Spot protein creatinine ratio (SPCr) and spot albumin creatinine ratio (SACr) in the assessment of pre-eclampsia: A diagnostic accuracy study with decision analytic model based economic evaluation and acceptability analysis

Protocol

Version 2.0
7th April 2015

Funded by NIHR Health Technology Assessment Programme (10/65/02)
Sponsored by The Newcastle upon Tyne Hospitals NHS Foundation Trust
Sponsor Reference (6213)
REC Reference (12/NE/0301)
ISRCTN82607486

PROTOCOL CONTACTS

Chief Investigator
Dr Jason Waugh
Consultant Obstetrician
The Newcastle upon Tyne Hospitals NHS Foundation Trust
Royal Victoria Infirmary
Newcastle upon Tyne
NE1 4LP
Email: Jason.waugh@nuth.nhs.uk

Principal Investigators
Dr Aarti Ullal
PI for City Hospitals Sunderland NHS Foundation Trust
Obstetrics and Gynaecology Unit
Sunderland Royal Hospital
Kayll Road
Sunderland
SR4 7TP
Email: Aarti.Ullal@chsft.nhs.uk

Dr Jason Waugh
PI for The Newcastle upon Tyne Hospitals NHS Foundation Trust
Royal Victoria Infirmary
Newcastle upon Tyne
NE1 4LP
Email: Jason.waugh@nuth.nhs.uk

Professor Andrew Shennan
PI for Guy's and St Thomas' NHS Foundation Trust
King's College London
Westminster Bridge Road
London
SE1 7EH
Email: Andrew.shennan@kcl.ac.uk

Dr Ramesan Navaratnarajah
PI for Barts and The London NHS Trust
Acute & Family Division
Women's Health Clinical Academic Unit
Department of Obstetrics and Gynaecology
Research Office, 6th Floor Labour Ward
The Royal London Hospital
London
E1 1BB
Email: ramesan.navaratnarajah@bartshealth.nhs.uk

Dr Helene Brandon
PI for Gateshead Health NHS Foundation Trust
Queen Elizabeth Hospital
Sheriff Hill
Gateshead

NE9 6SX
Email: Helene.brandon@ghnt.nhs.uk

Dr Shonag Mackenzie
PI for Northumbria Healthcare NHS Foundation Trust
North Tyneside General Hospital
Rake Lane
North Schields
NE29 8NH
Email: SHONAG.MACKENZIE@northumbria-healthcare.nhs.uk

Mr Umo Esen
PI for South Tyneside NHS Foundation Trust
Consultant Obstetrician & Gynaecologist
South Tyneside NHS Foundation Trust
Harton Lane
South Shields
NE34 0PL
Email: Umo.Esen@stft.nhs.uk

Co-Investigators

Prof Christopher Price
Department of Primary Health Care
Rosemary Rue Building
University of Oxford
Roosevelt Drive, Headington
Oxford
OX3 7FL
Email: cpprice1@gmail.com

Prof Stephen Robson
Institute of Cellular Medicine
3rd Floor, Leech Building
Newcastle University
Framlington Place
Newcastle upon Tyne
NE2 4HH
Email: s.c.robson@ncl.ac.uk

Prof Khalid Khan
The Blizard Institute
Centre for Health Sciences
Women's Health Unit
Barts and The London School of Medicine and Dentistry
Queen Mary, University of London
2 Newark Street
E1 2AT
Email: k.s.khan@qmul.ac.uk

Lay Representative

Ms Fiona Milne
Trustee "Action on Pre-eclampsia"
Freelance
32 St Lukes Rd

Brighton
BN2 9ZD
Email: fionamilne@talk21.com

Statistician
Dr Richard Hooper
Senior Lecturer in Medical Statistics
Centre for Health Sciences
Queen Mary, University of London
Abernethy Building
2 Newark Street
E1 2AT
Email: r.l.hooper@qmul.ac.uk

Health Economist
Ms Angela Devine
Queen Mary, University of London
Abernethy Building
2 Newark Street
London
E1 2AT
Email: a.devine@qmul.ac.uk

Clinical Scientist
Dr Edmund Lamb
East Kent Hospitals University NHS Foundation trust
Kent and Canterbury Hospital
Ethelbert Road
Canterbury, Kent
CT1 3NG
Email: edmund.lamb@ekht.nhs.uk

Senior Trial Manager
Professor Elaine McColl
Newcastle Clinical Trials Unit
1-4 Claremont Terrace
Newcastle University
Newcastle upon Tyne
NE2 4AE
Email: elaine.mccoll@ncl.ac.uk

Trial Manager
Jenn Walker
Newcastle Clinical Trials Unit
1-4 Claremont Terrace
Newcastle University
Newcastle upon Tyne
NE2 4AE
Email: Jenn.Walker@ncl.ac.uk

1. PROTOCOL SIGNATURE PAGE

Protocol authorisation signatories

Signature …….. Date ……

Dr Jason Waugh, Chief Investigator

Signature …….. Date ……

Dr Richard Hooper, Statistician

Signature …….. Date ……

Professor Elaine McColl, Senior Trial Manager

Principal/Chief Investigator signature

I confirm that I have read and understood protocol version 2.0 dated 7th April 2015. I agree to comply with the study protocol, the principles of GCP, research governance, clinical trial regulations and appropriate reporting requirements.

Signature …….. Date …….....

Print Name ……

Site Name/I.D……..

2. CONTENTS

3. ABBREVIATIONS

AE	Adverse Event
BMI	Body Mass Index
BP	Blood Pressure
CI	Confidence Interval
CI	Chief Investigator
CTU	Clinical Trials Unit
DBP	Diastolic Blood Pressure
DCF	Data Collection Form
GCP	Good Clinical Practice
GP	General Practitioner
HDP	Hypertensive Disorders in Pregnancy
HDU	High Dependency Unit
ISF	Investigator Site File
ITU	Intensive Therapy Unit
LCM	Local Co-ordinating Midwife
MHRA	Medicines and Healthcare Products Regulatory Agency
NICE	National Institute of Clinical Excellence
NICU	Neonatal Intensive Care Unit
NIHR	National Institute Health Research
OC	Oversight Committee
OR	Odds Ratio
PIS	Patient Information Sheet
PMG	Project Management Group
QALY	Quality Adjusted Life Year
R&D	Research and Development
RR	Relative Risk
RVI	Royal Victoria Infirmary, Newcastle
SACr	Spot Albumin Creatinine ratio
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SOP	Standard Operating Procedure
SoPC	Summary of Product Characteristics
SPCr	Spot Protein Creatinine ratio
SUSAR	Suspected Unexpected Serious Adverse Reaction
UK	United Kingdom

4. PROTOCOL SUMMARY

Short title:	DAPPA
Protocol version:	2.0
Protocol date:	7th April 2015
Chief Investigator:	Dr Jason Waugh
Sponsor:	The Newcastle upon Tyne Hospitals NHS Foundation Trust
Funder:	NIHR Health Technology Assessment programme
Study design:	**Prospective cohort study to evaluate the diagnostic accuracy of SPCr and SACr in comparison with 24 hour proteinuria in hypertensive pregnant women with suspected proteinuria. We will also undertake decision analytic modeling and cost effectiveness analysis.**
Primary objective:	To evaluate the diagnostic accuracy of quantitative assessments of SPCr and SACr (index tests) at different thresholds in predicting severe PE compared to 24 hour urine protein measurement
Secondary objectives:	To assess the accuracy of point of care assessments of SPCr and SACr at different thresholds in diagnosing PE compared to 24 hour urine protein measurement To identify the laboratory assay method of 24 hour proteinuria that is most accurate in the assessment of PE To estimate the accuracy of both quantitative and point of care assessments of SPCr and SACr at different thresholds in predicting adverse fetal outcomes To estimate the diagnostic utility of SPCr or SACr as a potential replacement for 24 hour protein estimation by developing a decision analytic model To assess the cost effectiveness using cost per correct diagnosis and cost per adverse outcome predicted as key measures
Primary outcome:	Severe PE as defined by NICE [5]
Number of study sites:	Up to 36
Study population/size:	1790
Study duration:	44 months

5. BACKGROUND

5.1 Clinical Background

Preeclampsia is a multisystem disorder of pregnancy associated with raised blood pressure and proteinuria. Hypertensive disorders in pregnancy (HDP) remain the second leading cause of direct maternal deaths in the UK and account for 20% of all stillbirths [9, 10]. One in 5 women with hypertension is diagnosed with PE, resulting in complex treatment and substantial health care costs [5]. Women with severe PE require high dependency care. Preeclampsia is also responsible for significant infant morbidity related to fetal growth restriction and prematurity resulting in prolonged neonatal intensive care treatment and lifelong handicaps; the additional NHS costs to care for a preterm baby born before 33 weeks and 28 weeks are £61,509 and £94,190 respectively [5]. £939 million in extra costs for care of preterm babies per year in the NHS are linked to neonatal care such as incubation, and hospital readmissions [5].

