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NOTTINGHAM CLINICAL TRIALS UNIT at the University of Nottingham

NHS Manchester University NHS Foundation Trust

MANCHESTER 1824 The University of Manchester

STUDY PROTOCOL

Screen and Treat with Aspirin to Reduce Pre-eclampsia

Protocol Version Number: Final Version 1.1

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Sponsor Reference Number	R130647
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CI and Sponsor Approval Page

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator (CI) agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Research Governance Framework for Health and Social Care 2005 and subsequent amendments, Good Clinical Practice (GCP) guidelines, the Sponsor's (and any other relevant) Standard Operating Procedures (SOPs), and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies and serious breaches of GCP from the study as planned in this protocol will be explained.

This protocol has been approved by:	
CI Name:	Professor Jenny Myers
Study Role:	Chief Investigator
Signature and date:	
Date:	__ __ - __ __ __-20 __ __ (dd-mmm-yyyy)

Sponsor approval	
Sponsor representative name:	
Signature and date:	
Date:	__ __- __ __ __-20 __ __ (dd/mmm/yyyy)
Sponsor statement: Where the University of Manchester takes on the Sponsor role for oversight of protocol development, signing of the IRAS form by the Sponsor will serve as confirmation of approval of this protocol.	

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The protocol was developed by the CI, co-investigators and members of the STARshiP Study Team at the coordinating centre. The STARshiP study team at the coordinating centre comprises of the Professor and Associate Professor of Clinical Trials, Senior and Trial Manager, Trial Co-ordinator, Senior and Trial Statisticians, Senior and Data Managers and Senior Research Fellow in eHealth.

The protocol has also been developed in collaboration with parents and public contributors, in several ways: (i) two parent co-investigators (Jane and Tom Harvey) who have lived experience of pre-eclampsia, (ii) 7 members of the STARshiP patient and public involvement (PPI) group, (iii) the Action on Pre-eclampsia Charity (APEC) and (iv) Bump2Baby Parents' Voices Facebook Group (c. 270 members) whose membership are people with an interest in maternal and newborn health research, including parents with lived experience of pregnancy resulting in different outcomes and pre-eclampsia.

A full list of study sites can be found on the website *www.starship.ac.uk*

Protocol Amendments

Amendment number	Protocol version number	Type of amendment	Summary of amendment

Abbreviations

Abbreviation	Term
ABPI	Association of the British Pharmaceutical Industry
AE	Adverse Event
APC	Admitted Patient Care (inpatient) for England
APEC	Action Against Pre-eclampsia Charity
ASPRE	Combined Multi-Marker Screening and Randomised Patient Treatment with Aspirin for Evidence-based Pre-eclampsia Prevention
BMI	Body Mass Index
CACE	Complier Average Causal Effect
CAG	Confidentiality Advisory Group
CC	Critical Care for England
CEA	Cost Effectiveness Analysis
CFIR	Consolidated Framework for Implementation Research
CI	Chief Investigator
CONSORT	Consolidated Standards of Reporting Trials
CR	Cluster Randomised
CRL	Crown Rump Length
CUA	Cost Utility Analysis
CV	Curriculum Vitae
DMC	Data Monitoring Committee
DMP	Data Management Plan
ECDS	Emergency Care Dataset
FMF	Fetal Medicine Foundation
FGR	Fetal Growth Restriction
GA	Gestational Age
GCP	Good Clinical Practice
GP	General Practitioner
HES	Hospital Episodes Statistics (England)
HSG	Health and Safety Guidance
ICC	Intracluster co-efficient
ICF	Informed Consent Form
ICER	Incremental Cost Effectiveness Ratio

ISRCTN	International Standard Randomised Controlled Trials Number
ITT	Intention to Treat
LDA	Low Dose Aspirin
LMNS	Local Maternity and Neonatal Systems
MAP	Mean Arterial Blood Pressure
MESH	Message Exchange for Social Care and Health
MoM	Multiple of the Median
MSDS	Maternity Services Dataset
NCTU	Nottingham Clinical Trials Unit
NHS	National Health Service
NICE	National Institute for Health & Care Excellence
NNRD	National Neonatal Research Database (England, Wales, and Scotland)
NNU	Neonatal Unit
NSC	National Screening Committee
ONS	Office for National Statistics for England and Wales
OP	Outpatient Appointments for England
PAPP-A	Pregnancy Associated Plasma Protein A
PE	Pre-eclampsia
PI	Principal Investigator
PICANet	Paediatric Intensive Care Audit Network
PIS	Patient Information Sheet
PlGF	Placental Growth Factor
PTB	Pre-term birth
QALY	Quality-Adjusted Life Year
RC	Randomised Controlled
RDN	Research Delivery Network
REC	Research Ethics Committee
REDCap	Research Electronic Data Capture
RDN	Research Delivery Network
RR	Relative Risk
SAP	Statistical Analysis Plan
SBL	Saving Babies Lives
SGA	Small for gestational age

