Project plan:

Safety, clinical effectiveness, diagnostic accuracy and cost effectiveness of blood-based tests for women with suspected pre-eclampsia

Project number	ID2018_49
Plan prepared :	12.04.2019

Short description and summary

The aim of this Health Technology Assessment (HTA) is to evaluate safety, effectiveness, diagnostic accuracy and cost-effectiveness of blood-based tests for women with suspected pre-eclampsia after 20 weeks' gestation. The commissionaire of this HTA is the Commissioning Forum.

Short title

Tests for pre-eclampsia

Project category and commissioner	
Product (program area)	Health Technology Assessment
Thematic areas	Diagnostic tests Pregnancy Pre-eclampsia Health Technology Assessment (HTA)
Commissioner:	Commissioning Forum (Bestillerforum RHF), consisting of four medical directors representing each of the Regional Health Authorities, and two delegates from the Norwegian Directorate of Health. The Forum's mandate is to prioritize HTA topics based on submitted proposals and horizon scanning reports.
Project management and participants	
Project manager	Hilde T. Myrhaug (HTM)
Responsible for the project	Øyvind Melien (ØM)
Internal project participants	Liv Merete Reinar (LMR) Anna Stoinska-Schneider (AS-S)

	Gyri H. Straumann (GHS) Espen Movik (EM) Signe Flottorp (SF) Kjetil G. Brurberg (KGB)
External project participants	Annetine Staff (Professor at the University of Oslo and Head of research and Consultant physician at the Division of Gynaecology and Obstetrics, Oslo University Hospital) Kjell Åsmund Salvesen (Head of Department of Obstetrics and Gynaecology, St. Olavs Hospital, and professor at Department of Clinical and Molecular Medicine, Norwegian University of Science and Technology) Kristin Viste (Consultant physician/clinical chemist, Hormone Laboratory, Haukeland University Hospital) Tor A. Hervig (Professor, Institute of Clinical Science, University of Bergen and Senior consultant Haugesund Hospital), Øyvin H. Eng (Consultant physician/clinical chemist at Department of Medical Biochemistry, Stavanger University Hospital)
Plan for replacement by project participants' absence	The person responsible for the project will replace the project participants when needed
Internal reviewers	Per M. Magnus and Signe Flottorp
External reviewers	For the project plan: Annetine Staff, Kjell Åsmund Salvesen, Kristin Viste and Tor A. Hervig For the HTA: Will be decided later

Mandate

Commissioning Forum representing the four Regional Health Authorities (Bestillerforum RHF in Norwegian) requested a Health Technology Assessment (HTA) from the Norwegian Institute of Public Health (Folkehelseinstituttet) within the National System for Managed Introduction of New Health Technologies within the Specialist Health Service in Norway (Nye Metoder). The aim of this HTA is to evaluate safety, effectiveness, diagnostic accuracy and cost-effectiveness of blood-based tests for pre-eclampsia. The project was initiated as a proposal for a single technology assessment from one of the manufacturers (Roche Diagnostics Norway). However, as multiple manufacturers were identified, it was converted into a full HTA (1). The mandate does not include evaluation of these tests for screening or for routinely testing of high risk groups in early pregnancy, according to the decision and clarification made by the Commissioning Forum on the 18th of March 2019 (2).

Objective

The objective of this HTA is to summarize and evaluate safety, effectiveness, diagnostic accuracy, cost-effectiveness and to calculate budgetary consequences of implementation of blood-based tests for predicting pre-eclampsia in gestational week 20 to 36 (+6 days) among pregnant women, where the syndrome is suspected, but not confirmed by clinical signs and findings. The blood-based tests for pre-eclampsia include Elecsys sFlt-1 & PIGF (Preeclampsia), Triage PIGF-test, DELFIA Xpress PIGF 1-2-3 test, BRAHMS sFlt-1 Kryptor/BRAHMS PIGF-pluss Kryptor PE ratio or other relevant blood-based tests for predicting pre-eclampsia after 20 weeks' gestation.