The potential impact of early and accurate assessment of PE is enormous. The reliable diagnosis of significant proteinuria is critical in women with gestational hypertension because it distinguishes between those with PE from those with isolated hypertension; this distinction determines future monitoring and management. Furthermore, the determination of the most appropriate threshold for abnormal proteinuria that predicts clinical outcome helps to better focus resource on high risk women and reduce unnecessary iatrogenic intervention. Currently women with suspected PE undergo 24 hour proteinuria testing mostly as in-patients to evaluate the severity of the condition. The cost associated with 24-hour protein measurement and additional testing needs to be evaluated against identifying women with PE and avoiding the mortality, morbidity and costs associated with undiagnosed PE.

NICE acknowledges the paucity of evidence relating to the diagnosis of significant proteinuria and the unclear prognostic value of various urinary protein thresholds [5]. They have highlighted the need for “large, high-quality prospective studies comparing the various methods of measuring proteinuria (automated reagent-strip reading devices, urinary protein : creatinine ratio, urinary albumin : creatinine ratio, and 24-hour urine collection) in women with new-onset hypertensive disorders during pregnancy” [5].

Our proposed study aims to address this shortfall in evidence by determining which method of measurement, and which diagnostic thresholds, are most accurate in predicting not just PE, but more importantly, clinically significant outcomes. This will help to inform decisions regarding clinical management of gestational hypertensive disorders during pregnancy.

5.2 Description of Technology

Index tests: Proteinuria estimation by urinary SPCr or urinary SACr in women with suspected PE is available as either a laboratory or point of care (POC) test. The POC SPCr and SACr are measured by urine reagent strip analysis on a semi-quantitative automated reader. SACr can also be measured on a fully quantitative device configured in a plastic cassette, the reaction being monitored in a benchtop photometer. These technologies are already in clinical use for screening albuminuria (and microalbuminuria) and proteinuria in both chronic kidney disease and diabetes.

Comparative test: Measurement of 24-hour urine protein is currently the gold standard for the assessment of proteinuria in pregnancy. However this test is associated with

significant costs related to hospital admission, as often women are admitted as an inpatient for up to 48 hours until the results become available. Furthermore, the measurement is subject to errors (in as many as 20% of patients) as a result of incomplete collection. Diagnosis of proteinuria in HDP also varies with the type of laboratory assay used [4].

A reliable, accurate and cost effective SPCr or SACr ratio test (laboratory or POC), that is equivalent or better than 24 hour protein estimation at predicting adverse maternal and fetal outcomes, could be employed as the primary test in the assessment of women with suspected PE. Furthermore, given the rising costs of inpatient care, the use of SPCr or SACr has the potential to deliver significant cost improvements. A clearer understanding of the threshold of proteinuria (by any measurement) that predicts increased risks of adverse maternal and fetal outcomes will allow the concentration of scarce NHS resource onto the more intensive monitoring of fewer women.

5.3 Summary of current evidence

Current recommendations for assessment of proteinuria vary. Recently published NICE guidelines in the UK suggest the use of automated reagent-strip reading device to detect proteinuria. In women with a result of 1+ or more, the use of spot SPCr or 24 hour urine collection is recommended to quantify proteinuria. Significant proteinuria is defined as SPCr greater than 30 mg/mmol or a validated 24-hour urine collection greater than 300 mg/24 hour. Where 24-hour urine collection is used to quantify proteinuria, a recognized method of evaluating completeness of the sample is recommended [5]. The Society of Obstetricians and Gynaecologists of Canada suggests using urinary dipstick testing to screen for proteinuria, with the definition of significant proteinuria similar to NICE guidelines [11]. The American College of Obstetricians and Gynaecologists consider 24 hour urine protein estimation of more than 300 mg as significant proteinuria for a diagnosis of PE [12].

5.4 Work leading to the trial

- *Diagnostic accuracy of SPCr / SACr in assessing proteinuria in women with HDP.*

Price et al [13] in 2005 and Cote et al [14] in 2008 performed a systematic review of 1214 women with gestational hypertension. SPCr, with a cut-off of 30 mg/mmol, had pooled sensitivity of 83.6% (95% CI 77.5-89.7%), specificity 76.3% (72.6-80.0%), likelihood ratio positive (LR+) 3.53 (2.83-4.49), and LR- 0.21 (0.13-0.31). Both authors concluded that SPCr was a reasonable “rule-out” test for proteinuria of 300 mg/day or more in HDP. However, laboratory assays in the primary studies were not well described. This led to the recommendation for future studies on SACr to predict significant proteinuria and clinical outcomes.

- *Evaluation of proteinuria thresholds and assays in predicting adverse clinical outcomes.*

The applicants have assessed the use of different laboratory assays to measure 24 hour proteinuria in pregnancy [4, 8]. The prevalence of proteinuria >300 mg/24 hour and hence the prevalence of PE differed between the two assays studied, (24.9% for Bradford assay (BA) and 70.1% for Benzethonium chloride assay (BCA)). The threshold of 300 mg/24 hours performed poorly as a predictor of adverse outcomes [15]. At the 500 mg/24 h threshold BCA assay predicted severe hypertension with an LR+ of 1.51 (95%CI 0.99-2.28) and small for gestational age with a LR+ of 1.72

(95%CI 1.11-2.66). However at the 500 mg/24 hour threshold the LR+ for BA for severe hypertension was 2.15 (95%CI 1.07-4.34), birthweight <10th centile (LR+: 2.79 95%CI 1.4-5.54) and biochemical disease (LR+: 2.47 95%CI 1.22-5.01). This data supports the recommendation from NICE for prospective studies to explore the relationship between individual assays for proteinuria and clinical outcome.

- *Point of care measurement of proteinuria.*

The applicants have also investigated point of care (POC) testing for proteinuria and albuminuria in pregnancy and PE [6]. SACr dipsticks and fully quantitative SACr were compared with 24 hour proteinuria [7]. Dipstick SACr testing did not improve detection rates whether automated or visual. Fully quantitative measurement of SACr was a better predictor than any dipstick technique; LR+ 14.6 (95% CI 6.74-31.8), LR- 0.069, (95% CI 0.030-0.16) [7]. In a systematic review of 6 studies of visual dipstick analysis, Waugh et al. [16] reported a pooled LR+ 3.48 (95% CI 1.66, 7.27) and a pooled LR- of 0.6 (95% CI 0.45, 0.8) for predicting 300 mg/24-hour proteinuria at the 1+ or greater threshold. We concluded that the accuracy of dipstick urinalysis with a 1+ threshold in the prediction of significant proteinuria is poor and therefore of limited clinical value [16].

