meta-analysis was carried out to assess the effects of multivitamin supplements on the risk of pre-eclampsia. Results were published in 2018 in the *Journal of the Formosan Medical Association* and researchers found that **vitamin D supplementation could significantly reduce the risk of pre-eclampsia. Similar**	Thank you for your comment. The committee noted that all pregnant women are now advised to take 10 µg (400 IU) Vitamin D daily when pregnant, and a multivitamin supplement is suggested as an appropriate way of achieving this (this advice is included in the NICE guideline on antenatal care, CG 62). The additional benefit of higher vitamin D doses or additional multivitamins in women with hypertension in pregnancy was therefore not prioritised for this review. We will pass your comment to the NICE surveillance

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				benefits were reported for multivitamin supplementation. In a 2014 single-blind, randomised clinical trial, 104 pregnant women aged 18 – 30 years were randomly assigned to receive either a multivitamin or multivitamin & mineral supplement for 20 weeks. The researchers found that birth weight and head circumference were increased in infants whose mothers received multivitamin-mineral supplements for 5 months during pregnancy compared with infants whose mothers received just multivitamin supplements. **Recommendation:** **Test Vitamin D status of women with hypertension in pregnancy. Supplement those who are deficient, with Vitamin D3.** Fu ZM, Ma ZZ et al. Vitamins supplementation affects the onset of preeclampsia. *J Formos Med Assoc*. 2018 Jan; 117(1):6-13. Asemi Z, Samimi M et al. Multivitamin versus multivitamin-mineral supplementation and pregnancy outcomes: a single-blind randomised clinical trial. *Int J Prev Med.* 2014 Apr; 5(4):439-46	team which monitors guidelines to ensure that they are up to date.
Lactation Consultants of Great Britain and the Association of	Summary of the protocol (PICO table)	Table 1	16	**Covert or overt Food Allergies:** The combination of a hypersensitive/dysregulated immune system and exposure to dietary antigens sets the stage for the clinical phenomenon commonly described as "food allergy." Diverse in frequency, duration, severity, and quality, **these immune-mediated adverse reactions to foods can precipitate or exacerbate a wide range of clinical manifestations including** rhino-conjunctivitis,	Thank you for your comment. The committee generated the list of interventions to be considered for this review from their experience and clinical knowledge. It was not possible to include all potentially relevant interventions in the search, and diagnosis of food allergy as a precipitating factor in hypertension in pregnancy was not prioritised for this review.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Naturopathic Practitioners				chronic sinusitis, dermatitis, epilepsy, migraine, **hypertension,** joint inflammation, and mental depression. The immunopathogenesis generally includes multiple mechanisms and is not limited to mediation via IgE antibodies and histamine. Indeed, the pathophysiology of "food allergy" is commonly seen with numerous (not singular) aberrations in physiological function. **Recommendation:** **Both IgE and IgG can be tested for and dietary recommendations provided based on test results. These interventions are likely to reduce multiple symptoms and morbidities.** Gaby AR. The role of hidden food allergy/intolerance in chronic disease. *Altern Med Rev.* 1998;3(2):90-100.	Thank you for also providing a reference about the role of food allergy in chronic disease but as this reference is not specific to a population of pregnant women with hypertension they would not have met the protocol criteria for inclusion in our evidence review. We will pass your comment to the NICE surveillance team which monitors guidelines to ensure that they are up to date.
Lactation Consultants of Great Britain and the Association of Naturopathic Practitioners	Summary of the protocol (PICO table)	Table 1	16	**An example to help remedy hypertension in pregnancy, illustrated using the recommendations:** Rather than immediately reaching for the prescription pad for patients with hypertension, a functional medicine practitioner will ask an array of questions geared toward identifying any underlying imbalances that might be contributing to the person's elevated blood pressure. The informed practitioner will be particularly cognisant of current research that strongly suggests hypertension is actually a chronic inflammatory disorder, for which oxidative stress is one of the primary triggers. Consequently, very important questions include: • What kind of diet does the person have? Particularly, what is the intake of refined carbohydrates, and is there exposure to oxidised fats?	Thank you for your comment. The committee agreed that dietary and lifestyle interventions were likely to play an important part in the ongoing management of hypertension. However, they recognised that there is a lack of evidence relating to these interventions in the pregnant population, which was the focus of these reviews. Therefore, although it was felt relevant to cross-refer to the adult hypertension guideline for general dietary and lifestyle advice on managing hypertension, they could not develop new recommendations specifically for pregnant women without identifying evidence which relates to this group.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				What kind of exercise does the patient engage in? For how long and how often? • Has there been any exposure to heavy metals, pesticides, or other environmental toxins that might be an ongoing source of oxidative stress? • What is the intake of antioxidants and essential fatty acids (that might have a mitigating effect on the disorder)? • What about electrolytes and trace elements, especially magnesium? • Are there any unresolved stresses in the person's life that might be causing hypothalamic-pituitary-adrenal imbalances that, in turn, could be adversely affecting the renin-angiotensin system, which could be upregulating NF Kappa B-mediated transcription of inflammatory mediators? • What coping strategies are utilized? • How well does the patient sleep at night? • Are there any symptoms suggestive of sleep apnoea? **The hallmarks of** cardiovascular disease (**hypertension**, coagulopathy, and endothelial dysfunction**) are secondary to upstream inputs controlled, in the main, by diet.** The DASH diet directly influences insulin sensitivity, oxidative stress, inflammation, lipid status, methylation, cardiocyte cellular energetics, membrane stability, and electrophysiologic dysfunction.	

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				These are the root functions that are imbalanced in all chronic degenerative diseases and cardiovascular disease in particular. Hu, *et al;* (2002) in "Optimal Diets for the Prevention of Coronary Disease," reviewed the extensive literature of the last two decades on the dietary influences on cardiovascular disease. They looked at dietary fats, carbohydrates, micronutrients, and phytonutrients. Their conclusions were summarized in three practical strategies: **Recommendations:** **1. Substitute non-hydrogenated unsaturated fats for saturated and *trans* fats** **2. Increase the consumption of omega-3 fatty acids from fish, fish oil supplements, or plant sources, and** **3. Consume a diet high in fruit, vegetables, nuts, and whole grains and low in refined grain products.** Further, they predicted that such a diet, together with regular physical activity, avoidance of smoking, and maintenance of a healthy body weight can prevent the majority of cardiovascular diseases in Western populations. This would include hypertension in pregnancy. **Note: Factors in gene transcription of inflammatory mediators, omega-3 fatty acids, fibre, probiotics and the addition of regular exercise — can collectively reduce systemic inflammatory mediators to a greater degree than pharmacological interventions.**	

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Interventions that reduce inflammation reduce overall morbidity and mortality across the disease spectrum. **High GI foods or GL meals lead to** hyperinsulinemia, elevated triglycerides, low HDL, **hypertension,** elevated waist-to hip ratio or visceral obesity, decreased adiponectin, autonomic dysfunction, non-alcoholic steatohepatitis, hyperuricemia, and hormonal disorders as well as mood swings, anxiety, depression, and fatigue. Pharmacologic modulators of inflammation have been proposed, including aspirin, non-steroidal anti-inflammatories (NSAIDs), and non-traditional anti-inflammatories such as statins, thiazolidinediones, and fibrates. **Recommendation:** **However, a comprehensive lifestyle approach—including the modulation of diet by reduction in saturated and *trans* fats and glycaemic load; use of multivitamins, supplemental antioxidants (key cell-signalling) would address the root causes of hypertension in pregnancy.** Hu, F. (2002). Optimal Diets for Prevention of Coronary Heart Disease. *JAMA*, 288(20), p.2569. Juraschek, S., Woodward, M., Sacks, F., Carey, V., Miller, E. and Appel, L. (2017). Time Course of Change in Blood Pressure From Sodium Reduction and the DASH Diet. *Hypertension*, 70(5), pp.923-929. Textbook of Functional Medicine, (2010) *Institute of Functional Medicine*	

