

# Hypertension in pregnancy: diagnosis and management

## Methods

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*Methods*

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*This methods chapter was developed by  
the National Guideline Alliance, hosted by  
the Royal College of Obstetricians and  
Gynaecologists*



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# 1 Development of the guideline

## 2 Remit

3 The National Institute for Health and Care Excellence (NICE) commissioned the  
4 National Guideline Alliance (NGA) to update the existing NICE clinical guideline on  
5 Hypertension in pregnancy: diagnosis and management (CG107, August 2010).

## 6 Declarations of interest

7 Committee members' and developers' declarations of interest were recorded  
8 according to NICE's 2014 conflicts of interest policy until 31<sup>st</sup> March 2018, and  
9 thereafter in accordance with NICE's 2018 conflicts of interest policy.

## 10 What this guideline update covers

### 11 Groups that are covered

- 12 • Women who present with hypertensive disorders for the first time during  
13 pregnancy.
- 14 • Women who have pre-existing hypertension and are planning pregnancy or are  
15 pregnant.
- 16 • Women who are pregnant and at increased risk of developing hypertensive  
17 disorders during pregnancy.
- 18 • The fetus until birth.

### 19 Clinical areas that are covered

20 The 2019 update to the guideline covers the following clinical issues:

- 21 • Interventions for chronic hypertension
- 22 • Interventions for pre-eclampsia
- 23 • Investigations and monitoring of gestational hypertension
- 24 • Postnatal management of hypertension
- 25 • Prediction of adverse outcomes in pre-eclampsia
- 26 • Diagnosis of proteinuria
- 27 • Recurrence of hypertension in future pregnancies, and long term consequences of  
28 hypertension in pregnancy

29 For further details please refer to the [surveillance report](#) on the NICE website that  
30 defined which sections of this guideline should be updated.

## 31 What this guideline update does not cover

### 32 Groups that are not covered

33 The guideline does not cover the following groups:

- 1 • Women with hypertension and diabetes (for care of these women refer to  
2 'Diabetes in pregnancy' NICE clinical guideline 63 [2008]).  
3 ○ Although this guideline update does not provide specific recommendations  
4 about the management of women with hypertension and diabetes during  
5 pregnancy, when searching for evidence women with diabetes and  
6 hypertension were not specifically excluded from reviews.  
7 • The infants of women who have had hypertensive disorders during pregnancy.  
8 ○ Although this guideline update does not provide specific recommendations  
9 about the management of babies born to women with hypertension, a number  
10 of outcomes for babies were considered in the evidence reviews, to ensure a  
11 proper balance of the risks and benefits of the interventions.  
12

# 1 Methods

2 This chapter sets out in detail the methods used to review the evidence and to  
3 generate recommendations for the update to this guideline. Recommendations that  
4 have not been updated were developed in accordance with the methods described in  
5 the previous 2010 NICE guideline

6 This guideline update was developed using the methods described in [Developing](#)  
7 [NICE guidelines: the manual 2014](#).

## 8 Developing the review questions and outcomes

9 The 7 review questions developed for this update to the guideline were based on the  
10 key areas identified by the [NICE surveillance program](#) as requiring an update. The  
11 review questions were drafted by NGA based on the surveillance report and were  
12 refined and validated by the committee. In addition, the committee highlighted 2  
13 topics additional to those highlighted by the surveillance report (assessment of  
14 proteinuria and assessment of risk in women with pre-eclampsia) and additional  
15 review questions were agreed with NICE and included in the update. The questions  
16 are summarised in Table 1.

17 The review questions were based on the following frameworks:

- 18 • intervention reviews: population, intervention, comparator and outcome (PICO)
- 19 • diagnostic test accuracy reviews: population, index test, reference standard and  
20 outcome (PIRO)
- 21 • prognostic reviews: population, presence or absence of a prognostic or predictive  
22 factor and outcome (PPO)

23 These frameworks guided the development of the review protocols, the literature  
24 searching process, the critical appraisal and synthesis of evidence and facilitated the  
25 development of recommendations by the committee.

26 Full literature searches, critical appraisals and evidence reviews were completed for  
27 each review question.

28 **Table 1: Description of review questions**

Evidence report	Type of review	Review question guideline <sup>1</sup>	Outcomes
A	Intervention	What interventions for chronic hypertension are effective at improving outcomes for women and infants?	<p><u>Outcomes for the baby:</u></p> <p><b>Critical outcomes:</b></p> <ul style="list-style-type: none"> <li>• Perinatal mortality                             <ul style="list-style-type: none"> <li>○ Stillbirth</li> <li>○ Neonatal death up to 7 days</li> </ul> </li> <li>• Small-for-gestational-age</li> </ul> <p><b>Important outcomes:</b></p> <ul style="list-style-type: none"> <li>• Birth weight</li> <li>• Gestational age at delivery</li> <li>• Preterm birth</li> </ul>

Evidence report	Type of review	Review question guideline <sup>1</sup>	Outcomes
			<ul style="list-style-type: none"> <li>• Admission to neonatal unit</li> <li>• Neurodevelopmental outcome</li> </ul> <p><u>Outcomes for the woman:</u></p> <p><b>Critical outcome:</b></p> <ul style="list-style-type: none"> <li>• Blood pressure control               <ul style="list-style-type: none"> <li>○ Severe hypertension</li> </ul> </li> </ul> <p><b>Important outcomes:</b></p> <ul style="list-style-type: none"> <li>• Superimposed pre-eclampsia</li> <li>• Placental abruption</li> <li>• Onset of labour</li> <li>• Mode of birth</li> <li>• Maternal death</li> </ul>
B	Intervention	What is the best strategy (including frequency) for monitoring gestational hypertension in women?	<p><u>Outcomes for the baby:</u></p> <p><b>Critical outcomes:</b></p> <ul style="list-style-type: none"> <li>• Perinatal mortality               <ul style="list-style-type: none"> <li>○ Stillbirth</li> <li>○ Neonatal death up to 7 days</li> </ul> </li> <li>• Small-for-gestational-age</li> </ul> <p><b>Important outcomes:</b></p> <ul style="list-style-type: none"> <li>• Gestational age at delivery</li> <li>• Admission to neonatal unit</li> </ul> <p><u>Outcomes for the woman:</u></p> <p><b>Critical outcome:</b></p> <ul style="list-style-type: none"> <li>• Severe hypertension (SBP <math>\geq</math> 160 and/or DBP <math>\geq</math> 110 mmHg)</li> </ul> <p><b>Important outcomes:</b></p> <ul style="list-style-type: none"> <li>• Progression to pre-eclampsia</li> <li>• Placental abruption</li> <li>• Mode of birth</li> <li>• Maternal death</li> </ul>
C	Clinical prediction	Which tests or clinical prediction models are accurate in identifying or predicting women at risk of severe	<p><u>Model performance</u></p> <p><b>Critical outcomes:</b></p> <ul style="list-style-type: none"> <li>• Discrimination (AUC/C-statistic)</li> </ul>