The POC technology proposed for study in this trial has been validated by the applicants [6]. We have also determined the reference range for SACr in the normal pregnant population [17]. Our study comparing semi-quantitative and fully quantitative POC tests for albuminuria and proteinuria found automated dipstick urinalysis to have better predictive values for significant proteinuria (LR+ 4.27, 95% CI 2.78 to 6.56; LR- 0.225, 95% CI 0.14 to 0.37) compared to conventional visual dipstick urinalysis (LR+ 2.27, 95% CI 1.47 to 3.51; LR- 0.635, 95% CI 0.49 to 0.82). Dipstick microalbumin/creatinine ratio testing did not improve overall detection rates with automated or visual testing. Fully quantitative POC of ACR was better than any dipstick technique (LR+ 14.6, 95% CI 6.74 to 31.8; LR- 0.069, 95% CI 0.030 to 0.16) [7]. These studies have informed the development of NICE CG 107 [5]: Assessment of Proteinuria in (HDP) and the development of the protocol.

- *Systematic review of tests that predict onset of preeclampsia.*

We have evaluated the accuracy of tests in predicting onset of PE by a systematic review of the literature (HTA No. 01/64/04). This study concluded that no current tests employed in screening for pre-eclampsia were sufficiently accurate or effective to become part of routine care. One of the recommendations from that project was to evaluate prognostic/predictive features like proteinuria that are associated with maternal and foetal complications once PE has started.

- *Systematic reviews on the accuracy of tests to predict complications in preeclampsia – TIPPS (Tests in the Prediction of Pre-eclampsia Severity) project.*

We have conducted systematic literature reviews to assess the predictive value of five of the commonly performed tests in PE. We analysed more than 25,000 citations and reviewed 60 relevant studies. Although we conducted good quality reviews including one on proteinuria it was hard to provide recommendations on the value of tests due to the deficiencies in the primary studies. However the data collated give face validity of the choice of tests that have been chosen for use in the proposal [15].

- *Development and validation of a Prediction model for Risk of complications in Early onset Pre-eclampsia (PREP).*

We have recently been funded by HTA to undertake the first prognostic study to develop a prediction rule for adverse outcomes in early onset PE that will provide personalised estimates of maternal and foetal risks. The PREP study will achieve this by validating the model in two prospective external datasets in Netherlands and Canada. The data from PREP will complement the proposed project in evaluating the association between proteinuria and adverse outcomes. Furthermore it will also provide valuable data on outcomes of women with severe PE to further populate the decision analytic model for economic evaluation.

6. AIMS OF THE STUDY

Our proposed study evaluates the measurement of proteinuria in women with suspected preeclampsia (PE). This includes women with gestational hypertension ≥140/90 mmHg and ≥ Trace proteinuria on automated dipstick analysis.

Primary Objectives:

1. To evaluate the diagnostic accuracy of quantitative assessments of SPCr and SACr (index tests) at different thresholds in predicting severe PE compared to 24 hour urine protein measurement

Secondary Objectives:

2. To assess the accuracy of point of care assessments of SPCr and SACr at different thresholds in diagnosing PE compared to 24 hour urine protein measurement
3. To identify the laboratory assay method of 24 hour proteinuria that is most accurate in the assessment of PE
4. To estimate the accuracy of both quantitative and point of care assessments of SPCr and SACr at different thresholds in predicting adverse fetal outcomes
5. To estimate the diagnostic utility of SPCr or SACr as a potential replacement for 24 hour protein estimation by developing a decision analytic model
6. To assess the cost effectiveness using cost per correct diagnosis and cost per adverse outcome predicted as key measures

7. STUDY DESIGN

Prospective cohort study to evaluate the diagnostic accuracy of SPCr and SACr in comparison with 24 hour proteinuria in hypertensive pregnant women with suspected proteinuria. We will also undertake decision analytic modeling and cost effectiveness analysis.

7.1 Primary outcome

The primary outcome is severe PE as defined by NICE [5]; women with severe hypertension (systolic BP ≥ 160 mmHg or diastolic BP ≥ 110 mmHg) and proteinuria or women with mild or moderate hypertension (systolic BP ≥ 140 mmHg and/or diastolic BP ≥ 90 mmHg) and proteinuria (≥ 300 mg/24-hour), with one or more of the following: severe headache, visual disturbances, problems with vision, severe pain just below the ribs or vomiting, papilloedema, signs of clonus (≥ 3 beats), liver tenderness, HELLP syndrome, platelet levels below 100×10^9/L, abnormal liver enzymes (ALT or AST >70 U/l).

We have chosen the primary outcome of severe PE because this is well accepted by clinicians and triggers clinical responses aimed at the safe delivery of the fetus whilst minimising maternal morbidity. All participating units in the study (and in the UK) have a clinical guideline for severe PE that is a core compliance standard for CNST (Clinical Negligence Scheme for Trusts) clinical risk assessment.

7.2 Secondary clinical outcomes

Maternal: Diagnosis of PE using a 24 hour proteinuria threshold of 300 mg/24 h

Fetal: Composite adverse perinatal outcome identified by Delphi survey of clinicians. This includes one or more of the following: perinatal or infant mortality, bronchopulmonary dysplasia, necrotising enterocolitis, grade III/IV intraventricular haemorrhage, cystic periventricular leukomalacia, or stage 3-5 retinopathy of prematurity and hypoxic ischaemic encephalopathy.

Costs: Health service data on bed use, surveillance visits as an inpatient, outpatient and peripartum health service resource use related to delivery, postnatal care and follow-up tests will be collected by the research midwife following delivery. These will include resource use for neonatal care. (see section 7: Economic evaluation).

7.3 Baseline assessments

For eligible women clinical details will be collected to confirm eligibility and that written consent has been obtained.

7.3.1 Collection of outcome data

Clinical data, on both mother and baby, will be collected at birth and discharge from hospital from the hospital case notes on to a DAPPA Data Collection Form (DCF). This will include those babies who are admitted to the NICU.

7.3.2 Women or Babies that are transferred

If a study woman or baby is transferred to another hospital the Study Office will be informed so that all women and babies can be followed up until discharge or death. Each transfer hospital will be asked to provide information relating to any of the Study outcomes that may have occurred during the women or babies stay in that hospital.

7.3.3 Minimisation of bias

The Study is prospective and observational and only those urinalysis results currently in clinical use will be revealed to clinicians. Other tests of proteinuria will be either blinded to clinicians or performed in batches after clinical management decisions have been made on stored samples.

Loss to follow-up for the clinical data will be negligible as this information will be collected before the woman is discharged from hospital. Neonatal outcome data for the small number of babies admitted to the neonatal unit will be collected through the midwives employed in each unit. Should either the woman or babies be transferred to another neonatal unit, data will be collected from all the hospitals that provide their care.

Loss of data regarding the health economic data collected at a week and 6 weeks from the woman will be minimised by the development of robust systems to maximise response rates.

7.4 Duration of study

This study will start in September 2012 and be completed at the end of April 2016. This includes a 6 month start-up phase to obtain permissions from MHRA, Multicentre Research Ethics Committee and local Research and Development Offices, together

with the development of data collection tools and questionnaires. Computer systems will be developed towards the end of this to support the collection of data outcomes.

We will have up to a total of 36 recruiting Maternity Units by December 2014. Accurate assessment of the numbers of women eligible, approached and recruited will be made and we anticipate that up to 70 women will be recruited per month.

Recruitment will finish in the Maternity Units at the end of November 2015. A further 6 months has been allowed for the analysis of the data obtained, with a 3 month extension for the submission date of the final report to the funder. The new funding contract end date will be 31 July 2016, with the final report to funder due in August 2016

7.5 Details of study design and procedures

This is a prospective cohort study to evaluate the diagnostic accuracy of SPCr and SACr in comparison with 24 hour proteinuria in hypertensive pregnant women with suspected proteinuria. We will also undertake decision analytic modeling and cost effectiveness analysis.