SOP	Standard Operating Procedure
SPREE	Screening programme for pre-eclampsia
SW	Stepped wedge
SW-CR	Stepped wedge cluster randomised
TMF	Trial Master File
TMG	Trial Management Group
TOC	Trial Oversight Committee
TRE	Trusted Research Environment
UKHSA	United Kingdom Health Security Agency
UKNU	United Kingdom Neonatal Collaborative
UON	The University of Nottingham
UtA-PI	Uterine Artery Doppler Pulsatility Index
WHO	World Health Organisation

Study Summary

Study Title	Screen and Treat with Aspirin to Reduce Pre-eclampsia
Short title	STARshiP
Study Design	Multi-centre, stepped-wedge cluster randomised study with an internal pilot phase and parallel economic evaluation.
Study Participant Population	Pregnant women/people in the first trimester of pregnancy.
Key Eligibility Criteria	
Trust Level Eligibility Criteria	**Trust level inclusion criteria:** • Located within England. • Have a minimum of 2500 births per year (latest full year data) in the participating National Health Service (NHS) Trust. ○ NHS Trusts with fewer than 2500 births per year may potentially be paired together to create a randomisation unit for the purpose of the study. • Committed to universal implementation of the Fetal Medicine Foundation (FMF) screening test within a specified time point following study commencement. **Trust level exclusion criteria:** • Already providing first trimester screening for pre-eclampsia (PE) as standard care or participating in another study implementing care pathways which include first trimester screening for PE. • Unable to commit to universal implementation of the FMF screening test within the specified timeframe. Trusts may still participate where they are able to make a commitment to performing UtA-PI measurement of the FMF screening test where feasible.
Individual level eligibility criteria (two levels of eligibility)	**Testing level inclusion criteria:** • All pregnant women/people receiving antenatal care prior to 16 weeks' gestation at participating NHS Trusts will be eligible to be screened (to ensure timely prescription of aspirin). The window for FMF testing is 11+2 to 14+1 weeks (crown rump length 45-84mm). Eligibility is not dependent on participation in the NHS Fetal Anomaly trisomy screening programme.

	Testing level exclusion criteria: • Known congenital anomaly incompatible with survival at birth, of a singleton or all multiple fetuses e.g. anencephaly. • Fetal demise/miscarriage before PE risk assessment completed. **Dataset level inclusion criteria:** All pregnant women/people with an early pregnancy screen captured as part of the study. Individuals may be included more than once if multiple early pregnancy screening episodes in different pregnancies are performed. Pregnant women/people who experience a miscarriage or stillbirth after early pregnancy screening will be included as they may have had testing for PE and PE may be implicated in the aetiology of their pregnancy loss. **Dataset level exclusion criteria:** Withdrawal of consent to use data, either through the local study specific opt out or the NHS data-opt out. Pregnancy outcome data for pregnant women/people screened during the transition phase for NHS Trusts will be collected but excluded from the primary outcome analysis; it will be available for use in secondary analyses.
Planned Sample Size	Approximately 224,000 pregnancies across 16 NHS Trusts will contribute to the primary outcome analysis. There will be an estimated 235,200 total pregnant women/people screened.
Planned Study Period	The study will collect screening data and subsequent pregnancy outcome data for a 34-month period.
Primary outcome	Iatrogenic preterm birth (PTB) rate (<37 weeks' gestation; including stillbirths).
Secondary outcomes	Maternal and neonatal outcomes from the PE core outcome set that are reported in routine healthcare datasets
Intervention	The FMF first trimester screening test, a clinical risk prediction model that uses clinical risk factors, uterine artery Doppler ultrasound measurements, Placental Growth Factor (PlGF) concentration blood test, and maternal blood pressure to quantify personal pre-eclampsia risk.

Comparator	Standard care by identification of maternal risk factors alone (according to National Institute for Health & Care Excellence (NICE) guidelines).
Health Economics	Objective: To undertake a health economic evaluation of the FMF screening test for PE in the whole study population and in pre-specified subgroups. Outcomes: incremental cost per iatrogenic PTB avoided, and incremental cost per quality-adjusted life year (QALY) gained.
Implementation Evaluation	Objective: To assess the acceptability of the two PE risk assessment methods, and subsequent management recommendations to maternity patients and service providers.