Background

Two to eight percent of pregnant women are diagnosed with pre-eclampsia worldwide (3). Pre-eclampsia has traditionally been characterised by new onset high blood pressure and proteinuria after gestational week 20. The definition of pre-eclampsia has however been altered over the last years, in recognition of the syndromic nature of pre-eclampsia. Proteinuria is therefore no longer a mandatory requirement for a pre-eclampsia definition in many updated guidelines like the guidelines from International Study of Hypertension in Pregnancy (ISSHP) (4) and the American College of Obstetrician and Gynecologists (ACOG) (5). These guidelines (which will also be reflected in the 2019 revised "Veilederen i Obstetrikk" of the Norwegian Society for Gynecology and Obstetrics, personal communication with Annetine Staff, the responsible chapter editor), therefore define pre-eclampsia as new onset hypertension arising after 20 weeks' gestation (Gestational hypertension) accompanied by one or more of the following new onset signs after 20 weeks' gestation:

1) Proteinuria
2) Other signs of maternal organ dysfunction, including one or more of the following:
    - Liver involvement (elevated transaminases, e.g. ALT or AST)
    - Neurological complications (e.g. eclampsia, stroke, persistent visual scotomata)
    - Hematological complications (thrombocytopenia, Disseminated Intravascular Coagulation; hemolysis)
    - Uteroplacental dysfunction (e.g. fetal growth restriction, stillbirth, abnormal fetal Doppler findings). This feature is however not included as a criteria for diagnosing pre-eclampsia in most medical birth registries and many national clinical guidelines, such as the ACOG (5).

Symptoms and signs of pre-eclampsia include strong headache, visual disturbance, epigastric pain, swelling of the hands, face or feet and low output of urine. Pre-eclampsia is potentially a life-threatening condition that requires hospital admission and close maternal and fetal monitoring. It may develop rapidly to seizures (eclampsia), HELLP syndrome (haemolysis, evaluated liver enzymes and low platelets), stroke (increased risk of cerebral haemorrhage due to maternal hypertension), disseminated intravascular coagulation and organ failure.

Current national and international guidelines recommend to induce delivery when a woman with pre-eclampsia has reached 37 gestational weeks, in order to avoid the severe complications mentioned above. In severe pre-eclampsia, with threatening maternal and/or fetal signs, delivery is effectuated when necessary at any gestational week. In Norway, 1/3 of all pre-eclamptic pregnancies are delivered preterm, often with a growth-restricted child, indicative of a more severe and premature placenta dysfunction in early-onset pre-eclampsia (6).

In Norway, women with expected normal pregnancies are offered eight consultations including ultrasound screening in second trimester, at gestational week 17-20 according to national guidelines for antenatal care (7). Most women attend more consultations and ultrasound examinations during pregnancy (8). At each consultation, assessments of blood pressure and testing of proteinuria by midwife or general practitioner are standard clinical assessments to identify pre-eclampsia. Risk factors for pre-eclampsia such as previous severe pre-eclampsia, chronic hypertension, renal disease (including renal transplantation), assisted reproductive therapies, diabetes mellitus, BMI>35, multiple pregnancies, or age > 40 years are evaluated at the first consultation. Pregnant women at high risk of developing pre-eclampsia are referred to specialist health care services for closer follow up (6), but any doctor in Norway is advised to recommend pre-eclampsia prophylaxis with low-dose oral aspirin in women deemed at high risk of developing pre-eclampsia, e.g. 75 mg daily until delivery (any gestational week) (9). At the moment, it is still unclear which groups will benefit the most of such prophylaxis, and whether the optimal dose is higher than the one previously recommended in Norway and UK (10). There is a general agreement that such prophylaxis should be started prior to gestational week 16 (and usually recommended from gestational week 12).

Different blood-based tests like Elecsys sFlt-1 & PIGF (Preeclampsia), Triage PIGF-test, DELFIA Xpress PIGF 1-2-3 test, BRAHMS sFlt-1 Kryptor/BRAHMS PIGF-pluss Kryptor PE ratio have been developed to predict suspected pre-eclampsia.