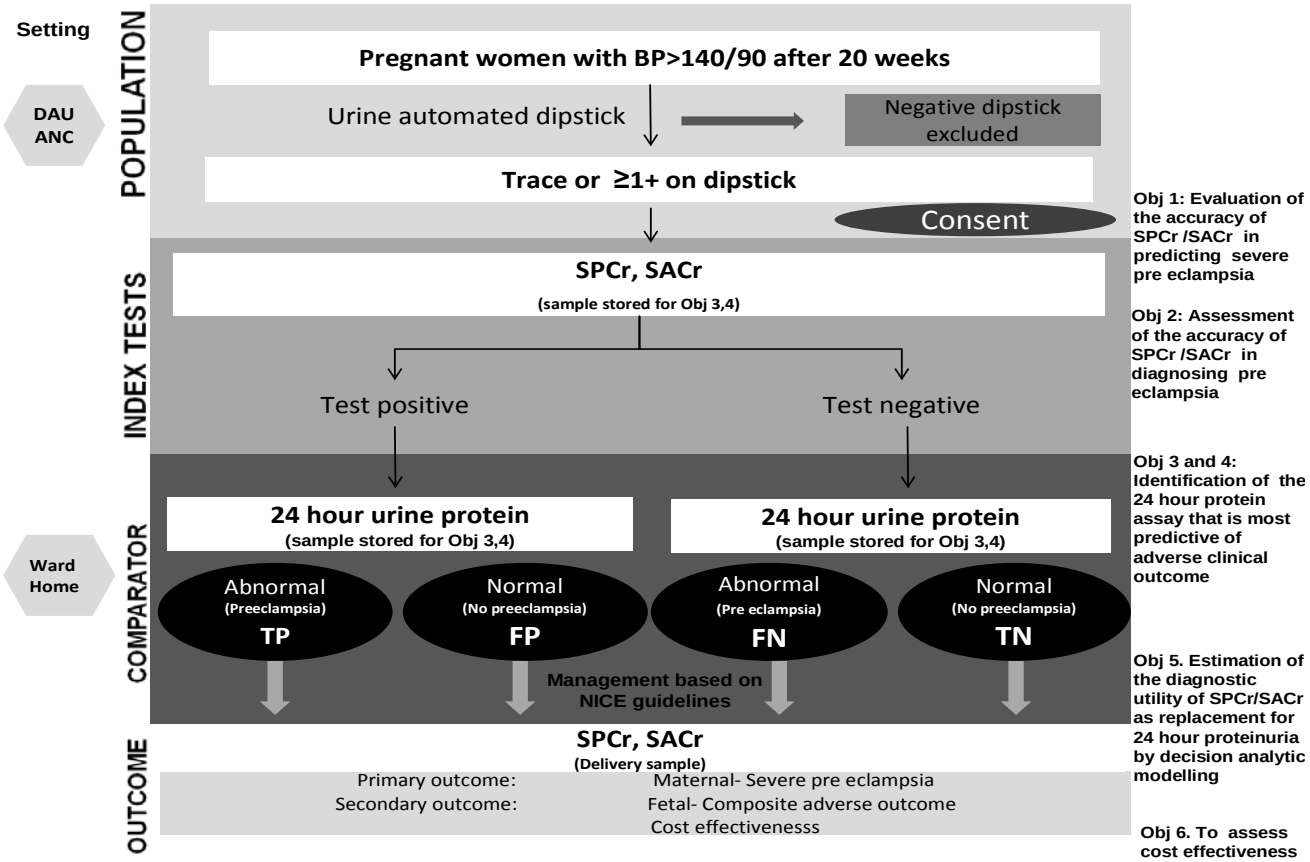


Figure 1: Flow chart for study design

8. HEALTH TECHNOLOGIES BEING ASSESSED

8.1 Index tests

Laboratory quantitative tests (Laboratory SPCr and SACr)

Urinary protein will be measured using a benzethonium chloride turbidimetric method in all recruiting hospitals. The reagent acts as a denaturing agent causing the formation of a fine suspension in the reaction mixture. The analytical range for the Benzethonium chloride assay is 68 to 2000 mg/L and the day-to-day precision is 1.4 – 3.0%.

The SACr will be measured using an automated chemistry analyzer. Albumin is measured using an immunoturbidimetric immunoassay. The analytical range of the assay is 5 to 500 mg/L, and the day-to-day precision is within the range 2.5 – 5.0%. The analytical range of the assay is 0.3 to 44.2 mmol/L and the day-to-day precision is between 1.5 – 3.0%.

The urine creatinine will be measured using an enzymatic reaction, in which creatininase hydrolyses creatinine to creatine, which is itself hydrolysed by creatinase to sarcosine and urea. The analytical range of the assay for SPCr is 0.3 to 44.2 mmol/L and the day-to-day precision is between 1.5 – 3.0%.

Point of Care tests (Semi quantitative reagent strip SACr).

The dipstick test for ACR comprises two test pads, the colours formed in the presence of albumin and creatinine being read using a reflectance meter; the system provides a semi-quantitative result. The detection of albumin is based on binding of Bis (3',3''-diiodo-4',4''-hydroxy-5',5''-dinitrophenyl)-3,4,5,6-tetrabromosulfonephthalein (DIDNTB) at pH 1.5. It has been shown to be specific for the detection of albumin. The detection limit of the method is 0.9 mmol/L (10 mg/Dl). The ACR is reported as one of the following ranges in conventional units (mg/g): <30, 30-300; or >300; or one of the following ranges in SI units (mg/mmol): <3.4, 3.4-33.9, or >33.9.

8.2 Comparative tests (24 hour proteinuria and 24 hour albuminuria)

The measurement of the total protein concentration in urine is difficult for several reasons. The quantity of total protein is much lower in urine than in serum and there is large sample-sample variation, as well as interference from non-protein substances [18]. There are a number of different assays for measuring urinary total protein. Most laboratories in the UK currently use turbidimetric or colorimetric assays. The two most common methods employed are the benzethonium chloride and pyrogallol methods; for this reason we plan to study the variation of performance of these two methods to give an overview of the variation found between laboratories. Either a protein or albumin concentration or a fully quantitative SPCr or SACr can be reported.

Total Protein will be measured using a benzethonium chloride turbidimetric method in our secondary reference lab to explore inter-laboratory variation from the recruiting centres. Additionally, total protein will be measured using the Pyrogallol Red method (Sigma, Saint Louis, Missouri, USA) on a Cobas Mira Plus (Roche Diagnostics, Basel, Switzerland). In the assay, a pyrogallol red-molybdate complex binds to basic amino acid groups of protein molecules causing an increase in absorbance measured at 600 nm. The analytical range of the assay is stated by the manufacturer to be 10 to 2000 mg/L urinary total protein.

9. STUDY CONDUCT

All eligible women will be invited to participate at each site. Women will be given trial information by the research midwife and a Participant Information Sheet (PIS) to keep, and then subsequently recruited following obtaining written consent.

As part of routine clinical care women are asked to provide a urine sample for protein analysis. In those women who consent to taking part in this study, an aliquot of the spot urine sample will be collected and stored at -80ºC. This spot urine will then be sent for a laboratory SPCr. Clinical management will be determined at this point based on the automated urine dipstick result and SPCr (as per routine practice). Women will then be asked to collect a 24 hour urine sample as either an in-patient or outpatient, dependent on the clinical care plan (as per NICE CG107) [5]. Those women with trace proteinuria and a SPCr <30mg/mmol (i.e. without clinical PE) will collect as an out-patient and those with a SPCr of >30 mg/mmol (i.e. with a clinical diagnosis of PE) will collect as an in-patient. An aliquot of this 24-hour urine sample will be stored at -80ºC for secondary analysis. Clinical management will be determined from the automated dipstick, the local laboratory SPCr and /or the local laboratory 24 hour urine collection performed locally.

Immediately prior to delivery, a further spot sample of urine will be taken and stored for later analysis. This will allow the maximum proteinuria level to be calculated as well as the increase in proteinuria from initial presentation.