Evidence report	Type of review	Review question guideline <sup>1</sup>	Outcomes
		complications from pre-eclampsia?	<ul style="list-style-type: none"> <li>• Calibration</li> </ul> <p><u>Accuracy of prediction:</u> <b>Critical outcome:</b></p> <ul style="list-style-type: none"> <li>• Sensitivity</li> </ul> <p><b>Important outcomes:</b></p> <ul style="list-style-type: none"> <li>• Specificity</li> <li>• Positive likelihood ratio</li> <li>• Negative likelihood ratio</li> </ul>
D	Intervention	What interventions are effective at improving outcomes for women and infants in women with pre-eclampsia?	<p><u>Outcomes for the baby:</u> <b>Critical outcomes:</b></p> <ul style="list-style-type: none"> <li>• Perinatal mortality               <ul style="list-style-type: none"> <li>○ Stillbirth</li> <li>○ Neonatal death up to 7 days</li> </ul> </li> <li>• Small-for-gestational-age</li> </ul> <p><b>Important outcomes:</b></p> <ul style="list-style-type: none"> <li>• Birth weight</li> <li>• Gestational age at delivery</li> <li>• Preterm birth</li> <li>• Admission to neonatal unit</li> <li>• Neurodevelopmental outcome</li> </ul> <p><u>Outcomes for the woman:</u> <b>Critical outcome:</b></p> <ul style="list-style-type: none"> <li>• Blood pressure control               <ul style="list-style-type: none"> <li>○ Severe hypertension</li> </ul> </li> </ul> <p><b>Important outcomes:</b></p> <ul style="list-style-type: none"> <li>• Eclampsia</li> <li>• HELLP (haemolysis, elevated liver enzymes, low platelet count)</li> <li>• Placental abruption</li> <li>• Onset of labour</li> <li>• Mode of birth</li> <li>• Maternal death</li> </ul>
E	Intervention	What is the optimal management of hypertension for women during the postnatal period?	<p><b>Critical outcomes:</b></p> <ul style="list-style-type: none"> <li>• Blood pressure control</li> <li>• Neonatal complications:               <ul style="list-style-type: none"> <li>○ Hypoglycaemia</li> <li>○ Hypothermia</li> </ul> </li> </ul>

Evidence report	Type of review	Review question guideline <sup>1</sup>	Outcomes
			<ul style="list-style-type: none"> <li>○ Blood pressure</li> <li>○ Bradycardia</li> <li>● Drug levels in breast milk</li> </ul> <p><b>Important outcomes:</b></p> <ul style="list-style-type: none"> <li>● Admission of baby into neonatal unit</li> <li>● Maternal breastfeeding</li> </ul>
F	Prognostic	What advice should be given to women at discharge from maternity care to reduce their risk for developing recurrent hypertension during a subsequent pregnancy, and their risk of longer term cardiovascular disease?	<p>Prevalence/proportion or relative effect size (e.g. adjusted relative risk, odds ratio or hazard ratio) of the following conditions/ events at any future date:</p> <ul style="list-style-type: none"> <li>● Cardiovascular disease/myocardial infarction/ heart disease/ ischaemic heart disease/ coronary heart disease/ major adverse cardiovascular events (MACE)</li> <li>● Mortality due to cardiovascular disease</li> <li>● Stroke</li> <li>● Hypertension</li> </ul> <p>Recurrence of any pregnancy hypertensive disorders in subsequent pregnancy:</p> <ul style="list-style-type: none"> <li>● pre-eclampsia</li> <li>● gestational hypertension</li> <li>● chronic hypertension</li> </ul>
G	Diagnostic accuracy	How effective are spot protein/creatinine ratio or albumin/creatinine ratio measurements as compared with a 24 hour urine collection for the identification of proteinuria in women with hypertensive disorders of pregnancy?	<p><b>Critical outcomes</b></p> <ul style="list-style-type: none"> <li>● Sensitivity</li> <li>● Negative likelihood ratio</li> </ul> <p><b>Important outcomes</b></p> <ul style="list-style-type: none"> <li>● Area under the curve</li> <li>● Positive likelihood ratio</li> <li>● Specificity</li> </ul>

1 AUC area under the curve; DBP diastolic blood pressure; HELLP haemolysis, elevated liver enzymes, low platelet count; MACE major adverse cardiovascular events; SBP systolic blood pressure

## 1 Searching for evidence

### 2 Clinical literature search

3 Systematic literature searches were undertaken to identify all published clinical  
4 evidence relevant to the review questions. This is a partial update of an existing  
5 guideline. New review protocols were drafted for the updated guideline, but the  
6 review protocols for the 2008 version of the guideline were taken into consideration  
7 at this stage. Evidence presented in the existing guideline was considered according  
8 to the new review protocol, and included in the updated guideline if it met the  
9 inclusion criteria for an individual review.

10 Databases were searched using relevant medical subject headings, free-text terms  
11 and study type filters where appropriate. Where possible, searches were restricted to  
12 retrieve articles published in English. All searches were conducted in the following  
13 databases: Medline, Medline-in-process, Embase, Health Technology Assessments  
14 (HTA), Cochrane Central Register of Controlled Trials (CCTR), Cochrane Database  
15 of Systematic Reviews (CDSR), and Database of Abstracts of Reviews of Effects  
16 (DARE). No date restrictions were placed on the searches, unless otherwise stated  
17 (and explained) in the individual review protocols for each review.

18 Due to the short timeframe for updating this guideline all the final versions of the  
19 searches were just run on the databases once. Any studies added to the databases  
20 after the date of the search (even those published prior to this date) were not  
21 included unless specifically stated in the text. No re-runs of searches were  
22 undertaken as it was not anticipated that additional evidence would be available that  
23 would lead to changes in the recommendations in the short timeframe over which this  
24 update was carried out.

25 Search strategies were quality assured by cross-checking reference lists of relevant  
26 papers, analysing search strategies from other systematic reviews and asking  
27 committee members to highlight any key, or additional, studies of which they were  
28 aware. Details of the search strategies, including study type filters that were applied  
29 and databases that were searched, can be found in Appendix B of each evidence  
30 report.

31 Searching for grey literature or unpublished literature was not undertaken.

### 32 Health economics literature search

33 Systematic literature searches were undertaken to identify all published health  
34 economic evidence relevant to the review questions. Individual searches for  
35 economic evidence for each question were undertaken alongside the searches for  
36 clinical evidence.

37 Databases were searched using relevant medical subject headings, free-text terms  
38 and, for searches undertaken in Medline, Medline-in-process, and Embase, a search  
39 filter was used to capture economic evaluations. Where possible, searches were  
40 restricted to retrieve articles published in English. All health economics searches  
41 were conducted in the following databases: Medline, Medline-in-process, Embase,  
42 Health Technology Assessments (HTA), and National Health Service Economic  
43 Evaluations Database (NHS EED).

1 Due to the short timeframe for updating this guideline all the final versions of the  
2 searches were just run on the databases once. Any studies added to the databases  
3 after the date of the search (even those published prior to this date) were not  
4 included unless specifically stated in the text. No re-runs of searches were  
5 undertaken.

6 Search strategies were quality assured by cross-checking reference lists of relevant  
7 papers, analysing search strategies from other systematic reviews and asking  
8 committee members to highlight any key, or additional, studies of which they were  
9 aware. Details of the search strategies, including study type filters that were applied  
10 and databases that were searched, can be found in Appendix B of each evidence  
11 report.

## 12 **Re-runs of literature searches**

13 Due to the short timeframe for updating this guideline, re-runs of literature searches  
14 were not performed as it was not anticipated that additional evidence would be  
15 available that would lead to changes in the recommendations.