An initial search for relevant systematic reviews on the topic of effectiveness and/or diagnostic accuracy of blood-based tests to predict suspected pre-eclampsia yielded three systematic reviews published in 2015 (11), 2017 (12), and 2018 (13). Wu et al (11) assessed the accuracy of biomarkers for predicting pre-eclampsia in first and early second trimester of pregnancy.
The literature searches in the two last reviews (12,13) that also assessed the accuracy of biomarkers for predicting pre-eclampsia were performed August 2017 and June 2017 respectively. We found one randomised controlled trial on the effectiveness of angiogenic factors (such as PlGF) in pregnant women from 2019 (14). This study informed about two ongoing studies with estimated completion dates within December 2019[1]. In addition, we identified a diagnostics guidance from NICE published May 2016 (15). The NICE guidance is based on a HTA report (systematic review and health economic analysis) also published in 2016 (16). NICE recommends the use of Triage PIGF test and Elecsys immunoassay sFlt-1/PIGF ratio including standard clinical assessment and subsequent clinical follow-up to help rule out pre-eclampsia in women presenting with suspected pre-eclampsia in second and third trimester (15). However, NICE do not recommend these tests for predicting/diagnosing pre-eclampsia, due to current lack of sufficient evidence. NICE also has a guideline on hypertension in pregnancy, which covers diagnosing and managing hypertension including pre-eclampsia (17). NICE revised their guideline in January 2017, and is updating some of the chapters, including the chapter on management (but not on diagnosis) of pre-eclampsia. The updated chapters are expected to be published in June 2019 (17).

There exist some systematic reviews on the safety, effectiveness, diagnostic accuracy, and cost-effectiveness of these blood-based tests for predicting pre-eclampsia in gestational week 20 to 36 (+6 days) among pregnant women (11-16). Most importantly, we have data from one randomised trial, and information from two ongoing randomised trials will probably be available within a year. The results of these studies will probably provide better evidence to inform the decision on the use of tests in women with suspected pre-eclampsia. Therefore, we aim to conduct a systematic review, consider updating a systematic review or disseminate results from systematic reviews based on these research questions:

1. What is the safety and effectiveness of Elecsys immunoassay sFlt-1/PlGF ratio, Triage PIGF-test, DELFIA Xpress PIGF 1-2-3 test, BRAHMS sFlt-1 Kryptor/BRAHMS PIGF-pluss Kryptor PE ratio or other relevant blood-based tests for predicting suspected pre-eclampsia in 2nd and 3rd trimester?

[1] https://clinicaltrials.gov/ct2/show/NCT02881073?cond=pre-eclampsia+AND+angiogenetic+factor+OR+placental+growth&rank=1 and https://clinicaltrials.gov/ct2/show/NCT02881073?cond=pre-eclampsia+AND+angiogenetic+factor+OR+placental+growth&rank=1

2. What is the diagnostic accuracy of Elecsys immunoassay sFlt-1/PlGF ratio, Triage PIGF-test, DELFIA Xpress PIGF 1-2-3 test, BRAHMS sFlt-1 Kryptor/BRAHMS PIGF-pluss Kryptor PE ratio or other relevant blood-based tests for predicting suspected pre-eclampsia in 2nd and 3rd trimester?
3. What is the cost-effectiveness and the budgetary consequences of implementation of the Elecsys immunoassay sFlt-1/PlGF ratio, Triage PIGF-test, DELFIA Xpress PIGF 1-2-3 test, BRAHMS sFlt-1 Kryptor/BRAHMS PIGF-pluss Kryptor PE ratio or other relevant blood-based tests for predicting suspected pre-eclampsia in 2nd and 3rd trimester?
4. What are the potential clinical benefits or side effects for the woman and her offspring in Norway if implementation of the Elecsys immunoassay sFlt-1/PlGF ratio, Triage PIGF-test, DELFIA Xpress PIGF 1-2-3 test, BRAHMS sFlt-1 Kryptor/BRAHMS PIGF-pluss Kryptor PE ratio or other relevant blood-based tests for predicting suspected pre-eclampsia in 2nd and 3rd trimester?

Methods

We will perform a systematic review, updating a systematic review or disseminate results from systematic reviews on safety and effectiveness in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (18) and a systematic review on the diagnostic accuracy in accordance with the PRISMA diagnostic test accuracy guideline (19).
The final report will be written as a systematic review or an overview over systematic reviews, depending on available literature.

We will follow a population, intervention, comparator, outcome and study design (PICO) framework to set parameters for our literature search and study selection. Further steps in this process are literature searches, study selection, risk of bias assessments, data extraction, analysis and dissemination of available evidence. We will use Grading of Recommendations Assessment, Development, and Evaluation (GRADE) to assess the certainty of evidence (20).