Women will be followed up until 6 weeks postnatal when their blood pressure and proteinuria results (from either hospital / primary care clinics) will confirm their pregnancy diagnosis. At this point a detailed collection of outcome data will be performed by the research midwife. Data will be abstracted from the hospital records for the maternal and neonatal outcomes at birth and discharge home.

The aliquots of urine will be sent in batches for secondary analysis at East Kent Hospitals Trust of 24-hour total albumin excretion by 2 different assays. The spot urine sample will also be tested using point of care testing for SPCr (semi-quantitative dipstick); POC SACr (semi-quantitative dipstick); and POC SACr (fully quantitative test). All data will be entered into a clinical data management software package supplied by MedSciNet configured to allow web-based entry from each of the seven clinical sites as well as the secondary analysis laboratory.

9.1 Selection of study participants

9.1.1 Setting

The trial will be conducted in up to 36 obstetric units in the UK, with an average of 70 women being recruited each month across all centres.

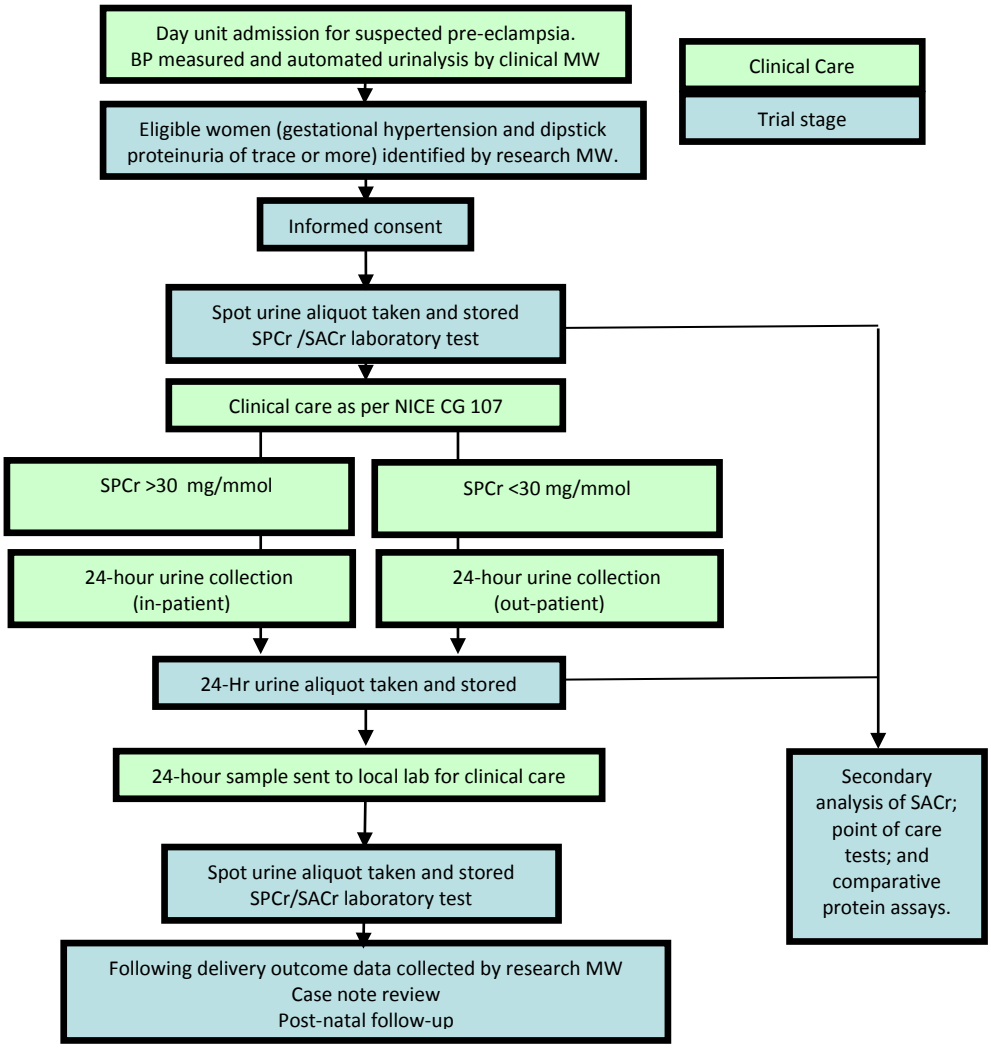
9.1.2 Inclusion criteria

Pregnant women aged between 16 and 45 years old who are more than 20 weeks gestation with confirmed gestational hypertension (systolic BP ≥ 140 mmHg and/or diastolic BP ≥ 90 mmHg) and trace or more proteinuria on automated dipstick urinalysis. This is below the threshold of 1+ considered “test positive” by NICE [5] and will thus allow exploration of the lower threshold for the index tests, i.e. below 300 mg/l protein.

9.1.3 Exclusion criteria

Exclusion criteria: Women with gestational hypertension but no proteinuria on automated dipstick urinalysis, sustained proteinuria from before 20 weeks gestation, pre-existing renal disease, pre-gestational diabetes and chronic hypertension.

Figure 2: Study Patient Flow and Clinical Care



10. ETHICS

10.1 Declaration of Helsinki

The Investigator will ensure that this study is conducted in full conformity with the current revision of the Declaration of Helsinki (last amended October 2000, with additional footnotes added in 2002 and 2004).

10.2 Guidelines for Good Clinical Practice (GCP)

The Investigator will ensure that this study is conducted in full conformity with The European Union Clinical Trials Directive, which requires clinical trials to be conducted according to the principles of Good Clinical Practice (GCP) and was implemented into UK Statute by the Medicines for Human Use (Clinical Trials) Amendment Regulations 2006.

10.3 Obtaining informed consent

A patient information leaflet (PIS) will be given to all women at the time of booking for antenatal care by the community and clinic midwives. The leaflet will also be made generally available and prominently displayed in various areas within the participating hospitals and their community antenatal clinics. The leaflets will also be translated into minority languages (Polish and Urdu) and made available on the internet. The information will detail the exact nature of the study and the implications of participation in the study. It will be clearly stated that the woman is free to withdraw from the study at any time and for any reason without prejudice to future care, with no obligation to give the reason for withdrawal. All women will have the opportunity to ask questions about the study and to have their questions answered.

10.4 Withdrawal criteria

In accordance with the current revision of the Declaration of Helsinki (amended October 2000, with additional footnotes added in 2002 and 2004), woman have the right to withdraw both herself and her baby from the study at any time and for any reason, without prejudice to their future medical care. She is not obliged to give any reason for this. Should this happen the women will be informed that the data already collected will be used for study purposes.

10.5 Independent Ethics Committee

A copy of the protocol, proposed consent form, and written participant information and any proposed advertising material will be submitted to an Independent Ethics Committee for written approval. The Chief Investigator will submit and, where necessary, obtain approval from the Independent Ethics Committee for all subsequent protocol amendments and changes to the informed consent documents. The Investigator will notify deviations from the protocol to the Independent Ethics Committee in accordance with local procedures.

10.6 Participant confidentiality

The Chief Investigator will ensure that all information about the mother and baby is kept confidential. The mother and baby will be identified by name (consent will have been given by the parents) and unique study number on the data collection forms. This information will be collected with the parent(s) consent to enable 6 week follow-up to be undertaken. All documents will be stored securely and kept in strict confidence in compliance with Data Protection Act (1998).

11. ADVERSE EVENT MONITORING AND REPORTING

11.1 Expected Serious Adverse Events (SAE's)

The following are adverse events that could reasonably be expected for this group of mothers and babies during the course of the Study and do not require immediate reporting:

- Eclampsia
- Maternal admission to HDU/ITU
- Admission to NICU
- Stillbirth / Neonatal Death
- Maternal Death

11.2 Serious (unexpected) adverse event (SAE) reporting procedures

All expected SAE's will be reported on the data collection forms and will be reviewed by the Project Management Group (PMG) at the end of the pilot study. If any of the serious adverse events listed above occur they will be reported to the Oversight Committee (OC) as described and will also be reviewed by the PMG at the end of the pilot study.