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Lactation Consultants of Great Britain and the Association of Naturopathic Practitioners	Summary of the protocol (PICO table)	Table 1	16	**Omega 3 Fatty Acids:** **A meta-analysis of 1,356 subjects concluded that fish oils are associated with a small but significant lowering in blood pressure.** **This appears to occur in patients with pre-existing** heart disease, lipid abnormalities or **hypertension**, but not in healthy subjects with normal blood pressure. **There is considerable evidence that Omega 3 fatty acids prevent cardiac arrhythmias, including inhibition of ventricular fibrillation and consequent cardiac arrest.** **This is highly relevant to reduce the risk profile of women with hypertension in pregnancy.** **Recommendation:** **Encourage pregnant women to eat small, oily fish in pregnancy (sardines, mackerel, anchovies, salmon, herring, trout) and / or high quality, high strength marine or algal oil supplements. These are likely to also benefit the foetus' brain, nervous system, visual system and immune system development.** Berry ME, Hirsch J. Does dietary linolenic acid influence blood pressure? *Amer J Clin Nutr.* 1986; 44:336-40. Connor SL, Connor WE. Are fish oils beneficial in the prevention and treatment of coronary artery disease? *Am J Clin Nutr*. 1997;66(4 Suppl):1020S-31S. Harris W. Fish oils, omega-3 polyunsaturated fatty acids, and coronary heart disease. *Backgrounder (Roche Vitamins Inc.)* 1997;2(1):1-8.	Thank you for your comment. The committee generated the list of interventions to be considered for this review from their experience and clinical knowledge. It was not possible to include all potentially relevant interventions in the search, and consumption of omega 3 fatty acids was not prioritised for this review. Dietary interventions were considered, therefore if evidence on fish intake relevant to pregnant women with chronic hypertension had been reported then this would have been included in the search. The committee were also aware that current NHS guidance for pregnant women suggests to consume oily fish no more than twice a week due to the possibility of contamination with pollutants. Thank you for also providing references about the role of fish oils but as these references are not specific to a population of pregnant women with hypertension they would not have met the protocol criteria for inclusion in our evidence review.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Harper CR, Jacobson TA. The fats of life: the role of omega-3 fatty acids in the prevention of coronary heart disease. *Arch Intern Med*.001;161(18):2185-92. Howe PRC. Fish oil supplements and hypertension. *ISSFAL newsletter*. 1996;3(4):2-5. Nestel P, Shige H, Pomeroy S. The n-3 fatty acids eicosapentaenoic acid and docosahexaenoic acid increase systemic arterial compliance in humans. *Am J Clin Nutr*. 2002;76(2):326-30. Singh RB, Dubnov G, Niaz MA, et al. Effect of an Indo-Mediterranean diet on progression of coronary artery disease in high risk patients (Indo-Mediterranean Diet Heart Study): a randomised single- blind trial. *Lancet*. 2002;360(9344):1455-61. Weiser, M., Butt, C. and Mohajeri, M. (2016). Docosahexaenoic Acid and Cognition throughout the Lifespan. *Nutrients*, 8(2), p.99.	
Lactation Consultants of Great Britain and the Association of Naturopathic Practitioners	Summary of the protocol (PICO table)	Table 1	16	**Fasting:** **Recommendation:** **Although fasting is not commonly prescribed during pregnancy, there is a risk-benefit analysis to be done between the potential negative effects of resistant hypertension versus the benefits of intermittent fasting (or fast-mimicking food regimes) in non-insulin dependent pregnant women.** Mattson, M., Longo, V. and Harvie, M. (2017). Impact of intermittent fasting on health and disease processes. *Ageing Research Reviews*, 39, pp.46-58.	Thank you for your comment. The committee generated the list of interventions to be considered for this review from their experience and clinical knowledge. It was not possible to include all potentially relevant interventions in the search, and intermittent fasting was not prioritised for this review. Thank you for also providing references about the role of fasting but as these references are not specific to a population of pregnant women with hypertension they would not have met the protocol criteria for inclusion in our evidence review and we cannot assume that the evidence can be extrapolated from hypertension in