Study inclusion and exclusion criteria

Our PICO framework helps the inclusion criteria to evaluate the suitability of studies. Due to different research questions, we will select articles according to the following inclusion criteria:

Table 1. Inclusion criteria for question 1 and 4 (safety and effectiveness)

Population	Pregnant women with suspected pre-eclampsia in 2nd or 3rd trimester (week 20 to 36 (+6 days))
Interventions	In addition to standard clinical assessment: • Elecsys preeklampsi sFlt-1 & PIGF • Triage PIGF-test • DELFIA Xpress PIGF 1-2-3 test • BRAHMS sFlt-1 Kryptor/BRAHMS PIGF-pluss Kryptor PE ratio • Other relevant blood-based tests for predicting pre-eclampsia in 2nd and 3rd trimester
Control	Standard clinical assessment, e.g. measuring blood pressure, testing urine for proteinuria, blood tests for haemoglobin (Hb), liver enzymes, bilirubin, headache, oedema, visual disturbance, foetal growth restriction or ultrasound
Outcomes	Mortality, morbidity (maternal and perinatal), admission, number of days admitted to hospital, number of days admitted at neonatal intensive care unit (NICU), consultations, induction of labour, caesarean, eclampsia, HELLP, gestational age, prematurity
Study design	Systematic reviews based on randomised controlled trials (RCTs), RCTs, non-randomized controlled trials, and controlled before-and-after studies. If we do not find relevant systematic reviews, we will include single studies published after 2002.

Table 2. Inclusion criteria for question 2 (diagnostic accuracy)

Population	Pregnant women with suspected pre-eclampsia in 2nd or 3rd trimester (week 20 to 36 (+6 days))
Index tests	• Elecsys preeklampsi sFlt-1 & PIGF • Triage PIGF-test • DELFIA Xpress PIGF 1-2-3 test • BRAHMS sFlt-1 Kryptor/BRAHMS PIGF-pluss Kryptor PE ratio • other relevant blood-based tests for predicting pre-eclampsia in 2nd and 3rd trimester Index tests used in conjunction with standard clinical assessment, or in conjunction with standard clinical assessment excluding quantitative determination of proteinuria
Comparison	Direct comparison between tests listed as index tests, e.g. diagnostic accuracy of *Elecsys preeklampsi sFlt-1 & PIGF* vs. *Triage PIGF*
Reference	A clinical diagnosis of pre-eclampsia based on other diagnostic tools: measuring blood pressure, testing urine for proteinuria, blood tests for haemoglobin (Hb), liver enzymes, bilirubin, headache, oedema, visual disturbance, foetal growth restriction and ultrasound with foetal growth assessment
Outcome	Sensitivity, specificity, predictive values, and likelihood ratios
Study design	Systematic reviews of cohort studies or cross sectional diagnostic accuracy studies including reference test, cross sectional diagnostic accuracy studies including reference test, cohort studies

Exclusion criteria

We will exclude studies based on:

- Patient groups at gestational weeks 1-19
- Use of these tests for screening purposes in first trimester
- Tests for pre-eclampsia that are not blood based
- Animal studies

Search strategy

We will primarily search for systematic reviews and HTAs. If relevant reviews are not found, or if the systematic reviews are older than 5 years, primary studies like randomised controlled trials, cross sectional studies in which the indexed tests are compared with a reference standard test and cohort studies will be used to address each question 1, 2, 4 either alone or to supplement the systematic reviews. We will only search for single-studies published after 2002. We will search in the following databases:

Systematic reviews & HTA

- CRD database, HTA (Centre for Reviews and Dissemination, University of York)
- Cochrane Database of Systematic Reviews (Wiley):
- Epistemonikos

- Embase (OVID)
- Medline (NLM)

Ongoing and planned systematic reviews and HTA:

- POP database
- PROSPERO

Primary studies
- Cochrane Central Register of Controlled Trials (Wiley)
- Medline (OVID)
- Embase (OVID)

Ongoing, completed or terminated (unpublished) trials
- Clinical Trials (National Institutes of Health, US)
- International Clinical Trials Registry Platform (WHO)
- Australian New Zealand Clinical Trials Registry

An information specialist (GHS) will plan and conduct the searches in collaboration with the research team. The search strategies will combine index terms and text words relating to population/problem (pre-eclampsia), intervention and index tests, adapting the search syntax to each database. An information specialist will peer review this work.