11.3 Evaluation of AEs and SAEs

Seriousness, causality, severity and expectedness should be evaluated by the PMG. As this study is observational and does not involve a change in clinical practice all such events will also have been referred to the units Risk Management group and have been reviewed clinically.

Assessment of Seriousness

The Investigator should make an assessment of seriousness using standard definitions in Appendix two.

Assessment of Causality

The Investigator must make an assessment of whether the AE/SAE is likely to be related to false negative results from proteinuria testing according to the following definitions.

Unrelated: where an event is not considered to be related to the Study test.

Possibly: although a relationship to the Study test cannot be completely ruled out, the nature of the event, the underlying disease, concomitant medication or temporal relationship make other explanations possible.

Probably: the temporal relationship and absence of a more likely explanation suggest the event could be related to the Study test.

Definitely: the test result was directly related to the AE/SAE.

Given that clinical protocols are not being altered by this study and that it is already accepted that all proteinuria tests have false negative results it is unlikely that such assessments will result in stopping the study unless there is a clear over expression of AE/SAE with particular test results. Alternative causes, such as natural history of the underlying disease, other risk factors and the temporal relationship of the event to the treatment, should be considered and investigated.

Assessment of Expectedness

If an event is judged to be an AR/SAR, the evaluation of expectedness should be made based on knowledge of the event and the relevant results.

11.4 Reporting of SAEs/SARs/SUSARs

Once the Investigator becomes aware that an SAE has occurred in a study participant, they must report the information to the Study Office within 24 hours. The SAE form must be completed as thoroughly as possible with all available details of the event. If the Investigator does not have all information regarding an SAE, they should not wait for this additional information before recording the SAE information.

The SAE report must provide an assessment of causality and expectedness at the time of the initial report to the Study Office, detailing Assessment of Causality and Assessment of Expectedness as described above.
The Study Office will notify the Sponsors and the CI of all events reported for assessment, via fax.

Contact details for reporting SAE(s)
Please send SAE Form(s) via Fax 0191 222 8901,
Attention NCTU DAPPA Trial Manager

All unexpected SAE's must be reported to the CI within one working day of discovery or notification of the event. A Standard Operating Procedure (SOP) outlining the reporting procedure for clinicians will be provided on the reverse of the SAE form. An SOP will also be available as part of the Study specific SOPs, which will outline the reporting procedure at the Study Office. All SAE information must be recorded on an SAE form and faxed to the CI if necessary. Additional information received for a case (follow-up or corrections to the original case) need to be detailed on a new SAE form.

The CI will report all suspected adverse reactions, which are both serious and unexpected (SUSAR/SAE's), to the Competent Authorities (MHRA) and Ethics Committee concerned. Fatal or life-threatening SUSARs must be reported within 7 days and all other SUSARs within 15 days.

In addition to the expedited reporting above, the CI shall submit, once a year, or on request, a safety report to the Competent Authority.

11.5 Follow up procedures

After initially recording an AE or recording and reporting an SAE, the Investigator is required to follow each participant until resolution. Follow up information on an SAE should be reported to the Study Office.

12. STATISTICS

12.1 The Revised Sample size Calculation

The sample size for the study was determined in order to show that a quantitative assessment of SPCr or SACr at a given cut-off can safely rule out the possibility of severe PE. In diagnostic testing terms, the test should have a LR- of 0.1 or smaller, and a sensitivity of at least 90% with high specificity. Previous studies suggest that SPCr or SACr (when fully quantitative), might achieve this.
To demonstrate with 80% power that sensitivity is at least 90% within 95% confidence limits, assuming that sensitivity is actually 95%, requires 240 women with severe PE.
In an interim analysis of the first 500 recruited women we found 78 who met a proxy definition of severe PE (primary outcome data not yet being available for most participants) – that is, a prevalence of 15.6%. This estimate is likely to be conservatively low, as 81 women (16.2%) out of the first 500 recruited women did not have enough data currently available to determine even the proxy outcome. Allowing for 14% of participants to have missing data on the primary outcome in the final analysis, we therefore need to recruit 1710 women with gestational hypertension and suspected PE to the study. We have based this 14% estimate on the preliminary analysis of the first recruited 1200 women.

12.2 Analysis

We aim to show that a quantitative assessment of SPCr or SACr can safely rule out the possibility of adverse outcomes. Diagnostic accuracy of laboratory and POC care measurements of SPCr and SACr at given cut-offs will be summarised using sensitivity, specificity, and positive and negative likelihood ratios, estimated using standard methods for proportions. Sensitivity and specificity at different cut-offs will be used to plot non-parametric receiver operating characteristic (ROC) curves for the different assays. Laboratory quantitative assessments of SPCr and SACr, POC are assays, and laboratory measures of 24-hour urine protein will be compared by looking at the difference between the areas under the respective ROC curves. Caution should be exercised if an ROC curve is used to select an “optimal” cut-off for a continuous test measure without validation in a separate sample. We will use our sample to validate cut-offs identified in previous research [7]. By restricting analyses to those women with 1+ or higher on the automated dipstick test, we will evaluate test performance in the population of women who would currently be referred for further testing. Because we may wish to consider making testing more inclusive, we will also analyse our entire sample to evaluate test performance in women with trace or higher on the automated dipstick test.

In addition we will use linear regression to explore the relationship between each SPCr/SACr measurement and the local measurement of 24-hour proteinuria (“linear” regression in the sense of a Normal model with linear link function; we will have a large enough sample to investigate non-linear associations between SPCr/SACr and 24-hour proteinuria). In particular, we will investigate whether the relationship is different at sites using different 24-hour assays, and whether these differences might be explained by measured patient characteristics. If there are differences between sites, our primary analysis of diagnostic accuracy will be stratified by the type of 24-hour assay used. To make use of the full sample, and to try and obtain more generalizable results, we will also fit multivariable logistic regression models for predicting outcomes using SPCr/SACr, site, and patient characteristics.

All analyses will be carried out using Stata v11 (Stata Corporation, College Station, Texas USA).

12.3 Economic evaluation

12.3.1 Perspective and cost data collection

We will take an NHS provider perspective when considering the test results and associated costs and effects for the following diagnostic testing options:

1. Dipstick alone
2. Dipstick + 24 hour urine protein (gold standard)
3. Dipstick + SPCr (laboratory)
4. Dipstick + SACr (laboratory
5. Dipstick + SPCr (point of care)
6. Dipstick + SACr (point of care)

We believe that the administration of the 24 hour urine protein, SPCr and SACr will be similar in costs. We will be able to verify whether this is true during our trial through a bottom up collection of data for a small subsample of tests at one study centre. We shall prospectively collect cost data on NHS resource use for this subsample through a time and motion study [20]. The main resources to be examined include:

1. the test
2. the equipment
3. staff time (lab technician, midwife, inpatient costs for 24-hour urine collection)

Study staff will observe and record the amount of staff time for each lab test. Information on unit costs will then be required to attach to each resource item in order that an overall cost per test can be calculated. Unit costs of the test and equipment will come from obtained from the company providing the test and equipment (Siemens Healthcare Diagnostics Limited, Sir William Siemens Square, Frimley, Surrey, GU16 8QD).Staff time will be drawn from routine sources [21].

12.3.2 Economic analysis

The test that diagnoses PE and severe PE with the highest sensitivity and specificity is likely to be have both the lowest cost to the NHS and the best outcomes in terms of better case management and consequently, Quality Adjusted Life Years (QALYs) lost. The most accurate test will provide cost savings for the NHS as false negatives will be treated earlier. If SPCr or SACr demonstrate an increase in diagnostic accuracy, a consequence would be a decrease in unnecessary hospitalisation and outpatient visits and associated costs in the false positives. The key driver of the costs in the economic evaluation by Meads was the poor sensitivities and specificities of the tests [22]. Accordingly, our economic evaluation will improve upon their work through the inclusion of the new information on sensitivity and specificity provided by our trial while also examining the cost-effectiveness of test combinations, which was not considered in the HTA report due to lack of information [22].