Study Flow Chart

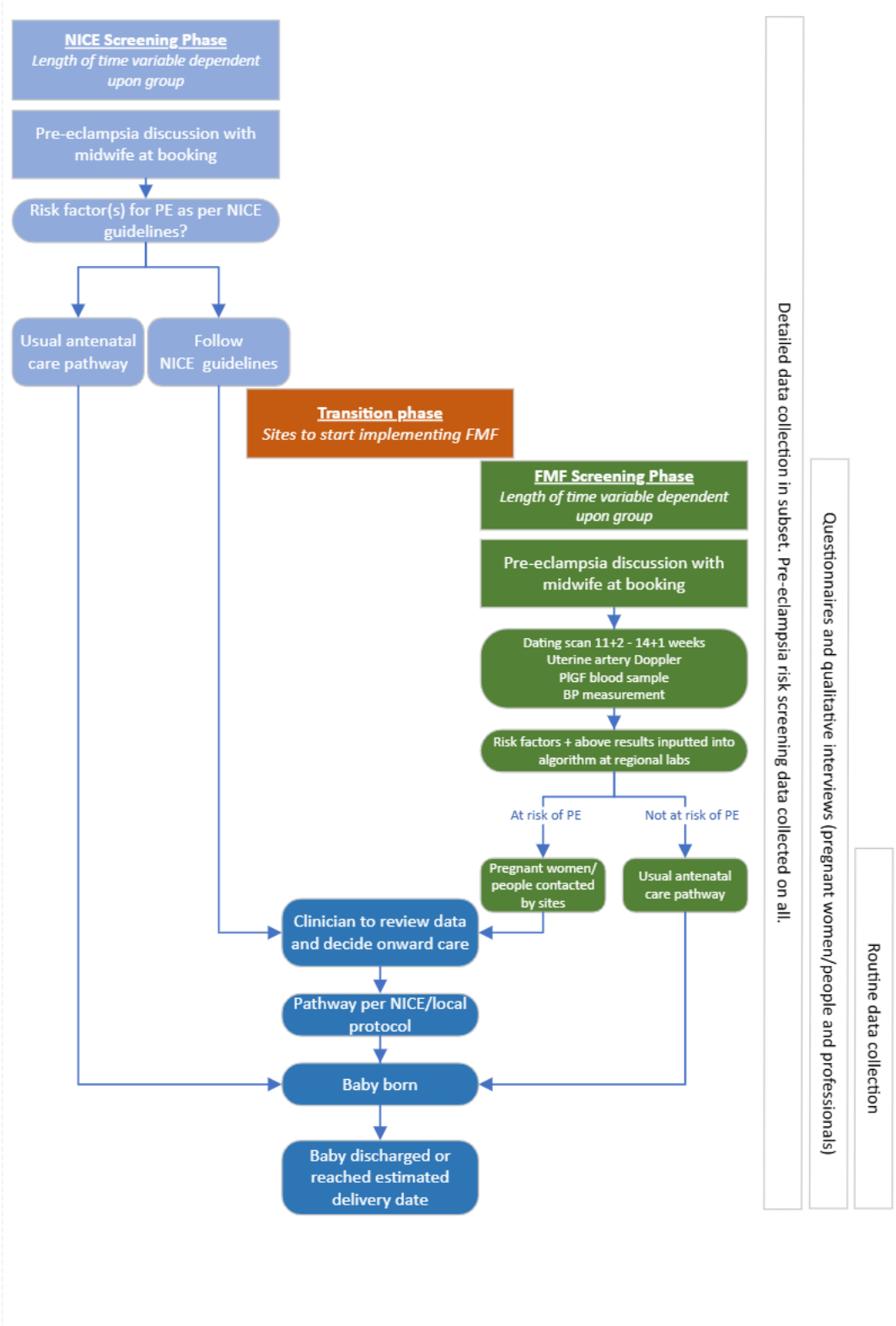

Figure 1 - Flow chart depicting the expected pathway within the NICE Screening Phase (National institute of Health and Care Excellence) and the FMF Screening Phase (Fetal Medicine Foundation).