The research team will examine the bibliographies of included articles for relevant titles not identified by the searches, contact experts and hand search relevant web sites.

Selection of studies

The team will follow a two-step strategy where articles for both reach questions are selected. Both steps will be carried out considering inclusion and exclusion criteria detailed above (Table 1, 2). Disagreement at either stage will be settled by discussion or consultation with a third person (SF).

Selection strategy:
1. Two reviewers (LMR, HTM) will independently assess title and abstracts of retrieved articles to determine relevant full-text articles to be examined
2. Subsequently, two reviewers (LMR, HTM) will independently assess the full-text articles to decide which articles will be included in the systematic review.

Assessment of methodological quality and risk of bias

We will evaluate the quality (risk of bias) using the Cochrane tools RoB 2.0 tool (revised toofor Risk of Bias in randomized trials) (21) and the The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies (22). For diagnostic accuracy studies, we will use the QUADAS checklist (23). Two review authors (LMR, HTM) will assess the quality of the included studies independently. We will resolve disagreements by discussions or, if required, by consulting one of the other review authors.

Data extraction and analyses

One review author (HTM) will extract data from the included studies and another review author (LMR) will verify the data. We will extract the following data:

- Information about the study (authors, year of publication, setting, study design, clinical trial identification number and funding source)
- Participant characteristics (number of participants in the trial, age, procedure to be performed during intervention)
- Intervention and control characteristics
- Characteristics of index tests and reference tests
- Outcomes for questions 1, 2, 4 (endpoints examined, methods used to analyse outcome data, length of follow up and loss to follow up). For diagnostic accuracy studies, we will extract the information about relevant diagnostic performance outcomes such as the number of true positives (TP), false positives (FP), false negatives (FN) and true negatives (TN), sensitivity, specificity, positive and negative predictive values, positive and negative likelihood ratios, prevalence and the area under the receiver operator characteristic (ROC) curve (AUC).

Statistical analyses

For randomised controlled trials: If homogenous randomized controlled trials are found, effect sizes will be combined in meta-analyses. We will express continuous outcomes as mean difference (MD) or standardized mean difference (SMD) with 95% confidence interval (CI). Dichotomous data will primarily be analysed by calculating relative risk (RR) and the corresponding 95% CI. Any meta-analysis will be based on a random-effect model, as we expect some degree of heterogeneity across different studies. We will analyse randomised trials and non-randomised studies of interventions separately. Outcomes and results which cannot be combined in meta-analysis will be presented narratively.

Questions about diagnostic accuracy will be analysed using custom statistical methods that depend on the operating characteristics of each test. If tests are performed in a way that suggest a common sensitivity and specificity summary points across studies, we will use a bivariate model developed by Reitsma and co-workers (24) to estimate a «Summary ROC curve». Subsequently, we will use para-estimates from this model to calculate a «Summary operating point» (estimates for sensitivity and specificity) with 95% confidence intervals. If summary

operating point can't be expected, for example due to different threshold strategies, we will develop an HSROC Model that describes expected sensitivities at different specificities. Analysis of diagnostic accuracy will be performed using the package *mada* (25) in R (26). A random effects model will be assumed due to heterogeneity in population and setting.

Subgroup and sensitivity analyses

If enough studies are available, we will perform subgroup analyses. We will also perform sensitivity analyses where we exclude studies assessed as having high risk of bias.

Grading the certainty of evidence

Two review authors (LMR, HTM) will independently assess the certainty of the evidence for each selected outcome using the GRADE approach (Grading of Recommendations Assessment, Development, and Evaluation (20). We will resolve disagreements by consulting SF or KGB. We will assess the certainty of the evidence to ascertain the strength of the study design, possible risk of bias, imprecision and inconsistency of the estimates, and indirectness and magnitude of effect, dose response gradient and potential confounding factors. GRADE classifies the certainty of the evidence as high, moderate, low, or very low for each outcome, as defined in the table below.