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Cheng, C., Villani, V., Buono, R., Wei, M., Kumar, S., Yilmaz, O., Cohen, P., Sneddon, J., Perin, L. and Longo, V. (2017). Fasting-Mimicking Diet Promotes Ngn3-Driven β-Cell Regeneration to Reverse Diabetes. *Cell*, 168(5), pp.775-788.e12. McCarty MF. A preliminary fast may potentiate response to a subsequent low-salt, low-fat vegan diet in the management of hypertension— fasting as a strategy for breaking metabolic vicious cycles. *Med Hypotheses.* 2003;60(5):624-633	adults to hypertension in pregnant women, particularly without consideration of the effects on the growing fetus.
Lactation Consultants of Great Britain and the Association of Naturopathic Practitioners	Summary of the protocol (PICO table)	Table 1	16	**Magnesium supplementation as a possible treatment adjunct for hypertension in pregnancy:** **A poor intracellular magnesium concentration, as found in** non-insulin-dependent diabetes mellitus (NIDDM) and in **hypertensive (HP) patients,** may result in a defective tyrosine-kinase activity at the insulin receptor level and exaggerated intracellular calcium concentration. **Both events are responsible for the impairment in** insulin action and a worsening of insulin resistance in non-insulin-dependent diabetic and **hypertensive patients**. By contrast, in NIDDM patients, daily magnesium administration, restoring a more appropriate intracellular concentration, contributes to improve insulin-mediated glucose uptake. Similarly, in HP patients, magnesium administration may be useful in decreasing arterial blood pressure and improving insulin-mediated glucose uptake. The benefits deriving from daily magnesium supplementation in NIDDM and HP patients are further supported by epidemiological studies showing that **high**	Thank you for your comment. The committee generated the list of interventions to be considered for this review from their experience and clinical knowledge. It was not possible to include all potentially relevant interventions in the search, and magnesium supplementation was not prioritised for this review. Thank you for also providing a reference about the role of magnesium but as this reference is not specific to a population of pregnant women with hypertension it would not have met the protocol criteria for inclusion in our evidence review. We will pass your comment to the NICE surveillance team which monitors guidelines to ensure that they are up to date.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				daily magnesium intake to be predictive of a lower incidence of NIDDM and HP. In conclusion, a growing body of studies suggest that **intracellular magnesium may play a key role in modulating** insulin-mediated glucose uptake and **vascular tone**. **Paolisso and Barbagallo further suggest that a reduced intracellular magnesium concentration might be the missing link helping to explain the epidemiological association between NIDDM and hypertension.** **Recommendation:** **Test for and supplement women who are deficient in magnesium and are therefore at risk of hypertension and/or IDDM in pregnancy.** Paolisso G, Barbagallo M. Hypertension, diabetes, and insulin resistance: the role of intracellular magnesium. *Am J Hypertens.* 1997;10(3):346-55.	
Lactation Consultants of Great Britain and the Association of Naturopathic Practitioners	Summary of the protocol (PICO table)	Table 1	16	**Recommendations:** **Functional medicine has the potential to revolutionise healthcare delivery, not only as a result of its anticipatory and preventive nature, but because the identification and supportive treatment of underlying contributing factors is the most effective means of addressing the health of the individual.** **By recognizing and treating functional disturbances, physicians can guide patients toward more advantageous environmental inputs, thereby saving millions of pounds in healthcare expenditures.**	Thank you for your comments and suggestions to manage pregnancy from a Functional Medicine Perspective. We have addressed your individual suggestions and comments above, in the relevant rows of the table, but the committee agreed that hypertension in pregnancy has a different aetiology compared to hypertension in the general population, which involves placental dysfunction, and which can lead to serious adverse consequences for the woman and her baby. This means that studies and treatment approaches valid in the general population may not be relevant or able to be extrapolated to pregnancy.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				The functional medicine model embraces the old adage "If you don't take time for your health, you'll have to take time for your illness." **To begin with, we must apply the same level of effort to these issues that we applied in the last 100 years to acute care, with its myriad (and often miraculous) drug and surgical interventions.** **Nothing less will suffice.** Textbook of Functional Medicine, (2010) *Institute of Functional Medicine*	
Lactation Consultants of Great Britain and the Association of Naturopathic Practitioners	Summary of the protocol (PICO table)	Table 1	16	**Recommendation:** **Strategy and Guidance for women suffering from hypertension in pregnancy – extract from DASH Diet (that also supports a healthy pregnancy outcome):** Consume 8-10 servings of fresh fruits and vegetables per day. •Eat foods higher in potassium, magnesium, calcium and fibre e.g. Fruits, vegetables, pulses. •Replace red meats with white skinless poultry, oily fish and pulses. •Replace high fat dairy with unprocessed low fat dairy •Replace trans-fat rich foods with nuts, seeds, avocados and MUFA rich oils. •Restrict sodium intake Optimise Weight (by reducing fat, not lean muscle mass) Stop Smoking Caffeine - reduce or discontinue Diet pills / energy drinks - reduce or discontinue	Thank you for your comment. As dietary interventions were specified on the protocol for the review of treatment of chronic hypertension, we would anticipate that any studies conducted on the DASH diet in a pregnant population would have been identified by the literature review. Studies conducted in the non-pregnant population were not relevant for this protocol, therefore could not be considered by the committee when drafting their recommendations.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				Alcohol, discontinue or reduce very significantly Exercise – increase aerobic & resistance Stress Management - address Sleep quality - address **Reduce or discontinue medications (under medical supervision) that increase blood pressure such as**: *NSAIDs / Cox-2 inhibitors* *Antihistamines* *Decongestants* *Corticosteroids* *Tricyclic antidepressants* *MAOI* *Lithium* *Liquorice* Textbook of Functional Medicine, (2010) *Institute of Functional Medicine*	
NHSE				Please look at the indication for Aspirin section and consider recommending a dose of 150mg at night which is what appendix C of the Saving Babies Lives Care Bundle recommends https://www.england.nhs.uk/mat-transformation/saving-babies/	Thank you for the comment. We have now amended the recommendations regarding the use of aspirin to state that a dose of 75-150mg is suitable, in line with Appendix C of the Saving Babies Lives Care Bundle which states: 'There is good evidence that the standard treatment dose should be 150mg at night from 12 weeks' gestation, though in some circumstances this may not be appropriate and lower doses (60-75mg) may be used (for example, women with hepatic or renal disease).'
NHSE				Could you align your fetal surveillance recommendations with the Saving Babies Lives Care Bundle as there is evidence that fetal biometry should not be repeated more frequently than every 3 weeks. Despite that evidence I think there is a clinical consensus that in the highest risk fetuses biometry at every 2 weeks is preferable.	Thank you for your comment. Evidence for fetal surveillance was not included in the scope for this partial update to the guideline, therefore the evidence has not been reviewed. However, the recommendations in the guideline are very similar to those in the Saving Babies' Lives Care Bundle – in

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					lower risk women with chronic hypertension fetal biometry is recommended every 4 weeks, in women with gestational hypertension it is recommended every 2 to 4 weeks, and in women with severe gestational hypertension or pre-eclampsia (who are at the highest risk) it is recommended every 2 weeks.
NHSE				Should the follow up appointment in recommendation 1.5.26 be delivered by the GP rather than the maternity service with onward referral for specialist kidney assessment as per 1.5.27	Thank you for your comment. Evidence for haematological or biochemical monitoring in the postnatal period was not included in the scope of this update to the guideline and therefore the evidence has not been reviewed. However, there were a number of recommendations throughout the guideline, including this one, which did not specify who should be carrying out postnatal reviews. These have now been clarified. For this recommendation, the committee agreed that the 3 month assessment of kidney function could be carried out by the woman's GP or specialist, and amended the recommendation to state this.
Obesity Group of the British Dietetic Association	Guideline	8	11-16	We support this update and in particular the more holistic approach implied by including weight management, exercise and healthy eating in addition to salt consumption.	Thank you for your comment.
Obesity Group of the British Dietetic Association	Guideline	8	17-18	We support the cross reference to the NICE guideline on hypertension in adults: diagnosis and treatment.	Thank you for your comment.
Obesity Group of the British	Guideline	28	4-6	We agree with the approach to monitor the blood pressure of breastfed babies especially those born prematurely.	Thank you for your comment

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Dietetic Association					
Obesity Group of the British Dietetic Association	Guideline	30	2-10	We strongly support the recommendation that evidence-based advice on breastfeeding is given to women and their partners so that they can make informed decisions about infant feeding. Breastfeeding rates are lower in those who are overweight especially those who are obese, and reassurance about the low levels of medication in breastmilk (along with monitoring of blood pressure of babies, see above) may help to encourage new mothers to breastfeed.	Thank you for your comment. The committee agreed that encouraging breastfeeding was important and women should be supported and advised to enable an informed choice, and have added a new recommendation (1.9.1) to emphasise this.
Obesity Group of the British Dietetic Association	Guideline	32	7-10	We support the cross reference to maintaining a healthy lifestyle and a healthy weight. We would also like to see specific recommendations made for long term follow up of these higher risk women.	Thank you for your comment. The committee did recognise that further evidence on long-term follow-up and prevention strategies was needed and made a research recommendation to this effect.
Obesity Group of the British Dietetic Association	Guideline	32-33	11-12 (p32) and 1-2 (p33)	We agree that future risk must be investigated including that related t high BMI (also point 1.10.5).	Thank you for your comment. The committee did recognise that further evidence on long-term follow-up and prevention strategies was needed and made a research recommendation to this effect.
Obesity Group of the British Dietetic Association	Guideline	49	n/a	We strongly support the more holistic approach implied by the move away from a focus only on salt consumption, to inclusion of body weight, activity and diet in addition.	Thank you for your comment
Obesity Group of the British Dietetic Association	Guideline	56	n/a	We strongly agree with the cross reference to breastfeeding, in particular in this group which may have a lower likelihood of breastfeeding.	Thank you for your comment.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Obesity Group of the British Dietetic Association	Guideline	58	n/a	We agree with the link to a section on breastfeeding as encouragement and support for breastfeeding is likely to be important in this group.	Thank you for your comment.
Obstetric Anaesthetists' Association	Guideline	general	general	The document makes no recommendations about avoiding NSAID drugs pre-eclampsia	Thank you for your comment. Analgesia was not included in the scope for this update, so the committee were unable to make any recommendations regarding this. Advice on post-partum analgesia is already included in the NICE guideline on postnatal care, which includes advice to avoid NSAIDs if there are contraindications.
Obstetric Anaesthetists' Association	Guideline	general	general	The guideline makes no comment about more general aspects of post partum care – in particular should women who are receiving magnesium for pre-eclampsia postnatally be kept nil by mouth?	Thank you for your comment. Post-partum care was not included in the scope for this update, and therefore the committee were unable to make recommendations regarding this.
Obstetric Anaesthetists' Association	Guideline	24	23	The guideline states 'Do not preload women who have severe pre-eclampsia with intravenous fluids before establishing low-dose epidural analgesia or combined spinal epidural analgesia. There is no comment about the role of preload before establishing spinal or epidural **anaesthesia** for CS	Thank you for your comment. This guideline covers the common scenario of fluid management where women with pre-eclampsia receive epidural analgesia. Historically, a fluid preload was given prior to an arterial vasodilator but this practice has changed, Preloading for women undergoing spinal or epidural anaesthesia needs to be undertaken very carefully, and would be under the direct control of the anaesthetist, and is beyond the scope of this guideline.
Roche Diagnostics Limited	Economic Model	Clinical inputs tab	General	The model is concerned with the population with a starting gestational age of 34 weeks. We believe this related to the PREP-S prediction model, however, we do recommended that clinical validation on the models actually used in clinical practice is essential as this is an important assumption. Previous recommendations looked at women	Thank you for your comment. The model was based on the fullPIERS risk assessment tool, as there was insufficient data on