16

## 17 **Call for evidence**

18 No call for evidence was made.

## 19 **Reviewing clinical evidence**

### 20 **Systematic review process**

21 The evidence was reviewed following these steps.

- 22 • Potentially relevant studies were identified for each review question from the  
23 relevant search results by reviewing titles and abstracts. Full papers were then  
24 obtained.
- 25 • Full papers were reviewed against pre-specified inclusion and exclusion criteria in  
26 the review protocols (in appendix A of each evidence review chapter).
- 27 • Key information was extracted on the study's methods, according to the factors  
28 specified in the protocols and results. These were presented in summary tables (in  
29 each review chapter) and evidence tables (in appendix D of each evidence review  
30 chapter).
- 31 • Relevant studies were critically appraised using the appropriate checklist as  
32 specified in [Developing NICE guidelines: the manual 2014](#).
- 33 • Summaries of evidence were generated by outcome (included in the relevant  
34 review chapters) and were presented in committee meetings.
- 35 • Results were summarised and reported in GRADE profiles (for intervention  
36 reviews and diagnostic test accuracy reviews).
- 37 • The use of GRADE has not been adopted for clinical prediction models or  
38 prognostic reviews. Quality assessment was therefore conducted at the individual  
39 study level for these reviews, rather than according to outcome.

40 All drafts of reviews were checked by a senior reviewer.

## 1 Type of studies and inclusion/exclusion criteria

2 Systematic reviews (SRs) with meta-analyses were considered the highest quality  
3 evidence to be selected for inclusion.

4 For intervention reviews, randomised controlled trials (RCTs) were included because  
5 they are considered the most robust study design for unbiased estimation of  
6 intervention effects. Based on their judgement, if the committee believed RCT data  
7 were not appropriate or there was limited evidence from RCTs, they agreed to  
8 include cohort studies with a comparative group. Due to the paucity of evidence  
9 regarding the use of antihypertensive medication in the postnatal period and a  
10 concern over drug safety in breast milk, non-comparative case series were also  
11 included for this review.

12 For the diagnostic test accuracy review regarding the diagnosis of proteinuria, cross-  
13 sectional or cohort studies of diagnostic test accuracy were considered for inclusion.

14 For the prognostic review regarding long term health risks and recurrence of  
15 hypertension in pregnancy, systematic reviews/meta-analyses of cohort studies  
16 (including individual participant data meta-analyses) were prioritised for inclusion. In  
17 the absence of such studies, prospective cohort studies (comparative and non-  
18 comparative) were considered for inclusion.

19 For the clinical prediction review, external validation studies of clinical prediction  
20 models were included. For individual prognostic tests, cross sectional or cohort  
21 studies of diagnostic test accuracy were considered for inclusion.

22 The committee was consulted about any uncertainty regarding inclusion or exclusion  
23 of studies. Excluded studies by review question with the reasons for their exclusion  
24 are listed in appendix K in each evidence report.

25 Posters, letters, editorials, comment articles, unpublished studies and studies not in  
26 the English language were excluded. Narrative reviews were also excluded, but  
27 individual references were checked for inclusion. Conference abstracts were not  
28 included.

29 For quality assurance of study identification, a random sample of 10% of the  
30 literature search results was sifted by a second reviewer for the following review  
31 questions:

- 32     • Which tests or clinical prediction models are accurate in identifying or predicting  
33       women at risk of severe complications from pre-eclampsia?

34 This question was selected as clinical prediction models are more complex reviews  
35 and therefore identification of relevant papers may be more prone to error.

- 36     • What is the best strategy (including frequency) for monitoring gestational  
37       hypertension in women?

38 This question was selected because it was the first review carried out by a reviewer  
39 who was new to the guideline.

- 40     • What advice should be given to women at discharge from maternity care to  
41       reduce their risk for developing recurrent hypertension during a subsequent  
42       pregnancy, and their risk of longer term cardiovascular disease?

1 This question was selected as it was a prognostic review, therefore paper selection  
2 was felt to be more challenging than with intervention reviews.

3 Discrepancies were resolved by discussion between the two reviewers and  
4 consultation with the guideline committee if necessary.

5 The inclusion and exclusion of studies was based on the review protocols, which can  
6 be found in appendix A of each evidence report. Excluded studies and the reasons  
7 for their exclusion are listed in appendix K of each evidence report. In addition, the  
8 committee was consulted to resolve any uncertainty about inclusion or exclusion.

## 9 **Methods of combining evidence**

### 10 **Data synthesis and reporting for intervention reviews**

#### 11 ***Pairwise meta-analysis***

12 Pairwise meta-analysis of homogeneous randomised trials was done using Review  
13 Manager 5 (RevMan 5) software. For binary outcomes, such as occurrence of  
14 adverse events, the Mantel-Haenszel method of statistical analysis was used to  
15 calculate risk ratios (relative risks, RRs) with 95% confidence intervals (CIs). A fixed  
16 effect model was used, unless significant heterogeneity was identified ( $I^2 > 50\%$ ).  
17 Where considerable heterogeneity was present (an  $I^2$  value of 50% or more),  
18 predefined subgroup analyses were performed. In the case of unexplained  
19 heterogeneity, possible causes were discussed with the committee before the final  
20 decision to pool data or not was made. A random effects model was used to  
21 generate pooled results when heterogeneity was unresolved using subgroup  
22 analysis.

23 For continuous outcomes, measures of central tendency (mean) and variation  
24 (standard deviation, SD) are required for meta-analysis. Data for continuous  
25 outcomes (such as blood pressure) were analysed using an inverse-variance method  
26 for pooling weighted mean differences.

27 Results from multiple observational studies of the same comparison were not pooled  
28 but presented as a range of effects due to the high risk of selection bias in  
29 observational studies, whereby differences in participant characteristics between  
30 treatment arms leads to a biased estimate of treatment effect.

31 Subgroups for stratified analyses were decided for some review questions *a priori* at  
32 the protocol stage if the committee identified biological or clinical characteristics  
33 which would affect the effectiveness of the intervention.

34 Forest plots were generated to present the results of meta-analyses and stratified for  
35 subgroup analyses (please see appendix E of each evidence report).

### 36 **Data synthesis and reporting for diagnostic test accuracy reviews**

#### 37 ***Meta-analysis***

38 Where appropriate, meta-analysis of diagnostic test accuracy was performed using  
39 the metandi and midas applications in STATA. A minimum of four studies was  
40 required to facilitate meta-analysis. Where this was not possible results were  
41 presented individually for each study.

1 Sensitivity, specificity, positive and negative likelihood ratios and area under the  
2 receiver operator characteristic (ROC) curve (AUC) with 95% CIs were used as  
3 outcomes for diagnostic test accuracy. These diagnostic accuracy parameters were  
4 obtained from the studies or calculated by the technical team using data from the  
5 studies.

6 Sensitivity and specificity are measures of the ability of a test to correctly classify a  
7 person as having a condition or not having a condition. When sensitivity is high, a  
8 negative test result rules out the condition. When specificity is high, a positive test  
9 result rules in the condition. An ideal test would be both highly sensitive and highly  
10 specific, but this is frequently not possible and typically there is a trade-off.