1 Background and Rationale

1.1 Background

Pre-eclampsia (PE), a hypertensive disorder specific to pregnancy, and fetal growth restriction (FGR; inadequate intrauterine growth) are leading causes of preterm birth (PTB) (birth before 37 weeks' gestation). PE develops after 20 weeks of pregnancy and generally, the earlier that the condition emerges, the more severe the consequences. Healthcare costs are incurred by high maternal morbidity [1] and the care of preterm babies. It is also associated with future cardiovascular disease [2]. There is no curative treatment for PE other than delivery of the baby [3], although pregnant women/people will be offered antihypertensive treatment if blood pressure remains over 140/90mmHg. To prevent maternal complications and fetal death, intensive surveillance of blood pressure, proteinuria and blood, liver and renal biomarker testing are carried out. When blood pressure remains high, or there is deterioration in renal, liver or neurological function, or other significant maternal complications, iatrogenic PTB, by induction of labour/caesarean birth, is indicated. Clinical prediction models are available to determine the most appropriate place of care and thresholds for intervention [4]. Management of PE manifesting before 37 weeks (preterm PE) is therefore a balance of prolonging the pregnancy for as long as possible (for fetal maturity) without compromising maternal health.

Nationally PTB leads to >50% of all perinatal deaths [5-7]. Neonatal intensive care is expensive, costing £2,500/day (average length of stay 14 days) for extremely preterm infants [5-8]. PTB survivors experience repeated childhood hospital attendances [8], and increased chance of intellectual impairment, educational support [9], cerebral palsy and chronic lung disease as well as being more likely to be disabled, and more likely to develop cardiometabolic disease as adults [10-14]. PTB is one of the largest single contributors to the Global Burden of Disease [15]. Prevention of PTB is therefore a high priority.

1.2 Current Practice

For decades, low dose aspirin (LDA) has been considered an effective preventative treatment for PE [16, 17], and is most effective in preventing births <32 weeks' gestation [18], when the consequences to the baby are most severe. Current National Institute for Health & Care Excellence (NICE) guidelines recommend aspirin prophylaxis for high-risk individuals based on PE risk factors [19].

Major risk factors (any 1 factor)	**Moderate risk factors** (2 or more factors)
• Hypertensive disease during a previous pregnancy. • Chronic kidney disease. • Autoimmune disease such as systemic lupus erythematosus or antiphospholipid syndrome. • Type 1 or type 2 diabetes, • Chronic hypertension [hypertension present at booking or before 20 weeks' gestation, or if	• Nulliparity. • Aged 40 years or older. • Pregnancy interval of more than 10 years. • Body mass index (BMI) of 35 kg/m^2 or more at first visit. • Family history of pre-eclampsia. • Multi-fetal pregnancy.

antihypertensives are being taken when referred to maternity services].	

Pregnancies at high risk of PE are those with any one major or two or more moderate risk factors from the list above. Those considered at high risk of PE are advised to take 150mg of aspirin daily from 12 weeks until the birth of the baby.

1.3 Alternative Testing Strategies

The risk of developing PE prior to 37 weeks gestation (preterm PE) can be derived and quantified by a clinical risk prediction model developed by the Fetal Medicine Foundation (FMF). A multimodal algorithm (hereafter "FMF screening test"), was developed over a series of observational studies [20-22] and is applicable in the first trimester (crown rump length (CRL) 45 – 84mm, equivalent to 11+2 to 14+1 weeks gestation). It incorporates maternal risk factors, maternal Mean Arterial blood Pressure (MAP), maternal circulating concentration of PlGF and Uterine artery Doppler Pulsatility Index (UtA-PI) [23]. All values are entered into a calculator algorithm (e.g. https://fetalmedicine.org/research/assess/preeclampsia/first-trimester for demonstration purposes only) which then produces an individual's risk score of developing preterm PE based on maternal history and additional biophysical or biomarkers measurements as available, in a manner equivalent to trisomy risk estimation. In previous studies [24], a preterm PE risk of greater than 1 in 100 has been considered a "high risk" result prompting consideration of LDA prophylaxis as per current practice with NICE screening.

1.4 Evidence for the FMF algorithm

The FMF algorithm was developed and internally validated by Nicolaides, Wright and colleagues at the Fetal Medicine Foundation. It has been externally validated in a 13 centre (six countries) multicentre randomised controlled (RC) study led by the same team as well as by independent researchers [20, 25, 26]. When combined with LDA prophylaxis taken from 11-14 weeks until 36 weeks gestation, the FMF screening test appears to double the detection rate for preterm PE in comparison to the NICE screening (82% vs 41%) [22]. When the FMF screening test is calibrated to produce a fixed screen positive rate of 10.3% and combined with LDA prophylaxis, preterm PE occurred in 3.4% of pregnant women/people, compared to 6.8% of pregnant women/people who were deemed at high risk using the NICE screening tool [22]. It also appears to outperform NICE screening for preterm PE, particularly in pregnant women/people from black and ethnic minority groups or those in their first pregnancy [27, 28].