We will construct a decision tree to extrapolate the costs and effects of the diagnostic test options beyond the time of our trial. This will build on the NICE Hypertension in Pregnancy Guideline to calculate the cost per QALY for each test [5]. The trial will provide us with the diagnostic accuracy of each test, which we will combine with data from the literature on QALYs lost and unit costs for true positives, true negatives, false positives and false negatives. True positives and true negatives will not require a QALY calculation. False positives will result in an unnecessary hospitalization for one day or an extra outpatient visit. While this could result in some decrease in QoL, NICE did not include this in their model due to the brevity of time it affects. Furthermore, our

lay representative maintained that for some of the women this hospitalisation would be a welcome rest from responsibilities. Consequently, we will calculate QALYs lost for false negatives only. Costs for each outcome will also build on the NICE model. Resource use will be prospectively collected for the women enrolled in the study. The main resources to be collected include:

1. Admissions to the hospital for labour and/or complications
2. Admissions to neonatal intensive care, high dependency units and special baby units.

Information on appropriate unit costs will then be attached to these resource use items. These costs will be collected from the participating hospital sites if possible and then supplemented with costs from routine sources, such as the Reference Costs Database [23].

Planned improvements to the NICE model include the examination of PE and severe PE as outcomes and trial data on prevalence of PE in women with gestational hypertension. Collecting data on the prevalence of PE is an important outcome of our trial as it was a key driver of results in the NICE model and also highly uncertain. We will also adapt the model to examine other relevant outcomes, such as cost per hospitalisation averted and cost per case of severe PE correctly identified.

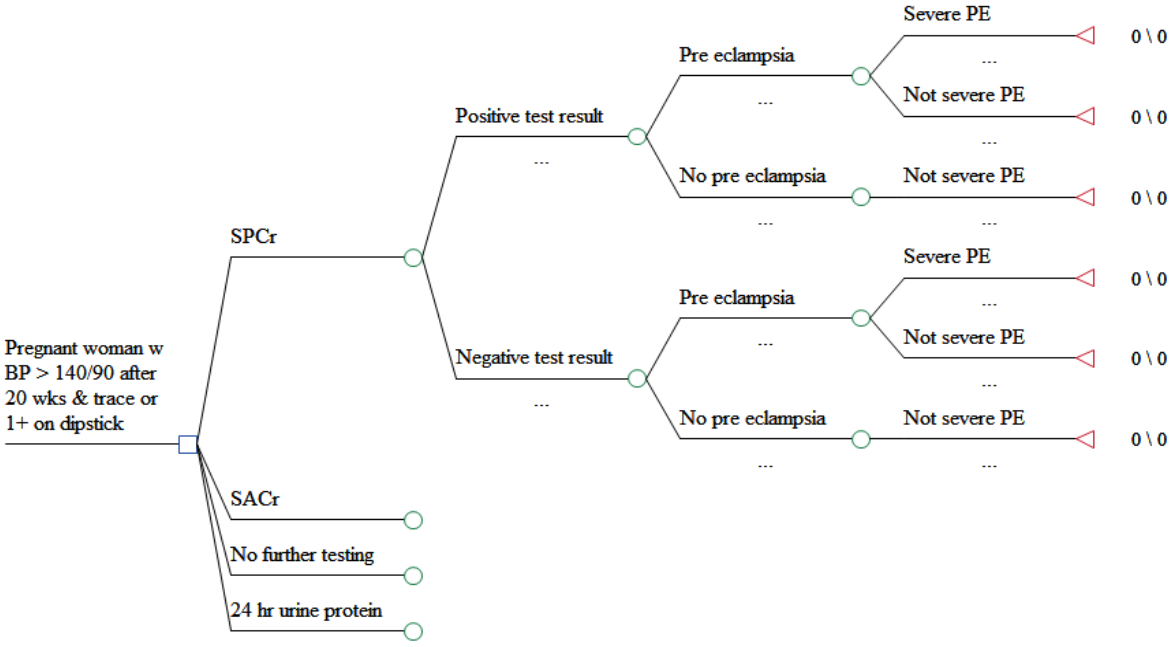


Figure 3 Decision tree to compare the cost effectiveness of different screening options for PE in women with gestational hypertension

12.3.3 Discounting

The time horizon for the difference in costs and benefits will be over the lifetime of the mother and child as in the NICE model [5]. Many of the costs and benefits will be experienced in future years. Using discounting, adjustments will be made to reflect this differential timing. The base-case analysis will adhere to the Treasury recommendation of 3.5% for public sector projects.

12.3.4 Presentation of results and sensitivity analysis

The economic analysis will result in a cost per QALY for each screening option as calculated by the decision tree. Using the costs to the NHS and QALY loss calculated for each screening option, we can calculate the Incremental Cost-Effectiveness Ratio (ICER) with 24 hour urine protein as the comparator, where:

ICER = (Cost of regime A – Cost 24 hour urine protein)/ (Utility of regime A – Utility 24 hour urine protein).
The ICER will allow us to see the relationship between the mean difference in cost and the mean difference in benefits for each screening option. In this way, the cost per QALY of each index test can be compared to current treatment.
Simple and probabilistic sensitivity analyses will be employed to explore the robustness of these results to plausible variations in key assumptions, such as prevalence of PE in women with gestational hypertension.

13. QUALITY CONTROL AND QUALITY ASSURANCE PROCEDURES

Compliance with protocol will be ensured by a number of procedures:

13.1 Site set-up and training

Site initiation visits will be performed before the first woman is enrolled at each site to ensure staff are fully trained in 'DAPPA' procedures, the protocol and the DAPPA database. Siemens, who are providing the Urinalysis machines for centres who require them, will travel to each centre to arrange for training in the machine. Refresher site training will be performed as required by the Trial Manager.

All sites will be monitored by the Newcastle Clinical Trials Unit by corresponding with sites remotely as agreed with the study Sponsor.

13.2 Data collection, processing and monitoring

All study data are:

- collected using DAPPA DCFs
- proceeded and monitored centrally for consistency, viability and quality at the Study Office
- screened for out-of-range data, with cross-checks for conflicting data within and between data collection forms using computerised logic checking systems
- referred back to the relevant centre for clarification in the event of missing items or uncertainty
- processed using a double data entry system by independent data clerks
- stored for 21 years

13.3 Monitoring data quality

All data will be monitored using central statistical monitoring for quality assurance (consistency, viability and quality) using bespoke data management systems. Central statistical monitoring is used to monitor patterns of recruitment at sites, frequency of outcomes found, time of recruitment etc.

The database will be supplied by MedSciNet, who will establish Study specific programs to extract certain fields from the database (as requested by the CI and to cross check information). These fields may include measures of eligibility criteria, duration of treatment and compliance.

The CI will review the results generated for logic and for any patterns or problems.

Outlier data will be investigated.

The CI with the PMG will decide if any action is required.

14. DATA HANDLING AND RECORD KEEPING

All trial data will be handled, computerised and stored in accordance with the Data Protection Act 1998. Caldicott Guardian approval will be sought at each site for access to and use of patient identifiable data.

All trial data will be entered onto a database supplied by MedSciNet. This will be a validated system built to standardised designs. Data coding and automated validation checks with message alerts for any problems are used to ensure data quality.. Access to the trials system is restricted to authorised users who have a username and secret password. Functionality on the application is restricted based on the users' role. A full audit log of all changes to trial data is maintained automatically by the system. Statisticians will use the data for analysis to produce the results of the pilot study.

MedSCiNet database and web application servers are protected by physical and electronic access security measures.