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				with a gestational age >26 weeks. We would also question the assumption that "All outpatient" care would have 100% specificity at 48hrs and 7 days.	diagnostic accuracy to use the PREP-S model at various risk levels. The model developed for this guideline is consistent with the gestational age in the evidence base and the recommendations also reflect that. A specificity of 100% for "all outpatient" care is correct by definition. A "negative" in this context is a patient who does not need inpatient management of complications. Therefore, if all patients are outpatients, there can be no false positives (an inpatient who does not need inpatient management of complications)
Roche Diagnostics Limited	Guideline	12	3-7	There is an evolving evidence base for the use of biomarkers such as PlGF in the risk assessment of early-onset pre-eclampsia (PE) in the 1st trimester. The PlGF assay in addition to the diagnosis and short term prediction of PE, is also intended for the use as one component, in combination with other parameters, to evaluate the risk of early-onset PE during the first trimester of pregnancy. Please see the evidence below which supports the use of the PlGF marker in this area. 1. Tsiakkas A, Cazacu R, Wright A, et al. Maternal serum placental growth factor at 12, 22, 32 and 36 weeks' gestation in screening for pre-eclampsia. Ultrasound Obstet Gynecol 2016;47:472-477. 2. Akolekar R, Syngelaki A, Poon L, et al. Competing risks model in early screening for preeclampsia by	Thank you for your comment. First trimester risk assessment for pre-eclampsia was not included in the scope for this update, therefore the committee were unable to review or comment on the evidence you have cited. However, thank you for bringing these papers to our attention and we will pass your comment to the NICE surveillance team which monitors guidelines to ensure that they are up to date.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				biophysical and biochemical markers. Fetal Diagn Ther 2013;33:8-15. 3. O'Gorman N, Wright D, Syngelaki A, et al. Competing risks model in screening for preeclampsia by maternal factors and biomarkers a t11-13 weeks gestation. Am J Obstet Gynecol 2016;214:103.e1-103.e12. 4. Poon LC, Kametas NA, Maiz N, et al. First-trimester prediction of hypertensive disorders in pregnancy. Hypertension 2009;53:812-818. 5. Poon LC, Nicolaides KH. First-trimester maternal factors and biomarker screening for preeclampsia. Prenatal Diagnosis 2014;34:618-627. 6. Akolekar R, Syngelaki A, Sarquis R, et al. Prediction of early,intermediate and late pre-eclampsia from maternal factors, biophysical and biochemical markers at 11-13 weeks. Prenat Diagn 2011;31:66-74.	
Roche Diagnostics Limited	Guideline	12	3-7	We recognise that due to the length of guidelines, hyperlinks are used to signpost readers to the relevant diagnostics guidance. We believe that the recommendations from the DG23 guideline should be briefly outlined here to provide clarification on the 'rule-out' nature of the test and to further support clinicians with their decision making for women presenting with suspected pre-eclampsia.	Thank you for your comment. We have now added a note to state that PlGF-based testing can be used to help 'rule-out' pre-eclampsia in women with suspected pre-eclampsia, as you have suggested.
Roche Diagnostics Limited	Guideline	12	3-7	It would be beneficial to define what constitutes "suspected pre-eclampsia" here. The guideline refers to "suspected pre-eclampsia" but does not elaborate on the inclusion criteria for this group of patients. Additionally, the definition	Thank you for your comment. The population of women in whom PlGF testing should be carried out in accordance with DG23 is explained in the DG23