Table 3: Definition of each category for certainty of evidence in GRADE

Grade	Definition
High	We are very confident that the true effect lies close to that of the estimate of effect
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Health economic evaluation

We will perform an assessment of cost-effectiveness and budgetary consequences of introducing predictive blood-based tests for pre-eclampsia as a routine strategy for women with suspected pre-eclampsia. In collaboration with the clinical experts, we will identify and draft all relevant alternative predictive strategies, which will be modelled as a decision tree. We will use Norwegian epidemiological data, when available, or best transferable European data, in absence of Norwegian data, as well as accuracy data, summarised in this HTA, to determine transition probabilities in the decision model. We will identify, quantify and

valuate all relevant cost (including both capital investments and operational costs including sample transportation) related to predictive blood-based tests for pre-eclampsia, as well as the current practice. In the cost calculation, we will identify and consider relevant alternative organisational scenarios (centralised versus decentralised organisation of testing).

The type of analysis will depend on the results of the search for clinical effectiveness and safety evidence. If there is evidence that predictive blood-based tests for pre-eclampsia can improve outcomes for the patient(s) (mother/fetus/newborn), we will perform a cost-effectiveness analysis (CEA). In absence of such evidence, we will perform a cost-minimization analysis (CMA), assuming that outcomes for the patient(s) are non-inferior to the current practice. The uncertainty around main parameters will be investigated with the help of sensitivity analyses.

We will assess the budgetary consequences of introducing the predictive blood-based tests for pre-eclampsia in Norwegian clinical practice by calculating the incremental (net) expenditure incurred following the adoption. All analyses will be performed in a health care perspective. The economic assessment will be performed by the health economists (AS-S and EM) in collaboration with the project leader and clinical experts.

Organisational consequences and implementation

To answer the question four and question on organisational consequences the external project participants will discuss organizational consequences and implementation of these blood-based tests in the specialist health care based on the results from this systematic review as well as their knowledge and experience. Since organisational aspects have direct impact on investment, operational and transportation costs, they will also be addressed in the health economic evaluation, where alternative organisational solutions will be considered.

Norwegian Institute of Public Health review process

We follow the process of the Norwegian Institute of Public Health where two external clinical experts appointed by Nye Metoder and two internal research directors are invited to review and give feedback on the protocol. Subsequently, the protocol will be approved by the management group of the HTA-unit (Klyngeledermøtet) and published at NyeMetoder.no and FHI.no. The final report will also be reviewed by two external experts and two internal research directors at NIPH. The final draft will be approved by the management group in the HTA-unit before submission to the commissioner. Publication (https://nyemetoder.no/metoder), will be done latest 10 days after submission to the commissioner.

Activities and schedule

We plan the following activities (for more information, see Table 4):

- Find and include external reviewers
- Discuss project plan with internal and external reviewers
- Approval of project plan
- Search for literature
- Select studies according to inclusion/exclusion criteria
- Evaluate methodological quality
- Extract data on efficacy and safety and conduct statistical analyses
- GRADE evaluation for each outcome
- Write and review the draft report
- Approve and submit the report