11 The following cut-offs were used when summarising the levels of sensitivity or  
12 specificity for the committee:

- 13 • very high: more than 95%
- 14 • high: more than 90%
- 15 • moderate: 75% to 90%
- 16 • low: 50% to 75%
- 17 • very low: less than 50%

18 Positive and negative likelihood ratios are measures of the association between a  
19 test result and the target condition. A positive likelihood ratio (LR+) greater than 1  
20 indicates a positive test result is associated with having the condition, whilst a  
21 negative likelihood ratio (LR-) less than 1 indicates a negative test result is  
22 associated with not having the condition. A high LR+ would indicate that a positive  
23 test is useful to rule in the condition whereas a low LR- would indicate that a negative  
24 test is useful to rule out the condition.

25 The following cut-offs were used when summarising the likelihood ratios for the  
26 committee:

- 27 • very useful test: LR+ higher than 10.0, LR- lower than 0.1
- 28 • moderately useful test: LR+ 5.0 to 10.0, LR- 0.1 to 0.2
- 29 • not a useful test: LR+ lower than 5.0, LR- higher than 0.2.

30 AUC shows true positive rate (sensitivity) as a function of false positive rate (1 minus  
31 specificity). The following cut-offs for AUC were used when determining the  
32 discriminative value of a test:

- 33 • the index test is worse than chance: lower than 0.50
- 34 • very poor: 0.50–0.60
- 35 • poor: 0.61–0.70
- 36 • moderate: 0.71–0.80
- 37 • good: 0.81–0.92
- 38 • excellent or perfect test: 0.91–1.00.

### 39 **Data synthesis and reporting for prognostic reviews**

40 The long term risks of hypertension during pregnancy were assessed with a  
41 prognostic review, including the risk of recurrent hypertension during following  
42 pregnancies. Adjusted odds ratios, relative risks and hazard ratios were reported for

1 long term outcomes (such as cardiovascular disease). The chance of recurrence of  
2 hypertensive disease in future pregnancies was assessed by considering the  
3 proportion of women who developed hypertensive disorders in subsequent  
4 pregnancies.

5 Because of variation across the studies in terms of population, the risk factor,  
6 outcome and statistical methods (including adjustments for confounding factors), the  
7 prognostic data were not pooled but results from individual studies were reported.

## 8 **Data synthesis and reporting for clinical prediction reviews**

9 The prediction of developing serious complications as a result of pre-eclampsia was  
10 assessed using a clinical prediction review, which included data from externally  
11 validated studies of clinical prediction models, as well as prognostic test accuracy  
12 data. Validation studies were conducted in different populations of women, which  
13 may lead to varying model accuracy across the studies. Therefore data were not  
14 pooled, but the results of individual validation studies are reported separately.

15 Most of the included studies reported sensitivity and specificity, positive and negative  
16 likelihood ratios. There were interpreted in a manner analogous to those for  
17 diagnostic test accuracy reviews (see above).

18 Discrimination makes reference to the tool's ability for distinguishing between who  
19 will and will not develop the outcome. This is reflected in the sensitivity and specificity  
20 of the model to identify women or babies with adverse outcomes. It is also  
21 represented by the AUC, and for this review good discrimination was defined as >  
22 0.75.

23 Calibration represents how well expected outcomes (as predicted by the model) and  
24 observed outcomes agree. This was reported as risk stratification (i.e. the percentage  
25 of women in each defined risk category who developed adverse outcomes);  
26 likelihood ratios and/or the observed:expected (O:E) ratio. Good calibration was  
27 defined as a O:E ratio between 0.8 and 1.2 (as suggested by Debray 2017). The  
28 accuracy of prediction may vary according to the risk that a model predicts. For  
29 example, a prediction model may be very accurately calibrated at the extreme levels  
30 of risk, such that a prediction of <1% gives a very precise and correct estimation of  
31 risk. However, the accuracy of the model may be reduced at other levels. Therefore  
32 likelihood ratios are calculated for each individual risk level, as reported in the  
33 articles. The following cut-offs were used when summarising the likelihood ratios for  
34 the committee:

- 35 • very informative result: LR+ higher than 10.0, LR- lower than 0.1
- 36 • moderately informative result: LR+ 5.0 to 10.0, LR- 0.1 to 0.2
- 37 • uninformative result: LR+ lower than 5.0, LR- higher than 0.2.

38 The terminology "informative result" as opposed to "useful test" was used for this  
39 review, as results from the same prediction model may be helpful (informative) or not  
40 helpful (non-informative), depending on how well the model is calibrated for that  
41 particular risk level.

42

## 1 Appraising the quality of evidence

### 2 Intervention reviews

#### 3 **GRADE methodology (the Grading of Recommendations Assessment, Development and Evaluation)**

5 For intervention reviews, the evidence for outcomes from the included studies was  
6 evaluated and presented using GRADE, which was developed by the international  
7 GRADE working group.

8 The software developed by the GRADE working group (GRADEpro) was used to  
9 assess the quality of each outcome, taking into account individual study quality  
10 factors and the meta-analysis results. The clinical evidence profile tables include  
11 details of the quality assessment and pooled outcome data, where appropriate, an  
12 absolute measure of intervention effect and the summary of the quality of evidence  
13 for that outcome. In this table, the columns for intervention and control indicate  
14 summary measures of effect and measures of dispersion (such as mean and SD or  
15 median and range) for continuous outcomes and frequency of events (n/N; the sum  
16 across studies of the number of participants with events divided by sum of the  
17 number of participants) for binary outcomes. Reporting or publication bias was taken  
18 into consideration in the quality assessment and reported in the clinical evidence  
19 profile tables if it was apparent.

20 The selection of outcomes for each review question was decided when each review  
21 protocol was discussed with the committee, and was informed by committee  
22 discussion and by key papers.

23 The evidence for each outcome in the intervention reviews was examined separately  
24 for the quality elements listed and defined in Table 2. Each element was graded  
25 using the quality levels listed in Table 3.

26 The main criteria considered in the rating of these elements are discussed below.  
27 Footnotes were used in the GRADE profiles to describe reasons for grading a quality  
28 element as having serious or very serious limitations. The ratings for each  
29 component were combined to obtain an overall assessment for each outcome (Table  
30 4).

31 **Table 2: Description of quality elements in GRADE for intervention reviews**

Quality element	Description
Risk of bias	Limitations in the study design and implementation may bias the estimates of the treatment effect. High risk of bias for the majority of the evidence decreases confidence in the estimate of the effect.
Inconsistency	Inconsistency refers to an unexplained heterogeneity of results or findings.
Indirectness	Indirectness refers to differences in study population, intervention, comparator and outcomes between the available evidence and the review question, such that the effect estimate is changed. This is also related to applicability or generalisability of findings.
Imprecision	Results are imprecise when studies include relatively few patients and/or few events and thus have wide confidence intervals around the estimate of the effect. Imprecision results if the confidence

Quality element	Description
	interval includes the clinically important threshold (minimally important difference – see below).
Publication bias	Publication bias is a systematic underestimate or an overestimate of the underlying beneficial or harmful effect due to selective publication of studies.

1 **Table 3: Levels of quality elements in GRADE**

Levels of quality elements in GRADE	Description
None/ no serious	There are no serious issues with the evidence.
Serious	The issues are serious enough to downgrade the outcome evidence by 1 level.
Very serious	The issues are serious enough to downgrade the outcome evidence by 2 levels.

2 **Table 4: Levels of overall quality of outcome evidence in GRADE**

Overall quality of outcome evidence in GRADE	Description
High	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low	Any estimate of effect is very uncertain.