15. PROJECT MANAGEMENT

Dr Jason Waugh will be responsible for overall project management and supervision of the staff. He will ensure that targets are met, data collections tools are developed, recruitment is successful, data are collected and managed effectively and that follow-up is completed. This will also include visits to the Maternity Units collaborating and 'trouble-shooting' any problems that arise.

He will be responsible with the Project Management Team, which will comprise all co-applicants whose individual expertise is listed below.

Professor S.C.Robson	Obstetrician	University of Newcastle
Professor K.H.Khan	Obstetrician	University of London
Dr S.Thangaratinan	Obstetrician	University of London
Professor A.Shennan	Obstetrician	University of London
Ms Angela Devine	Health Economist	University of London
Dr Richard Hooper	Statistician	University of London
Dr Edmund Lamb	Clinical Scientist	East Kent Hospitals University NHS Foundation Trust
Professor Chris Price	Biochemist	University of Oxford
Ms Fiona Milne	Lay Representative	APEC (Action on Preeclampsia)
Professor Elaine McColl	Senior Trial Manager	Newcastle CTU
Ms Jenn Walker	Trial Manager	Newcastle CTU

It is envisaged that a Trial Steering Committee and a Data Monitoring Committee will be required for the study – invitations outstanding.

15.1 Participating sites

Sites participating in the project should:

- use NICE Hypertension in Pregnancy Guideline CG 107 for the management of hypertensive disorders in Pregnancy.

16. RISK ASSESSMENT

The CI assessed the study using a tool designed by Barts and the London NHS Trust. Overall, the study was considered to be a minor risk, broken down as follows:

- Patient/study population - Minor risk as subject group not considered vulnerable as they are able to give informed consent and may benefit from taking part
- Intervention – Minor risk as involves a clinical intervention, which represents no deviation from normal management
- Chief Investigator - Minor risk as supported by well trained and experienced team
- Monitoring arrangement – Moderate risk as Study team GCP/Research Governance team qualified and will undertake internal governance monitoring. Independent assessor identified if required
- Information/personal data – Minor risk as data anonymised when contact with participant completed, no data will be sent outside the UK, and there is clear provision for archiving and clear process for results dissemination
- Protocol – Minor risk as clear complete rationale and scientific justification together with clearly defined proposal
- Finance – Minor risk as fully funded by HTA and with R&D contract in place
- Consent – Minor risk as clearly defined process for informed consent with named midwife in place in each Maternity Unit, a clearly defined recruitment process, clearly identified risks and benefits and a clearly and concise consent form and patient information sheet

17. INSURANCE AND INDEMNITY

The pilot study is funded by the HTA scheme of the National Institute of Health Research (NIHR).

NUTH NHS Foundation Trust will act as a Sponsor and will provide clinical trials insurance.
The Sponsor is responsible for ensuring proper provision has been made for insurance or indemnity to cover their liability and the liability of the Chief Investigator and staff.

The following arrangements are in place to fulfil the Sponsor's responsibilities:

- The Protocol has been designed by the CI and researchers employed by NUTH and collaborators. NUTH has insurance in place (which includes no-fault compensation) for negligent harm caused by such Protocol design by the CI and researchers employed by NUTH.
- The Sites involved in the Study will be liable for clinical negligence and other negligent harm to individuals taking part in the Study and covered by the duty of care owed to them by the Sites concerned. The Sponsor requires individual Sites participating in the Study to arrange for their own insurance or indemnity in respect of these liabilities.

Sites which are part of the United Kingdom's National Health Service will have the benefit of NHS Indemnity.

18. PUBLICATION POLICY

The CI will co-ordinate dissemination of the data from the Study. All contributors will be listed at the end of the report, with their contribution to the pilot study identified. Acknowledgement will include all local investigators, the Study Office and staff.

19. REFERENCES

[1] Menzies J et al. Current CHS and NHBPEP criteria for severe preeclampsia do not uniformly predict adverse maternal or perinatal outcomes. Hypertens Pregnancy 2007;26: 447-62.
[2] Chappell LC et al. Assessment of proteinuria in pregnancy. BMJ. 2008; 336(7651): 968-9
[3] Kuo VS et al. Proteinuria and its assessment in normal and hypertensive pregnancy. Am J Obstet Gynecol 1992; 167: 723-8
[4] Waugh J et al. Effect of concentration and biochemical assay on the accuracy of urine dipsticks in hypertensive pregnancies. Hypertens Preg.2001;20:205-17
[5] NICE. The management of hypertensive disorders during pregnancy CG107, 2010. London.
[6]. Waugh J et al. Validation of the DCA 2000 microalbumin:creatinine ratio urinanalyzer for its use in pregnancy and preeclampsia. Hypertens Pregnancy. 2003; 22:77-92.
[7]. Waugh JJ et al. Optimal bedside urinalysis for the detection of proteinuria in hypertensive pregnancy: a study of diagnostic accuracy. BJOG. 2005; 112: 412-7
[8]. Waugh J et al. Urine protein estimation in hypertensive pregnancy: which thresholds and laboratory assay best predict clinical outcome?. Hypertens Pregnancy. 2005; 24: 291-302
[9] Centre for Maternal and Child Enquiries (CEMACE), Saving Mothers Lives: reviewing maternal deaths to make motherhood safer: 2006-08. The Eighth Report on Confidential Enquiries into Maternal Deaths in the United Kingdom, 2011. BJOG 118 (Suppl. 1): 1-203
[10] Centre for Maternal and Child Enquiries (CEMACE), Perinatal Mortality 2008, 2010.
[11] Helewa ME et al. Report of the Canadian Hypertension Society Concensus Conference: 1. Definitions, evaluation and classification of hypertensive disorders in pregnancy. CAMJ 1997; 157: 715-25
[12] Hypertension in pregnancy. ACOG Technical Bulletin No. 219. Washington DC: ACOG, January 1996
[13] Price CP et al. Use of protein:creatinine ratio measurements on random urine samples for prediction of significant proteinuria: a systematic review. Clin Chem. 2005 Sep;51(9):1577-86.
[14] Cote, AM et al. Diagnostic accuracy of urinary spot protein:creatinine ratio for proteinuria in hypertensive pregnant women: systematic review. BMJ, 2008. 336 (7651): 1003-6.
[15] Thangaratinam, S. et al. Estimation of proteinuria as a predictor of complications of pre-eclampsia: a systematic review. BMC Med 2009. 7: 10.
[16]. Waugh JJ, Clark TJ, Divakaran TG, Khan KS, Kilby MD. Accuracy of urinalysis dipstick techniques in predicting significant proteinuria in pregnancy. Obstet Gynecol. 2004; 103: 769-77
[17]. Waugh J, Bell SC, Kilby MD et al. Urinary microalbumin/creatinine ratios: reference range in uncomplicated pregnancy. Clin Sci (Lond). 2003; 104: :103-7.
[18] Lamb EJ et al. How should proteinuria be detected and measured? Ann Clin Biochem. 2009 ; 46: 205-17
[19] Waugh J et al. The effect of urine volume and biochemical assay on the accuracy of dipstick urinalysis. Hypertens Pregnancy. 2001; 20:205-217
[20] Daniels, J., et al., Rapid testing for group B streptococcus during labour: a test accuracy study with evaluation of acceptability and cost-effectiveness. Health Technol Assess, 2009. 13: 1-154, iii-iv.
[21] Curtis, L., Unit costs of health & social care. 2008: Personal Services Research Unit.

[22] Methods of prediction and prevention of pre-eclampsia: systematic reviews of accuracy and effectiveness literature with economic modelling. Meads March 2008 HTA report.
[23] NHS reference costs 2008-09 [published 28 January 2010]. London: Department of Health; 2010;
(http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_111591)
[24] Pope C et al (2006) 'Analysing qualitative data' in Pope et al (Eds) Qualitative Research in Helath Care. Blackwell/BMJ books, Malden MA and Oxford.
[25] Lewin S et al. Interventions for providers to promote a patient-centred approach in clinical consultations (Review). Cochrane Collaboration 2009 Issue 1 Wiley.