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				is not clearly stated in the ISSHP 2018 guidelines that were recently published so there are no guidelines that clinicians can go to, to seek clarification on this.[1] We believe that having guidance on this would support clinicians and healthcare professionals select the right patients that would benefit from PlGF based testing. 1. Brown MA, Magee LA, Kenny LC, Karumanchi SA, Mccarthy FP, Saito S, et al. The hypertensive disorders of pregnancy: ISSHP classification, diagnosis & management recommendations for international practice. Pregnancy Hypertension. 2018;13:291–310.	guidance and users of this guideline should therefore use the hyperlink to access further information.
Roche Diagnostics Limited	Guideline	12	3-7	There is a clear variation across the UK in the uptake of the NICE guidance DG23 (2016) which recommends the use of the sFlt-1/PlGF ratio test (in conjunction with standard clinical practice) to rule out pre-eclampsia. There is a pivotal UK study which is due to be published before this guideline is finalised. We believe that this study will support clinicians with decision making and with the barriers to implementation and should therefore be included in this guideline. We would therefore ask for the guideline committee to review the publication date of this guideline so that the findings of this study can be incorporated and to consider how they can support with the uptake of these diagnostics guidance in the future. Please could the guideline committee also advise on whether we can expect an update for the DG23 guideline and if so, what the timelines for this are. 1. National Institute for Health and Care Excellence. NICE guideline DG23. PlGF-based testing to help	Thank you for your comment. PlGF-based testing is recommended by NICE and should be offered in accordance with DG23 and the committee were aware that its use would be encouraged by the NHS England Accelerated Access Collaborative funding. Thank you for making us aware that there is a new study due to be published relating to the use of PlGF testing. The evidence base for the use of PlGF-based testing was not reviewed as part of this guideline update, but we will pass your comment to the NICE surveillance team which monitors guidelines to ensure that they are up to date.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				diagnose suspected pre-eclampsia (Triage PlGF test, Elecsys immunoassay sFlt-1/PlGF ratio, DELFIA Xpress PlGF 1-2-3 test, and BRAHMS sFlt-1 Kryptor/BRAHMS PlGF plus Kryptor PE ratio). Available at: https://www.nice.org.uk/guidance/dg23 [Last accessed [26/02/19]	
Roche Diagnostics Limited	Guideline	15	14-22	We believe that clarification is required on the use of the validated models fullPIERS and PREP-S to guide decision making in the management of pre-eclampsia. The hyperlinks currently signpost the reader to the risk calculators with a brief explanation however the guideline would benefit from listing the parameters used in the calculator and the interpretation of the results. Reference to the inclusion of biomarker testing to update the fullPIERS risk prediction model is made however the wording here suggests that these biomarker tests are solely those that are Alere-funded. This should be updated to reflect the availability of the other NICE recommended PlGF based testing. We would also ask the guideline committee to consider how these models are communicated to healthcare professionals to support the uptake of these in routine practice.	Thank you for your comment. As the online calculators for the risk models are cross-referenced within the guideline, and free to use, the committee considered that inclusion of all the individual parameters included in the risk prediction models was unnecessary. Clinicians would need to use the online risk calculators, therefore it is necessary to navigate to the relevant webpages in order to calculate the risk score. The evidence report does not discuss the possibility of updating the prediction models with other biomarkers. The prognostic accuracy of sFlt/PlGF ratio was included in the evidence review, but was found not to be useful to predict adverse maternal outcomes, and was therefore not recommended. The use of PlGF-based testing for women with suspected pre-eclampsia is recommended in a separate section of the guideline and includes only a cross-reference to the existing NICE guidance, DG23. The evidence for PlGF-based testing was not reviewed as part of this update but information about the brands of tests is included in the DG23 guidance.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					The committee agreed that inclusion of the fullPIERS and PREP-S models in this guideline would bring them to the attention of healthcare professionals for local implementation.
Royal College of General Practitioners	Guideline	7	1	The albumin:creatinine ratio (ACR) is more widely used than the protein:creatinine ratio (PCR) in primary care. The proposed threshold for ACR is different to that for micro-albuminuria in diabetes/renal disease. The committee should consider highlighting that the threshold for ACR is different within this population in the recommendations.	Thank you for your comment. The committee agreed that the different ACR threshold used in hypertension in pregnancy should be explained, and have added a sentence to the rationale and impact section to explain this, which states: 'The committee were aware that this threshold is different to that used for detection of microalbuminura in the non-pregnant population. However, they agreed that, on the basis of the evidence reviewed, it was appropriate to use a threshold of 8 mg/mmol for pregnant women.'
Royal College of General Practitioners	Guideline	7	7	The use of the term "chronic hypertension" is confusing in primary care although we realise it is widespread in obstetrics. These patients usually have essential hypertension or secondary hypertension. It might be clearer for primary care to include a clarification such as "pre-existing"	Thank you for your comment. Whilst the committee agree that the terminology is different to that commonly used in primary care, they were aware that some women receive a diagnosis of hypertension for the first time during pregnancy. Therefore, although the hypertension was likely to have pre-dated the pregnancy, women do not perceive themselves as having "pre-existing" hypertension and find that terminology confusing. They therefore agreed to keep the current terminology of "chronic" hypertension to describe this group of women.
Royal College of General Practitioners	Guideline	8	24	There needs to be clarification of what "sustained" means in this context	Thank you for your comment. The committee discussed whether it was possible to define "sustained", but agreed that the time at which BP measurement would be repeated depends on many variables – such as the degree of hypertension, the gestation of the pregnancy, the setting (primary or

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					secondary care, inpatient or outpatient). Therefore it was considered appropriate to leave this to the discretion of the individual clinician, rather than define a specific time period.
Royal College of General Practitioners	Guideline	9	3	The committee should consider making a recommendation on how to cope with self-monitored blood pressure would be helpful.	Thank you for your suggestion. Some evidence on automated blood pressure readings was identified as part of the review, and the committee recognise the importance of identifying both white coat hypertension and masked hypertension. However, the evidence base for how to integrate self-monitored blood pressure readings in pregnancy with those taken in the clinic is currently lacking. Therefore the committee were unable to develop specific recommendations to give guidance on interpreting these readings.
Royal College of General Practitioners	Guideline	15	14	The committee should consider making a recommendation referring to assessment in primary care by a GP clarifying when should a GP refer a woman to the midwife with suspected pre-eclampsia. It may be appropriate here to note the ANC guidance in the LETR.	Thank you for your comment. Recommendation 1.5.1 states that women with pre-eclampsia should be assessed by a healthcare professional trained in the management of hypertensive disorders of pregnancy and therefore a GP suspecting pre-eclampsia would need to refer the woman for further assessment. The antenatal care guidance recommends increased surveillance in women at risk of pre-eclampsia but does not provide more detailed referral guidance so it has not been referenced here.
Royal College of General Practitioners	Guideline	20	9	The guideline offers a medical review with GP or specialist at both 2 and 6-8 weeks after transfer to community care but gives no guidance to GPs as to what to do. For example: when should they change medications back to those recommended in the adult guideline? At what point should they consider the need for long term medication? Is it reasonable to stop treatment and do ABPM if this is the case and if so then at what stage? At the moment offering	Thank you. Recommendation 1.5.20 states that a detailed care plan should be provided on discharge to community care, to provide individualised guidance for GPs.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				a review with no guidance is difficult for primary care and potentially will lead to sub optimal care. The committee should consider making recommendations in this area.	
Royal College of General Practitioners	Guideline	32	Table 6	The RCGP believes that with the additional information this will be a useful resource for both GPs and women	Thank you for your comment.
Royal College of Nursing	General	General	General	The Royal College of Nursing (RCN) welcomes the update of the NICE Hypertension in pregnancy: diagnosis and management guidelines.	Thank you for your comment.
Royal College of Nursing	General	General	General	The document seems comprehensive and we have no further comments to make on it.	Thank you for your comment.
Royal College of Obstetricians and Gynaecologists	Guideline	General		These recommendations are good, clear and easy to follow. I feel that this is a very well written and evidenced guideline.	Thank you for your comment.
Royal College of Obstetricians and Gynaecologists	Guideline	4-5 and 9	14-5 and 17-18	I think it is important do imply some uncertainty around the dose of aspirin, i.e. 75 or 82 or 150mg. There does seem to be a dose related response, but also uncertainty around safety at the higher doses. https://www.ajog.org/article/S0002-9378(18)30232-1/fulltext	Thank you for your comment. The evidence reviewed for the treatment of chronic hypertension included evidence of some benefit with aspirin doses ranging from 50 mg to 150 mg a day and the committee were therefore aware there is some uncertainty about the optimal dose of aspirin. The committee were also aware that other national guidelines may recommend 150 mg, and agreed that inconsistency between national guidelines is unhelpful. They therefore agreed to amend the recommended dose of aspirin to give a range of 75-150 mg, as they were aware of evidence

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					for the effectiveness of both 'low doses', 75 mg and 150 mg of aspirin.
Royal College of Obstetricians and Gynaecologists	Guideline	12	3-7	Placental growth factor-based testing is, to my knowledge, not widely available. It might be important to state that NICE DG23 (2016) says that placental growth factor-based testing is recommended to help rule-out, but not to 'rule-in' pre-eclampsia.	Thank you for your comment. PlGF-based testing is recommended by NICE and should be offered in accordance with DG23 and the committee were aware that its use would be encouraged by the NHS England Accelerated Access Collaborative funding. To clarify this recommendation we have now added the statement that PlGF-based testing is to be used as a 'rule-out' test as you suggest.
Royal College of Obstetricians and Gynaecologists	Guideline	12	3-7	For PLGF - this test is not readily available in routine clinical practice. What is the additional benefit of doing this test to diagnose pre-eclampsia ove the current clinical and laboratory investigations which are currently available?	Thank you for your comment. PlGF-based testing is recommended by NICE and should be offered in accordance with DG23. The evidence base for the use of PlGF-based testing was not reviewed as part of this guideline update, but can be found as part of the DG23 documents on the NICE website.
Royal College of Obstetricians and Gynaecologists	Guideline	15	14-20	The authors of the PREP study recognise that evaluation of the impact of this model in clinical practice has not been performed. However it does apply to a UK population. Im not clear that this model should be implemented in practice without supporting evidence of benefit in the target population	Thank you for your comment. The committee considered that the PREP model was specifically developed in the UK population, its performance has been validated in an external dataset, and it was therefore reasonable to include it, along with the fullPIERS model, as an option to help guide treatment decisions. However, the committee agreed that although the models are considered to be helpful as an adjunct to help guide decision-making, they do not replace clinical assessment and the clinical judgement of healthcare professionals. The guideline has therefore been amended to emphasise the importance of a full clinical assessment, with admission to hospital if there are any concerns for the well-being of the