3 **Assessing risk of bias in intervention reviews**

4 Bias is a systematic error, or a consistent deviation from the truth in the results.  
5 When a risk of bias is present the true effect can be either under- or over-estimated.

6 It should be noted that a study with a poor methodological design does not  
7 automatically imply high risk of bias; the bias is considered individually for each  
8 outcome and it is assessed whether this poor design will impact on the estimation of  
9 the intervention effect.

10 For systematic reviews of RCTs the AMSTAR checklist was used to assess risk of  
11 bias. For RCTs the Cochrane risk of bias tool for RCTs was used and for  
12 observational studies the Newcastle-Ottawa scale was used (see Appendix H in  
13 [Developing NICE guidelines: the manual 2014](#)). The review on postnatal  
14 management of hypertension included a number of case series, and the quality of  
15 these articles was assessed using the Institute of Health Economics checklist for  
16 case series (Moga 2012).

17

## 1 **Assessing inconsistency in intervention reviews**

2 Inconsistency refers to unexplained heterogeneity of results of meta-analysis. When  
3 estimates of the treatment effect vary widely across studies (that is, there is  
4 heterogeneity or variability in results), this suggests true differences in underlying  
5 effects. Inconsistency is, thus, only applicable when statistical meta-analysis is  
6 conducted (that is, results from different studies are pooled). For outcomes derived  
7 from a single study 'no serious inconsistency' was used when assessing this domain,  
8 as per GRADE methodology (Santesso 2016).

9 Statistical heterogeneity was assessed by visually examining the forest plots, and by  
10 considering the chi-squared test for significance at  $p < 0.1$  or an I-squared  
11 inconsistency statistic. Where considerable heterogeneity was present (an I-squared  
12 value of 50% or more), predefined subgroup analyses were performed. In the case of  
13 unexplained heterogeneity, possible causes were discussed with the committee  
14 before the final decision to pool data or not was made.

15 When no plausible explanation for the heterogeneity could be found, the quality of  
16 the evidence was downgraded in GRADE by 1 or 2 levels for the domain of  
17 inconsistency, depending on the extent of heterogeneity in the results (>50% or  
18 >75%).

## 19 **Assessing indirectness in intervention reviews**

20 Directness refers to the extent to which the populations, intervention, comparisons  
21 and outcome measures are similar to those defined in the inclusion criteria for the  
22 reviews. Indirectness is important when these differences are expected to contribute  
23 to a difference in effect size, or may affect the balance of harms and benefits  
24 considered for an intervention.

## 25 **Assessing imprecision and clinical significance in intervention reviews**

26 Imprecision in guidelines concerns whether the uncertainty (CI) around the effect  
27 estimate means that it is not clear whether there is a clinically important difference  
28 between interventions or not (that is, whether the evidence would clearly support one  
29 recommendation or appear to be consistent with several different types of  
30 recommendations). Therefore, imprecision differs from the other aspects of evidence  
31 quality because it is not really concerned with whether the point estimate is accurate  
32 or correct (has internal or external validity). Instead, it is concerned with the  
33 uncertainty around the point estimate. This uncertainty is reflected in the width of the  
34 CI.

35 The 95% CI is defined as the range of values within which the mean value will fall on  
36 95% of repeated samples, were this procedure to be repeated. The larger the trial,  
37 the smaller the 95% CI and the more certain the effect estimate.

38 Imprecision in the evidence reviews is assessed by considering whether the width of  
39 the 95% CI of the effect estimate is relevant to decision-making, taking each outcome  
40 in isolation. This assessment also involves effect size thresholds for clinical  
41 importance (the minimally important difference, MID) for benefit and for harm.

42 If the effect estimate CI includes clinically important benefit (or harm) there is  
43 uncertainty over which decision to make (based on this outcome alone). The CI is

1 consistent with 2 possible decisions and so this is considered to be imprecise in the  
2 GRADE analysis and the evidence is downgraded by 1 level ('serious imprecision').

3 An effect CI including clinically important benefit, clinically important harm and no  
4 effect is consistent with 3 possible decisions. This is considered to be very imprecise  
5 in the GRADE analysis and the evidence is downgraded by 2 levels ('very serious  
6 imprecision').

### 7 **Minimally important differences**

8 The literature was searched for established MIDs for the selected outcomes in the  
9 evidence reviews. In addition, the committee was asked whether they were aware of  
10 any acceptable MIDs in the clinical community.

11 If no published or acceptable MIDs were identified, the committee considered  
12 whether it was clinically acceptable to use the GRADE default MIDs to assess  
13 imprecision. For binary outcomes, the MIDs of RRs of 0.80 and 1.25 were used. For  
14 continuous outcomes, GRADE default MIDs are half of the baseline SD of the control  
15 group. As no published MID values were identified, the committee agreed that  
16 GRADE default MID values were to be used as a starting point for all outcomes and  
17 any exception to their application based on the committee's consideration of clinical  
18 acceptability were noted and explained in the evidence review.

### 19 **Diagnostic accuracy reviews**

#### 20 **Modified GRADE methodology for diagnostic test accuracy reviews**

21 The GRADE approach was modified to assess the quality of evidence about  
22 diagnostic test accuracy by adapting the principles of GRADE for intervention  
23 reviews as described below. Four domains were considered: risk of bias,  
24 indirectness, inconsistency and imprecision. Each domain was rated as 'no serious',  
25 'serious' or 'very serious'. These domains were then combined to give the overall  
26 certainty in the body of evidence, rated as 'very low', 'low', 'moderate' or 'high'.

#### 27 **Assessing risk of bias in diagnostic test accuracy reviews**

28 Risk of bias in diagnostic test accuracy studies was assessed using the risk of bias  
29 items from the QUADAS-2 checklist (see appendix H in [Developing NICE guidelines:  
30 the manual 2014](#)). An overall risk of bias judgement was for each study was reached  
31 by considering the QUADAS-2 bias domains together. The risk of bias for the body of  
32 diagnostic test accuracy evidence was based on the risk of bias from the individual  
33 studies but with consideration of how much each study contributed to the overall  
34 evidence base.

#### 35 **Assessing indirectness in diagnostic test accuracy reviews**

36 Indirectness was assessed using the applicability items from the QUADAS-2  
37 checklist. An overall indirectness judgement was for each study was reached by  
38 considering the QUADAS-2 applicability domains together. The indirectness for the  
39 body of diagnostic test accuracy evidence was based on the indirectness of the  
40 individual studies but with consideration of how much each study contributed to the  
41 overall evidence base.

1 **Assessing inconsistency in diagnostic test accuracy reviews**

2 Where the results of multiple studies were pooled for meta-analysis, inconsistency  
3 was assessed using the  $I^2$  value, in a manner analogous to that for intervention  
4 reviews (high inconsistency with an  $I^2 > 50\%$ , very high inconsistency with an  $I^2 > 75\%$ ).  
5 If studies were not pooled then inconsistency was rated as “no serious  
6 inconsistency”.

7 **Assessing imprecision in diagnostic test accuracy reviews**

8 Imprecision was judged by comparing the CI of the estimate of sensitivity or  
9 specificity to clinical decision thresholds agreed beforehand by the committee. The  
10 committee decided whether sensitivity or specificity was the most important for  
11 decision making and agreed two threshold values. First a threshold for high  
12 sensitivity/specificity (above which the test would be definitely recommended) and  
13 second a threshold for low sensitivity/specificity (below which the test would not be  
14 recommended). If the CI of the estimate of sensitivity or specificity included one of  
15 these thresholds then the evidence was downgraded for serious imprecision,  
16 because it was consistent with two possible decisions. If the CI included both these  
17 thresholds then the evidence was downgraded for very serious imprecision because  
18 it was consistent with three possible decisions.