Date for commision

27. February 2017

Start date (for FHI.no): 15.02.2019

End date: 15.05.2020

Table 4. Activities and schedule

Activities	Responsible	Start	Finish
Invite and include external experts	RHA forum (Bestillerforum)/ØM	----	21.02.2019
Discuss the mandate with external experts and the internal project group (lag) (meeting)	HTM/ØM	01.03.2019	01.03.2019
Clarification of mandate	HTM/ØM/RHA	08.03.2019	21.03.2019
Start to write project plan	HTM/LMR/AS-S	13.03.2019	28.03.2019
Collect data for health economic analysis	AA-S/EM	15.02.2019	
Project plan accepted by internal project members	Internal project group	28.03.2019	11.04.2019
Revise and send project plan to external experts (external peer review)	HTM	15.04.2019	
Project plan accepted by internal reviewers and external experts			29.04.2019
Revise and send project plan to internal review	HTM	15.04.2019	29.04.2019
Revise and send project plan to Klyngeledelsen	HTM		07.05.2019
Approval of project plan by Klyngeledelsen	Klyngeledelsen		14.05.2019
Plan and run literature search	GS	27.04.2019	15.05.2019
Selection of articles (screening)	LMR/HTM (AS-S, SF)	16.05.2019	16.06.2019
Selection of full text articles	LMR/HTM (AS-S, SF)	17.06.2019	18.08.2019
Assess risk of bias in included articles	LMR/HTM (SF)	19.08.2019	20.09.2019
Data extraction (table characteristics of included articles)	LMR/HTM (SF)	23.09.2019	27.10.2019
Extract data and plan models for health economic analysis	AS-S, EM	19.08.2019	20.09.2019
Data analysis	KGB (HTM)	23.09.2019	27.11.2019
Conduct health economic analyses	AS-S, EM	20.09.2019	27.11.2019
GRADE	LMR/HTM (SF)	27.11.2019	20.12.2019
Write other considerations (organisational considerations?)	Kristin Viste?		
Write and finalize the systematic review/HTA	HTM/Internal project group	01.11.2019	15.01.2020
Revise, send draft to external experts for comments and approval	HTM	15.01.2020	15.02.2020
Send draft to internal peer review	HTM	15.01.2020	31.01.2020
Revise, send draft to external peer review	HTM	24.02.2019	16.03.2020
Send and approval of report by Klyngeledelsen	HTM/Klyngeledelsen	24.03.2020	31.03.2020
Send HTA to Bestillerforum and publish at FHIs webpage	HTM	15.05.2020	

Publication / dissemination

The final product will be a report from Division of Health Services, Norwegian Institute of Public Health, under Nye Metoder (https://nyemetoder.no/metoder), and possibly a scientific article.

Indexing for web page

“Pre-Eclampsia” and “Diagnostic Techniques and Procedures”

Internal pregnancy and preexpampsia related projects/publications

There are five projects/publications published from Norwegian Institute of Public Health on this topic (for more information, follow the links below).

https://www.fhi.no/nyheter/2017/svangerskapsforgiftning/

https://www.fhi.no/cristin-prosjekter/aktiv/metabolomics-ivf-og-svangerskapsutfall/

https://www.fhi.no/cristin-prosjekter/aktiv/genetiske-studier-av-preeklampsi/

https://www.fhi.no/cristin-prosjekter/avsluttet/god-prediksjon-av-preeklampsi/

https://www.fhi.no/cristin-prosjekter/aktiv/internasjonal-studie-for-tidlig-diagnostikk-av-svangerskapsforgiftning/

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Appendix

Glossary

Pre-eclampsia	New onset hypertension arising after 20 weeks' gestation (Gestational hypertension) accompanied by ONE or MORE of the following new onset signs after 20 weeks' gestation : 1.Proteinuria 2. Other signs of maternal organ dysfunction, including one or more of the following: o Liver involvement (elevated transaminases, e.g. ALT or AST) o Neurological complications (e.g. eclampsia, stroke, persistent visual scotomata) o Hematological complications (thrombocytopenia, Disseminated Intravascular Coagulation; hemolysis) o Uteroplacental dysfunction (e.g. fetal growth restriction, stillbirth, abnormal fetal Doppler findings).
Proteinuria	o ≥0.3 g per 24 hours (time-consuming and rarely performed nowadays) o Spot urine protein / creatinine ratio> 0.3 mg/mmol (equals > 0.26 mg/mg) o ≥ 1+ proteinuria on urine dip stick test (acceptable if above tests are unavailable), preferably on at least two occasions
RCTs	Randomised controlled trials
Second to third trimester	Week 13 to the end of the pregnancy
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
Commissioning Forum	An Ordering Forum, Bestillerforum RHF, consisting of the four medical directors (one for each regional health authority) and two delegates from the Norwegian Directorate of Health, has the mandate to prioritize the STAs and HTAs to be conducted on the basis of submitted proposals and horizon scanning reports
HTA	Health technology assessment includes a systematic review of safety, effectiveness and cost effectiveness analysis. It might include organisational and ethical considerations.
CEA	Cost-effectiveness analysis, a form of economic analysis that compares the relative costs and outcomes (effects) of different

	courses of action (treatment/diagnostic strategies). The outcomes are measured and presented in natural units.
CMA	Cost minimization analysis, a form of economic evaluation comparing the costs of alternative interventions that have equal effects
Budget impact analysis	Financial and organizational consequences of adopting a new health care technology without directly taking health consequences into account