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					woman or baby. The models can be used in addition to this process. The committee agree that further research may be undertaken to evaluate the impact of introducing such models into practice, and would expect the results of this research to be reviewed in any future update of this guideline.
Royal College of Obstetricians and Gynaecologists	Guideline	17	1	BP measurement – it might be helpful to say 'At least every 48 hours; more frequently if the woman is admitted to hospital'.	Thank you for your comment. This change has been made as you suggested.
Royal College of Obstetricians and Gynaecologists	Guideline	25	1-3	It's isn't clear what 'whose BP has not responded to treatment' means in this context. Over what time period? 10 minutes? 20minutes? What BP threshold ie how much of a response?	Thank you for your comment. The committee agreed that a response to treatment was difficult to define, and that this should be left to the judgement of the individual clinician.
Royal College of Obstetricians and Gynaecologists	Guideline	26	3-4	If other agents should not be used in ecampsia what should clinicains do about ongoing seizures not responding to a second dose of magnesium?	Thank you for your comment. The committee agreed that women with seizures not responding to a second dose of magnesium would already be in a critical care setting and would require individualised and specialist anaesthetic support (which may include intubation and intravenous anaesthetics), but that this detail was outside the scope of this guideline, so additional recommendations to cover this scenario were not added.
Royal College of	Guideline	29 and 30,		"Careful follow-up of the infant for possible signs of hypotension is recommended." This statement cites no	Thank you for your comment. This footnote is the MHRA guidance on the use of ACE inhibitors and

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Paediatrics and Child Health		footnotes		evidence; it is in the passive voice, where did this recommendation come from and what is meant by 'careful'. The definition of 'hypotension' in the context of outpatient care needs to be explained. Furthermore, the signs of hypotension that are sought need to be defined, including who should be looking for this, whether it is the parents or practitioners. The guidance has already stated that the amounts of drug passing into breast milk are minimal, so as with almost all other drugs, well below any plausible threshold for physiological effect, therefore this suggestion does not provide much help and it is suggested this should be omitted.	angiotension II receptor blockers during breast feeding and as such we have to include it verbatim, although it is not based on evidence we have reviewed and is in the passive voice. However, the corresponding recommendation (1.9.3) has been amended to provide more specific information on monitoring babies for hypotension while in hospital and on discharge home.
Royal College of Physicians	General	General	General	The RCP is grateful for the opportunity to respond to the above consultation. In doing so we would like to endorse the response submitted by the Renal Association. We have also liaised with our experts and would like to make the following comments.	Thank you for your comment and for liaising with your experts.
Royal College of Physicians	Guideline		Post partum management	There is no mention of the need to avoid NSAIDs for post partum analgesia in women with pre-eclampsia especially if there is AKI / risk of pulmonary oedema.	Thank you for your comment. Post-partum analgesia was not included in the scope for this update, so the committee were unable to make any recommendations regarding this. Advice on post-partum analgesia is already included in the NICE guideline on postnatal care, which includes advice to avoid NSAIDs if there are contraindications.
Royal College of Physicians	Guideline		Table 2	Urea will increase in response to steroid administration and is not a good marker of renal function – suggest replace in all instances with creatinine.	Thank you for your comment. The committee agreed with your comment, and have replaced 'urea and electrolytes' with the term 'renal function' in Table 1 and Table 2 of the guideline.
Royal College of Physicians	Guideline		Table 3	Another consideration may include starting induction of labour before deterioration is more severe that may necessitate a CS rather than vaginal delivery. This leaves time to get the woman delivered vaginally before she gets	Thank you for your comment. Table 3 and recommendation 1.5.7 both provide guidance on when to consider planned early birth and this, in conjunction with the involvement of a senior obstetrician

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				too sick. Also some mention of platelet count and allowing regional anaesthesia/analagesia before it drops too low may be appropriate here.	(recommendation 1.5.8) should be used to guide decisions about when birth is likely to be best for both the women and her baby, whether this involves planned vaginal birth or caesarean section. The committee agreed that it was difficult to be more precise than this regarding the optimal mode and timing of birth, but noted that there was ongoing research which may provide further guidance in the future. Guidance regarding platelet count and epidural anaesthesia is covered by NICE guideline NG121 on intrapartum care for women with existing medical conditions or obstetric complications and their babies, and this is already cross-referenced from section 1.7 on intrapartum care.
Royal College of Physicians	Guideline	12	Table 1	Blood tests: Our experts question why the developers advocate urea rather than creatinine. This does not reflect current clinical practice and our experts suspect this may be a typo.	Thank you for your comment. References to "urea and electrolytes" have now been replaced with "renal function" throughout the document.
Royal College of Physicians	Guideline	15	1.5.4	Using the PIERS calculator and entering yes for the patient had breathlessness and abnormal liver function tests the calculated risk of abnormal maternal outcome is 21% ie not above the suggested threshold of 30 % for admission. Serum albumin is not included in the PIERS model and I would challenge this calculator to predict the woman at risk of pulmonary oedema / abruption or indeed eclampsia	Thank you for your comment. The recommendations relating to the use of fullPIERS and PREP-S models have been amended to clarify that they should be used as an adjunct to help guide decision-making and not to replace clinical assessment and the clinical judgement of healthcare professionals. The use of the models was included with the aim of reducing variance in current practice, as it appears that some maternity units have a very high threshold for admission. We have now moved the recommendations relating to the use of the models after the list of clinical features which may warrant hospital admission, and clarified that any one (or more)