19 **Prognostic reviews**

20 **GRADE methodology for prognostic reviews**

21 The GRADE approach was not used to assess the quality of evidence for prognostic  
22 reviews. Quality assessment of outcomes was based upon risk of bias assessment  
23 for outcomes from individual studies.

24 **Assessing risk of bias in prognostic reviews**

25 Risk of bias in individual prognostic studies was assessed using the risk of bias items  
26 from the QUIPS checklist (see appendix H in Developing NICE guidelines: the  
27 manual 2014). An overall risk of bias judgement for each study was reached by  
28 considering the QUIPS bias domains together.

29 **Clinical prediction model reviews**

30 **GRADE methodology for clinical prediction model reviews**

31 The GRADE approach was not used to assess the quality of evidence for clinical  
32 prediction model reviews. Quality assessment of outcomes was based upon the risk  
33 of bias assessment for individual studies. A modified GRADE approach was used to  
34 assess the quality of evidence regarding prognostic test accuracy by adapting the  
35 principles of GRADE for diagnostic accuracy reviews, as described above. Four  
36 domains were considered: risk of bias, indirectness, inconsistency and imprecision.  
37 Each domain was rated as ‘no serious’, ‘serious’ or ‘very serious’. These domains  
38 were then combined to give the overall certainty in the body of evidence, rated as  
39 ‘very low’, ‘low’, ‘moderate’ or ‘high’.

40

## 1 **Assessing risk of bias in clinical prediction model reviews**

2 Risk of bias in individual clinical prediction studies was assessed using the risk of  
3 bias items from the CASP checklist (see appendix H in Developing NICE guidelines:  
4 the manual 2014). An overall risk of bias judgement for each study was reached by  
5 considering the CASP bias domains together.

6

## 7 **Evidence statements**

8 Evidence statements are summary statements presented in each evidence review  
9 highlighting the key features of the clinical evidence presented. The wording of the  
10 evidence statements reflects the certainty or uncertainty in the estimate of effect. The  
11 evidence statements are presented by outcome or theme and encompass the  
12 following key features of the evidence:

- 13 • the quality of the evidence
- 14 • the number of studies and the number of participants for a particular outcome or a  
15 particular risk factor or theme
- 16 • the clinical importance of the effect and an indication of its direction (for example,  
17 if a treatment is clinically important (beneficial or harmful) compared with another,  
18 or whether there is no clinically important difference between the tested  
19 treatments), or a summary of the effect size of the prognostic factor or accuracy of  
20 a diagnostic test.

## 21 **Economic evidence**

22 The aim of the health economic input to the guideline was to inform the committee of  
23 potential economic issues related to hypertension in pregnancy and to ensure that  
24 recommendations represented a cost effective use of healthcare resources. Health  
25 economic evaluations aim to integrate data on healthcare benefits (ideally in terms of  
26 quality-adjusted life-years (QALYs)) with the costs of different care options. In  
27 addition, the health economic input aimed to identify areas of high resource impact.  
28 These are recommendations which might have a large impact on Clinical  
29 Commissioning Groups' or Trusts' finances and so need special attention.

## 30 **Reviewing economic evidence**

31 The titles and abstracts of papers identified through the searches were independently  
32 assessed for inclusion using predefined eligibility criteria summarised in Table 5.

### 33 **Table 5: Inclusion and exclusion criteria for the systematic reviews of** 34 **economic evaluations**

Inclusion criteria
Studies from Organisation for Economic Co-operation and Development (OECD) countries were included, as the aim of the review was to identify economic information transferable to the UK context.
Study population matches scope.
Clinical condition and interventions assessed identical to those considered in the clinical evidence review.

#### Inclusion criteria

Studies include sufficient details regarding methods and results to enable methodological quality to be assessed and results to be extracted.

Full economic evaluations (cost utility, cost effectiveness, cost benefit or cost consequence analyses) that assess both the costs and outcomes associated with the interventions of interest.

#### Exclusion criteria

Conference abstracts, poster presentations or dissertation abstracts with insufficient methodological details

Cost-of-illness type studies

Non-English language study

1 Once the screening of titles and abstracts was complete, full versions of the selected  
2 papers were acquired for assessment. The applicability and quality of evidence was  
3 assessed using the economic evaluations checklist as specified in [Developing NICE](#)  
4 [guidelines: the manual 2014](#). The economic evidence study selection for each  
5 question is presented in appendix G of the evidence report. Existing economic  
6 evidence considered in the guideline is provided in the respective evidence chapters.

## 7 Health economic modelling

8 As well as reviewing the published economic literature, as described above, new  
9 economic analysis was undertaken in selected areas prioritised by the committee in  
10 conjunction with the health economist. Topics were prioritised on the basis of the  
11 following criteria, in accordance with [Developing NICE guidelines: the manual 2014](#):

- 12 • the overall importance of the recommendation, which may be a function of the  
13 number of people affected and the potential impact on costs and health outcomes  
14 per patient
- 15 • the current extent of uncertainty over cost effectiveness, and the likelihood that  
16 economic analysis will reduce this uncertainty
- 17 • the feasibility of building an economic model.

18 The committee prioritised the following review questions where it was thought that  
19 economic considerations would be particularly important in formulating  
20 recommendations:

- 21 • Question 3. Which tests or clinical prediction models are accurate in identifying or  
22 predicting women at risk of severe complications from pre-eclampsia?

23 The full methods and results of de novo economic analyses are reported in appendix  
24 J of the evidence report. When new economic analysis was not prioritised, the  
25 committee made a qualitative judgement regarding cost effectiveness by considering  
26 existing economic evidence, expected differences in resource and cost use between  
27 options, alongside clinical effectiveness evidence identified from the clinical evidence  
28 review.

## 29 Cost effectiveness criteria

30 NICE's report [Social value judgements: principles for the development of NICE](#)  
31 [guidance](#) sets out the principles that committees should consider when judging  
32 whether an intervention offers good value for money. In general, an intervention was

1 considered to be cost effective if any of the following criteria applied (given that the  
2 estimate was considered plausible):

- 3 • the intervention dominated other relevant strategies (that is, it was both less costly  
4 in terms of resource use and more clinically effective compared with all the other  
5 relevant alternative strategies), or
- 6 • the intervention cost less than £20,000 per QALY gained compared with the next  
7 best strategy, or
- 8 • the intervention provided clinically significant benefits at an acceptable additional  
9 cost when compared with the next best strategy.

10 The committee's considerations of cost effectiveness are discussed explicitly under  
11 the 'Cost effectiveness and resource use' headings of the relevant sections. When  
12 new economic analysis was not prioritised and when no existing economic evidence  
13 was available, the committee made a qualitative judgement regarding cost  
14 effectiveness by considering expected differences in resource and cost use between  
15 options, alongside clinical effectiveness evidence identified from the clinical evidence  
16 review.