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					of these features should be used to identify if there are any concerns for the wellbeing of the woman or baby, which would include signs of impending pulmonary oedema or eclampsia. The suggested risk threshold of 30% has also been removed, as we agree this may cause confusion if clinical criteria and scores indicate differing courses of action.
Royal College of Physicians	Guideline	15	28	Our experts question how clinicians will spot ' a sustained BP > 160 if it is only being measured every 48 hours as an out patient	The committee discussed whether it was possible to define "sustained", but agreed that the time at which BP measurement would be repeated depends on many variables – such as the degree of hypertension, the gestation of the pregnancy, the setting (primary or secondary care, inpatient or outpatient). Therefore it was considered appropriate to leave this to the discretion of the individual clinician, rather than define a specific time period. However, the committee have amended Table 2 to state that blood pressure may be measured more frequently than every 48 hours if women are admitted to hospital.
Royal College of Physicians	Guideline	17	Table 2	Dipstik / proteinuria testing. If the woman is already diagnosed with pre-eclampsia our experts question the value of checking urine twice a week (suggest stipulate that this is only relevant for women diagnosed with pre-ecampsia without/ before the appearance of significant proteinuria	Thank you for your comment. Table 2 has now been amended to state that repeated dipstick proteinuria testing should only be carried out if clinically indicated.
Royal College of Physicians	Guideline	18	10	There is no mention of pulmonary oedema / orthopnoea – patients should be delivered before frank pulmonary develops or o2 sats drop <90% and the importance of history of orthopnoea / PND should be flagged here.	Thank you for your comment. We have now amended this list to make it clearer that it is not an exhaustive list of indications for planned early birth, and other features may be taken into account.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Royal College of Physicians	Guideline	18	11	This refers to any deterioration in serum creatinine – confirming that reference to urea in table 1 and 2 is a mistake.	Thank you for your comment. We have amended the wording to "renal function" so it is consistent throughout the guideline.
Royal College of Physicians	Guideline	27 – line 17	Table 4	Rather than just oliguria – suggest add AKI here.	Thank you for your comment. Medical management of severe hypertension, severe pre-eclampsia and eclampsia was not included in the scope for this update so the evidence was not reviewed. The committee discussed the use of 'acute kidney injury' but as they had not reviewed the evidence were unable to define what level of AKI would be appropriate and so did not change the recommendation.
Royal College of Physicians	Guideline	33	19	Although we agree that testing for heritable thrombophilia is not indicated – there should be a recommendation to screen for antiphospholpid syndrome in those women delivered before 34 weeks due to utero-placental insufficiency which includes pre-eclampsia (so particularly those with a small baby).	Thank you for your comment. As you have noted, the guideline already contains a recommendation (1.10.8) about testing for thrombophilia. This topic was not one of the areas prioritised for this update, so the evidence was not reviewed.
Royal College of Physicians and Surgeons (Glasgow)	Guideline	General	General	The Royal College of Physicians and Surgeons of Glasgow although based in Glasgow represents Fellows and Members throughout the United Kingdom. While NICE has a remit for England, many of the recommendations are applicable to all devolved nations including Scotland. They should be considered by the relevant Ministers of the devolved governments. The College welcomes this updated Guideline in an important area. Maternal Health is a priority area within the College.	Thank you for your comment.
Royal College of Physicians	Guideline	General	General	Throughout the document, the word fetal is used whereas in the United Kingdom it is usual to spell the word foetal	Thank you for your comment. The committee agreed that 'fetal' was now standard terminology throughout

Stakeholder	Document	Page No	Line No	Comments	Developer's response
and Surgeons (Glasgow)					the UK and is the accepted spelling for use in NICE guidelines.
Royal College of Physicians and Surgeons (Glasgow)	Guideline	General	General	Our reviewer considered that the changes made to this guideline are a positive step and make the management of hypertensive disorders in pregnancy more straightforward. The change in categorisation of severity of hypertension is much clearer now that there are 2 categories rather than 3. It was felt that this wouldl be positively received.	Thank you for your comment.
Royal College of Physicians and Surgeons (Glasgow)	Guideline	5	2	It is Systemic Lupus Erythematosus and not Erythematosis	Thank you for your comment. This was an error in the 2010 guideline which had been carried over but has now been corrected.
Royal College of Physicians and Surgeons (Glasgow)	Guideline	12	3	Although there is NICE guidance available on the use of PIGF (Placental Growth Factor) testing to diagnose pre-eclampsia, this test is not available in all units. This recommendation is challenging to implement in practice.	Thank you for your comment. PlGF-based testing is recommended by NICE and should be offered in accordance with DG23 and the committee were aware that its use would be encouraged by the NHS England Accelerated Access Collaborative funding.
Royal College of Physicians and Surgeons (Glasgow)	Guideline	15	14	Our reviewer felt that the introduction of the scoring methods for maternal risk prediction is a very positive move. However, neither of the scoring methods are currently in everyday practice in many units. There is therefore and education issue which needs to be addressed.	Thank you for your comment. The committee are aware that the use of these models is not yet in routine practice, but think that the implementation of the guideline will help facilitate awareness of the models. The NICE implementation team will be made aware that this is a change in practice for many units.
The Pelvic Partnership	General	General	General	The Pelvic Partnership is happy with the content in the draft guideline and appreciates the consultative approach adopted by NICE.	Thank you for your comment.
UK Drugs in Lactation	Evidence Review E	20	49	There does not seem to be adequate reasoning why amlodipine has been recommended as the second line	Thank you for your comment. Although the SPS website has been consulted as part of this evidence

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Advisory Service				choice calcium channel blocker. There seems to have been no consideration at all (from the discussion summary) for the use of verapamil or nicardipine which are the preferred second line choice calcium channel blockers in terms of breastfeeding. This is clearly stated on the SPS website: https://www.sps.nhs.uk/articles/safety-in-lactation-drugs-for-hypertension/	review, it was not the sole source of information used when developing recommendations, and was used in conjunction with the clinical evidence identified and the committee's expertise and experience. The committee did not consider the use of verapamil for the treatment of hypertension in the postnatal period and the literature review did not identify any evidence on the efficacy or safety of verapamil to treat hypertension in these women. The committee were aware that hypertension is usually treated with dihydropyridine calcium channel blockers (such as nifedipine, nicardipine and amlodipine) as these agents have a greater effect at relaxing vascular smooth muscle compared to verapamil. Some evidence was identified relating to the levels of nicardipine in breast milk. However, the committee agreed that nicardipine was not used in the UK to treat hypertension in pregnancy or in the postnatal period and therefore there was less experience of its use in breastfeeding compared to nifedipine and amlodipine which are both widely used. This lack of use and experience with nicardipine is acknowledged on the SPS website.
UK Drugs in Lactation Advisory Service	Evidence Review E	21	41 - 43	The Review states that the Specialist Pharmacy Services website database was consulted, and a link is provided. This database is provided by ourselves, the UK Drugs in Lactation Advisory Service. However, the link that is provided indicates that the information has not been used in its entirety. The link takes you through to all of the therapeutic Group Summaries available, which discusses classes of drugs in more general terms and their use in breastfeeding. There is also a separate database which	Thank you for the comment. We can confirm that the full information provided by the Specialist Pharmacy Services website was consulted by the committee. The hyperlink in the evidence review has been amended to link directly to the section on drugs for hypertension in breastfeeding.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				assesses individual drugs, and the indication is that this has not been consulted.	
UK Drugs in Lactation Advisory Service	Guideline	General	General	There may well be situations in which patient refuses medicine recommendations, or other options may need to be used for a variety of reasons during the breastfeeding period, and therefore a sign post to the UK Drugs in Lactation Advisory Service would be helpful in overcoming these obstacles in what could be used in such circumstances. A link to out page on the SPS website could be used: www.sps.nhs.uk/ukdilas which provides all our contact details.	Many thanks for your comment. We agree that clinicians and women may wish to use other resources to obtain information about medicines during breast feeding. It is not NICE policy to include links to non-NICE resources from the guideline itself but we will suggest this link is included on the 'Information for the public' section on the NICE website page relating to this guideline.
UK Drugs in Lactation Advisory Service	Guideline	29	10	Disgaree with the recommendation that atenolol is the beta-blocker of choice. The evidence review has rightly concluded that for both atenolol and labetalol the evidence is very poor. Although there is slightly more evidence for atenolol use in breastfeeding, this still represents extremely low numbers and quality. This is not an isolated situation, and because the evidence separating the drugs can be so fractional, we cannot purely rely on the evidence base. We have to consider the theoretical risk of the drug getting into the breast milk, using pharmacokinetic principles. Pharmacokinetically, labetalol offers a much safer profile compared to atenolol. Atenolol has very low protein binding (16% versus 50% for labetalol) therefore more free drug is available to pass into breast milk. Atenolol also has higher bioavailability once the infant ingests (60% versus 40%). From the evidence that is available to date, it supports this theory and levels measured in milk are greater for atenolol than labetalol (average relative infant dose for atenolol is 6.6% of the weight adjusted maternal dose compared to 0.6% for labetalol). Atenolol is also renally excreted to a far greater extent (85% versus 5% for labetalol), presenting a	Thank you for your comment. The committee agreed that labetalol could be a suitable alternative to atenolol and have added it to the recommendation as an alternative to atenolol, but have also emphasised that once daily medicines should be used wherever possible. The guideline already states that choice of antihypertensive medicines should be based on a woman's preference, as you have suggested.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
				much higher risk for accumulation in infants. This does not make atenolol a contra-indication, because overall the levels reported in milk are still low, but the balance is in favour for labetalol; the recommendation in the guidline cannot be dictated by dosing frequency alone. It would be reasonable to continue to include both labetalol (first line) or atenolol (second line) depending on patient preference.	
UK Drugs in Lactation Advisory Service	Guideline	29	13	Although diuretics and angiotensin receptor blockers generally are not recommended, they can be used if there is a need. The wording should therefore be softened as they are not completely contra-indicated. Add to first sentence '*Where possible*, avoid using diuretics…'	Thank you for your comment. This change has been made as you suggested.
UK Drugs in Lactation Advisory Service	Guideline	30	1	There monitoring advice that is given needs to be expanded and could be included here as advice to the woman, particularly since they will need advice to monitor their infants once they go home. A woman cannot monitor for 'hypotension' per se and therefore, with any antihypertensive medicines we would advise monitoring for drowsiness, lethargy, pallor, poor feeding and weight gain.	Thank you for your comment. The committee agreed that women cannot be expected to monitor their babies for hypotension and so have amended the recommendation to include the symptoms you have suggested, as well as 'cold peripheries'.
UK Drugs in Lactation Advisory Service	Guideline	30	9 and 10	This is an important point, and is the exact reason why labetalol should continue to be recommended in the guideline, since a woman may well feel that increased dosing is worth it for an infant being exposed to a drug with theoretically much less risk.	Thank you for your comment. The committee agreed that labetalol could be a suitable alternative to atenolol and have added it to the recommendation as an alternative to atenolol, but have also emphasised that once daily medicines should be used wherever possible.
UK National Screening Committee	Guideline	General		Thank you for giving the committee the opportunity to comment on this guideline update. It is clear that the proposed 'Hypertension in pregnancy: diagnosis and management' guideline does not recommend screening for hypertension in pregnancy in every pregnant woman in the UK.	Thank you for your comment. The committee agreed that blood pressure measurement and urinalysis for protein was an integral part of routine antenatal care, and is covered by the NICE antenatal care guideline. Women are therefore routinely screened to detect hypertension in pregnancy.

Stakeholder	Document	Page No	Line No	Comments	Developer's response
University Hospital Southampton NHS Foundation Trust	Guideline	12 Table 1		For women with uncomplicated pregnancy related hypertension, the frequency of ultrasound might be more flexible. Repeating every 2 weeks with mild hypertension, without other risks and with a reassuring initial scan seems overly sensitive. We would prefer adjustment to wording to allow individual flexibility depending on clinician preferences.	Thank you for your comment. Table 1 states that for women with hypertension, scans should be repeated as clinically indicated. Repeated scanning every 2 weeks would only apply to women who had persistent, severe hypertension. We have now clarified this in the table that and also clarified that when BP falls below 160/110 mmHg then management should be as for the 'hypertension' column of the table.
University Hospital Southampton NHS Foundation Trust	Guideline	12	3	We are uncertain about the recommendation to '' offer Placental growth factor (PlGF)-based testing ...'' And feel this requires more evidence to support suggested benefits to clinical care. Earlier diagnosis of pre-eclampsia is an attractive hypothesis however, numbers will be small especially in this situation when the mother has already presented with possible pre-eclampsia and is therefore likely to subsequently be on an enhanced surveillance/screening pathway. Economic evaluation also needs confirmation.	Thank you for your comment. PlGF-based testing is recommended by NICE and should be offered in accordance with DG23. The evidence base and economic evaluation for the use of PlGF-based testing was not reviewed as part of this guideline update, but can be found as part of the DG23 documents on the NICE website.
University Hospital Southampton NHS Foundation Trust	Guideline	13	1	We are not aware of any significant maternal differences between nifedipine and labetalol apart from the different side-effect profiles. We are, however aware that antenatal exposure to beta-blockers including labetalol is likely to have significant implications for the management of the newborn including hypoglycaemic screening and treatment. Therefore we suggest equal emphasis based on local opinion and policy between labetalol and nifedipine	Thank you for your comment. The committee agreed that there was no good evidence to demonstrate superior efficacy of one agent over the other. However, given the lack of evidence, as labetalol is specifically licensed for use during pregnancy, it is standard for NICE guidelines to include this as the preferred medication. The committee were aware that beta-blockers may lead to hypoglycaemia in newborn babies, but agreed that babies would be routinely monitored after birth and

Stakeholder	Document	Page No	Line No	Comments	Developer's response
					that it was not necessary to make any specific recommendations relating to this.
University Hospital Southampton NHS Foundation Trust	Guideline	17	2	We are not aware of any significant maternal differences between nifedipine and labetalol apart from the different side-effect profiles. We are, however aware that antenatal exposure to beta-blockers including labetalol is likely to have significant implications for the management of the newborn including hypoglycaemic screening and treatment. Therefore we suggest equal emphasis based on local opinion and policy between labetalol and nifedipine.	Thank you for your comment. The committee agreed that there was no good evidence to demonstrate superior efficacy of one agent over the other. However, given the lack of evidence, as labetalol is specifically licensed for use during pregnancy, it is standard for NICE guidelines to include this as the preferred medication. The committee were aware that beta-blockers may lead to hypoglycaemia in newborn babies, but that babies would be routinely monitored after birth and they agreed it was not necessary to make any specific recommendations relating to this.
University Hospital Southampton NHS Foundation Trust	Guideline	25	23	We are not aware of any clear relationship between fetal Doppler's to the severity of pre-eclampsia beyond or over that of maternal BP and symptoms, as already described higher in the list. Suggest that this addition does not help the list and might adversely include women who have abnormal Doppler's only?	Thank you for your comment. Medical management of severe hypertension, severe pre-eclampsia and eclampsia was not included in the scope for this update but the committee agreed that failure of fetal growth and abnormal Doppler were not indications for the use of magnesium sulfate, and have removed these from the list.
University Hospitals Birmingham	Guideline	4	14	There is now good quality evidence to increase the dose of Aspirin from 75mg to 150mg for prevention of pre-eclampsia in pregnancy. The recommendation regarding this in the draft guideline states 75mg	Thank you for your comment. Although the evidence for this recommendation was not reviewed as part of the update, the committee were aware that other national guidelines may recommend 150 mg, and agreed that inconsistency between national guidelines is unhelpful. They therefore agreed to amend the recommended dose of aspirin to give a range of 75-150 mg, as they were aware of evidence for the effectiveness of both 'low doses', 75 mg and 150 mg of aspirin.