## 17 **Developing recommendations**

### 18 **Updating existing recommendations**

19 Although a number of sections of the 2010 guideline had not been prioritised for  
20 updating by the NICE surveillance report, the committee identified a number of  
21 recommendations in these sections where practice had changed, new technology  
22 had become available, or health policy had changed. In addition the committee  
23 identified a number of recommendations which were not written in the current NICE  
24 style or terminology. As part of the update process the committee therefore reviewed  
25 the sections of the guideline which were not being formally updated and made minor  
26 edits to some of the recommendations to improve clarity, ensure they reflected  
27 current best practice, or correct recommendations that no longer were applicable.  
28 These changes are clearly marked in yellow in the guideline version for consultation,  
29 and the changes and reasons for them summarised in Table 2 of the update  
30 information at the end of the guideline.

### 31 **Guideline recommendations**

32 Recommendations were drafted on the basis of the committee's interpretation of the  
33 available evidence, taking into account the balance of benefits, harms and costs  
34 between different courses of action. When clinical and economic evidence was of  
35 poor quality, conflicting or absent, the committee drafted recommendations based on  
36 the members' expert opinion. The considerations for making consensus-based  
37 recommendations include the balance between potential harms and benefits, the  
38 economic costs or implications compared with the economic benefits, current  
39 practices, recommendations made in other relevant guidelines, patient preferences  
40 and equality issues.

41 The main considerations specific to each recommendation are outlined under the  
42 'The committee's discussion of the evidence' headings within each chapter as well as  
43 the 'rationale and impact' section in the short guideline.

1 For further details please refer to [Developing NICE guidelines: the manual 2014](#).

## 2 Research recommendations

3 When areas were identified for which good evidence was lacking, the committee  
4 considered making recommendations for future research. For further details please  
5 refer to [Developing NICE guidelines: the manual 2014](#).

## 6 Updating definitions

7 The previous clinical guideline, published in 2010, contained a list of definitions for  
8 conditions included in the guideline. These included definitions for chronic  
9 hypertension, eclampsia, gestational hypertension, pre-eclampsia and severe pre-  
10 eclampsia. These definitions had been agreed by the 2010 guideline committee were  
11 based on the committee's consensus. On commencement of the guideline update it  
12 was noted that the definition of pre-eclampsia contained in this list of definitions are  
13 not in line with the most recent definition of pre-eclampsia developed by the  
14 International Society for the Study of Hypertension in Pregnancy (ISSHP) (Brown  
15 2018). The committee agreed that the ISSHP definition was widely accepted in  
16 clinical practice and that having a different definition in the NICE guideline could lead  
17 to inconsistency and confusion amongst UK clinicians.

18 The 2010 guideline used only the presence of hypertension and proteinuria to define  
19 pre-eclampsia, without reference to systemic features of the disease. All other major  
20 international definitions recognise the multisystem nature of pre-eclampsia and have  
21 broadened their criteria to reflect multi-organ involvement in the clinical presentation  
22 in line with the ISSHP (American, Canadian, Australasian society definitions). There  
23 is currently a lack of clarity for health care professionals, as both the narrower NICE  
24 definition and the wider international definitions incorporating multisystem features  
25 are used variably in clinical practice. There is similar lack of clarity for women who  
26 may hear mixed messages and access conflicting information on the internet. It is  
27 likely that women with multi-organ features (e.g. kidney injury, liver dysfunction,  
28 clotting abnormalities) are at similar (if not higher) risk of adverse pregnancy  
29 outcomes, compared to those with proteinuria alone.

30 The committee discussed the differences between the two definitions which are  
31 summarised in Table 6.

32 **Table 6: Comparison of NICE and ISSHP definitions of pre-eclampsia and**  
33 **severe pre-eclampsia**

Condition	NICE definition <sup>a</sup>	ISSHP definition <sup>b,c</sup>
Pre-eclampsia	<p>New hypertension presenting after 20 weeks with significant proteinuria.</p> <ul style="list-style-type: none"> <li>Significant proteinuria: urinary protein:creatinine ratio &gt; 30 mg/mmol or a validated 24-hour urine collection result shows &gt; 300 mg protein.</li> <li>Degrees of hypertension:</li> </ul>	<p>New onset of hypertension (&gt;140 mmHg systolic or &gt;90 mmHg diastolic) after 20 weeks gestation and the coexistence of one or more of the following new-onset conditions:</p> <ol style="list-style-type: none"> <li>Proteinuria (spot urine protein/creatinine &gt;30 mg/mmol [0.3 mg/mg] or &gt;300 mg/day or at least 1 g/L [2 + ] on dipstick testing) OR</li> <li>Other maternal organ dysfunction:</li> </ol>

Condition	NICE definition <sup>a</sup>	ISSHP definition <sup>b,c</sup>
	<ul style="list-style-type: none"> <li>○ Mild: Diastolic blood pressure 90–99 mmHg, systolic blood pressure 140–149 mmHg.</li> <li>○ Moderate: Diastolic blood pressure 100–109 mmHg, systolic blood pressure 150–159 mmHg.</li> <li>○ Severe: Diastolic blood pressure ≥ 110 mmHg, systolic blood pressure ≥ 160 mmHg.</li> </ul>	<ul style="list-style-type: none"> <li>• renal insufficiency (creatinine ≥90 umol/L; 1mg/dL)</li> <li>• liver involvement (elevated transaminases – ALT or AST &gt;40 IU/L ± right upper quadrant or epigastric abdominal pain)</li> <li>• neurological complications (such as eclampsia, altered mental status, blindness, stroke, clonus, severe headaches, persistent visual scotomata)</li> <li>• haematological complications (thrombocytopenia – platelet count below 150,000/μL, DIC, haemolysis) OR</li> </ul> <p>3. Uteroplacental dysfunction (such as fetal growth restriction, abnormal umbilical artery (UA) Doppler waveform analysis, or stillbirth)</p>
Severe pre-eclampsia	Pre-eclampsia with severe hypertension and/or with symptoms, and/or biochemical and/or haematological impairment.	<p>No clinical distinction made between mild and severe pre-eclampsia in usual clinical practice. Instead, all cases of pre-eclampsia should be treated in the knowledge that the condition can change rapidly. Clinical findings that warrant closer attention include:</p> <ul style="list-style-type: none"> <li>• ongoing or recurring severe headaches</li> <li>• visual scotomata,</li> <li>• nausea/ vomiting, epigastric pain, oliguria</li> <li>• severe hypertension</li> <li>• progressive derangements in laboratory tests such as rising creatinine or liver transaminases or falling platelet count</li> <li>• failure of fetal growth or abnormal Doppler findings.</li> </ul>

- 1 (a) NICE clinical guideline 107, 2010  
2 (b) Brown 2018  
3 (c) Tranquilli 2013  
4

- 5 The committee discussed the adoption of the ISSHP definition in preference to the  
6 existing NICE definition and took into account two aspects when making this  
7 decision:
- 8 • What are the implications of adopting the ISSHP definition on the existing
  - 9 recommendations in the guideline, including those which were not being updated?
  - 10 • Was the methodology behind the development of the ISSHP definitions at least as
  - 11 robust as the development of the NICE definitions?

1 **Implications of updating the 2010 NICE definition to be in accordance with the**  
2 **ISSHP definition**

3 Studies for inclusion in the 2010 NICE guideline were selected if they included  
4 'women with pre-eclampsia' and the individual definitions used in each paper were  
5 not specified. Many studies in the literature reviewed in the NICE 2010 guidance did  
6 not state the definition used and as the ISSHP definition had been published in 2001,  
7 some studies conducted after this date would likely have utilised this ISSHP  
8 definition. Women who meet the ISSHP definition largely overlap with those meeting  
9 the NICE 2010 definition. However, the ISSHP definition also includes an additional  
10 small subset of women who have multi-organ features at presentation without  
11 proteinuria; the large majority of whom go on to develop proteinuria during the course  
12 of their disease. The implications of this is that there is no group of women identified  
13 by the ISSHP multi-organ definition to whom the recommendations made in 2010  
14 guidance would not apply, as all definitions describe a single entity of 'pre-  
15 eclampsia', which has been recognised as a multi-organ disease since 1993  
16 (Roberts 1993). This has been variably described by definitions over the decades but  
17 now has international consensus for the current multi-organ definition.

18 ***Pre-eclampsia***

19 As studies included in the NICE 2010 guideline refer to 'women with pre-eclampsia'  
20 using a range of definitions (or no specific definition), the committee proposed that  
21 guidance for women with pre-eclampsia applies equally to all women who meet the  
22 ISSHP definition of the disease. Current NICE 2010 guidance already requires  
23 assessment of all of the features highlighted in the multi-organ criteria for the ISSHP  
24 definition and therefore there is no indication for changing the assessment  
25 recommendation. In addition, all aspects of the care pathways in the 2010 full  
26 guidance are valid with this ISSHP definition and do not require change.

27 ***Severe pre-eclampsia***

28 Current NICE 2010 guidance refers to 'severe pre-eclampsia', defined only as 'pre-  
29 eclampsia with severe hypertension and/or with symptoms, and/or biochemical  
30 and/or haematological impairment', without specifying thresholds. Table 7 shows that  
31 these features align with those listed in the ISSHP guidance (Tranquilli 2013).

32 **Table 7: Comparison of NICE and ISSHP features of severe pre-eclampsia**

NICE features <sup>a</sup>	ISSHP features <sup>b,c</sup>
severe hypertension and proteinuria	severe hypertension (and another feature)
symptoms	ongoing or recurring severe headaches, visual scotomata
biological impairment	nausea/ vomiting, epigastric pain, progressive derangements in laboratory tests such as rising creatinine rising liver transaminases
haematological impairment	falling platelet count

33 (a) NICE clinical guideline 107, 2010

34 (b) Brown 2018

35 (c) Tranquilli 2013

1 With this degree of correlation, if the ISSHP definition for severe pre-eclampsia was  
2 adopted, the same care pathways would apply as are currently recommended in the  
3 2010 NICE guideline.

#### 4 **Methodology behind the development of the ISSHP definitions**

5 The introduction to the 'Development of the guideline' section of the 2010 full  
6 guideline acknowledges that the definitions used are 'broadly consistent with those  
7 agreed by the International Society for the Study of Hypertension in Pregnancy  
8 (ISSHP), and further acknowledges that 'although the definition of pre-eclampsia  
9 used in this guideline requires significant proteinuria, pre-eclampsia is a clinical  
10 syndrome and both clinical signs and symptoms and haematological or biochemical  
11 abnormalities can occur in the absence of significant proteinuria.'

12 It is unclear why the committee for the 2010 guideline did not adopt the ISSHP  
13 criteria in full, but instead elected to use the narrower definition of pre-eclampsia, as  
14 the process behind this is not described in the guideline itself or the committee  
15 meeting minutes. There is no documentation of any formal consensus process to  
16 produce the modified definitions.

17 In order to assess the robustness of the process used to develop the ISSHP  
18 guideline, the Appraisal of Guidelines for Research and Evaluation (AGREE II)  
19 instrument was used. The assessment was carried out by 2 members of the NGA  
20 technical team and the scores led to overall quality ratings for the 6 domains of the  
21 instrument ranging from 6% to 75% (a nominal value of  $\geq 70\%$  is usually deemed to  
22 represent high quality). However, although these ratings are low, the development of  
23 the definitions by a consensus group of expert clinicians is more robust and  
24 transparent than the process used for the 2010 guideline.

25 In addition to the use of the AGREE II instrument, the change in disease definition  
26 was reviewed using the checklist developed by Doust (Doust 2017). This is a  
27 checklist of items to consider when modifying a disease definition and the results of  
28 this review are shown in Table 8.

29 **Table 8: Checklist of items to consider when modifying a disease definition**

Checklist item	Outcome
Definition: What are the differences between the previous and the new definition?	The ISSHP definition includes a wider range of conditions that co-exist with hypertension and does not limit the co-existing condition to just proteinuria.
Number of people affected: How will the new disease definition change the incidence and prevalence of the disease?	There may be an increase in the number of women diagnosed as having pre-eclampsia as the ISSHP definition is broader.
Trigger: What is the trigger for considering the modification of the disease definition?	Confusion between clinicians as the NICE guideline recommendations to treat pre-eclampsia rely on a definition which is different to the ISSHP definition.
Prognostic ability: How well does the new definition of disease predict clinically important outcomes compared with the previous definition?	The co-existing conditions included in the ISSHP definition are important markers of the severity of the disease and the likelihood of women experiencing complications.

Checklist item	Outcome
Disease definition, precision and accuracy: What is the repeatability, reproducibility, and accuracy (when estimations are possible) of the new disease definition?	The ISSHP definition includes clearly defined biochemical and haematological and ultrasound parameters so is likely to lead to an accurate and reliable diagnosis.
Benefit: What is the incremental benefit for patients classified by the new definition versus the previous definition?	The ISSHP definition will allow women who have onset of hypertension after 20 weeks, with other clinical signs but not proteinuria to enter the treatment pathway for pre-eclampsia. Early identification and treatment of these women may reduce the likelihood of severe complications of pre-eclampsia.
Harm: What is the incremental harm for patients classified by the new definition versus the previous definition?	No harms have been identified.
Net benefit and harms: What is the net benefit and harm for patients classified by the new definition versus the previous definition?	The new definition will reduce confusion amongst women and clinicians, allow earlier identification of some women with pre-eclampsia and may reduce the likelihood of severe complications of pre-eclampsia.

## 1 Summary and conclusions

2 The committee agreed that the options for the update of the definition of pre-  
3 eclampsia were:

- 4 • Make no change from 2010 guidance - but clinical colleagues and members of the  
5 committee have confirmed that the ongoing confusion is unhelpful
- 6 • Follow the approach taken in 2010 in relation to implementation of the ISSHP  
7 definition, but with unmodified rather than selective adoption of the definition

8 The committee concluded that, based on their discussions, their review of the  
9 differences between the definitions and the likely impact on the guideline, it was  
10 reasonable to follow the second of these approaches and adopt the ISSHP definition  
11 of pre-eclampsia.

## 12 Validation process

13 This guidance is subject to a 6-week public consultation and feedback as part of the  
14 quality assurance and peer review of the document. All comments received from  
15 registered stakeholders are responded to in turn and posted on the NICE website at  
16 publication. For further details please refer to [Developing NICE guidelines: the  
17 manual 2014.](#)

## 18 Updating the guideline

19 Following publication, and in accordance with the NICE guidelines manual, NICE will  
20 undertake a review of whether the evidence base has progressed significantly to alter  
21 the guideline recommendations and warrant an update. For further details please  
22 refer to [Developing NICE guidelines: the manual 2014.](#)

## 1 **Funding**

- 2 The NGA was commissioned by NICE to develop this guideline.

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