In the ASPRE study [24, 29], using the FMF screening test to target LDA prophylaxis, 11% of the population screened positive. 60% of these individuals were randomised to 150mg LDA or placebo. A 63% relative reduction in preterm PE was observed (preterm PE 4.3% vs 1.6%) [30]. A reduction in preterm small for gestational age (SGA) birthweight was also seen, predominantly among those with PE. Re-analysis of the data from SPREE and ASPRE studies suggests that 40% and 70% of preterm and extremely preterm SGA birthweight births could be prevented by LDA prophylaxis among pregnancies assessed as high PE risk by the FMF screening test [26]. Two further studies have reported similar reductions in preterm PE rates; a single site United Kingdom (UK) study reported 80% reduction [27], a larger Australian private healthcare study reported an adjusted relative risk (RR) of PE of 0.70 (95% Confidence

Interval [CI] 0.58-0.84)) and PTB of 0.92 (95% CI 0.88–0.97) compared with an unscreened population [31].

1.5 Implications of first trimester screening for PE

Widespread adoption of a more sensitive early pregnancy PE screening test and targeting of LDA prophylaxis has the potential to dramatically reduce National Health Service (NHS) costs. This would be achieved through reduced maternal surveillance, hospital admission, operative birth, and high dependency care associated with reduced incidence of preterm PE. Neonatal admissions and length of stay would be reduced, and health and social care costs impacted through decreased childhood hospital admissions, cerebral palsy, and chronic lung disease.

The FMF screening test has not been widely adopted in the UK or internationally. Concerns regarding cost effectiveness and implementation logistics, given the low prevalence of severe/early-onset disease (0.8%), need to be addressed. In an NHS Trust hospital with 4,500 births annually, the annual cost of FMF screening test (£177,345 using PlGF measurement) would be balanced by the expected neonatal cost savings from the 17 cases of preterm PE prevented [18, 20, 21, 30] if each case cost ≥£10,450. In reality, the cost per preterm PE case is variable. Short term neonatal costs exceed £100,000 alone for the earliest born, smallest babies [8, 32].

The United Kingdom National Screening Committee (UK NSC) define the criteria for appraising the viability, effectiveness and appropriateness of a population screening programme [8, 32]. In November 2022, the UK NSC restated its position that *population* screening for PE is not recommended. The consequences of PE are different depending on when it happens during pregnancy. The UK NSC review divided the evidence into two groups: preterm PE and term PE. Screening for **all** PE and **term** (i.e. ≥37 weeks' gestation) PE is not recommended because there is:

- No test that is reliable at predicting mothers who will develop PE in these populations.
- Not enough evidence for a treatment to prevent **term** PE in mothers at risk.

The UK NSC stated there may be enough evidence to support screening for **preterm** PE because there is evidence:

- To support a possible screening test in this population that uses maternal risk factors together with results from prenatal ultrasound and blood.
- From one good quality study, that LDA (150 mg) given from 11 to 14 weeks of pregnancy until 36 weeks is safe and can reduce the risk of developing **preterm** PE in mothers shown to be at risk.

2 Study Rationale and Design Justification

2.1 Justification for the STARshiP study

The UK NSC recommended that more work should be done to evaluate the harms and benefits of a universal, population-based screening programme, recognising that screening for preterm PE could be considered as criteria 4 and 9 of the criteria for viability, effectiveness and appropriateness of a screening programme are fulfilled. STARshiP will address other UK NSC criteria namely:

- Criteria 11: There should be evidence from high quality randomised controlled (RC studies that the screening programme is effective in reducing mortality or morbidity. Where screening is aimed solely at providing information to allow the person being screened to make an 'informed choice', there must be evidence from high quality studies that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened. The STARshiP randomised study will provide further evidence for this criterion.
- Criteria 12. There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/ intervention) is clinically, socially, and ethically acceptable to health professionals and the public. The mixed methods evaluation within STARShiP would provide this evidence.
- Criteria 13. The benefit gained by individuals from the screening programme should outweigh any harms, for example from overdiagnosis, overtreatment, false positives, false reassurance, uncertain findings, and complications. The STARshiP randomised study will provide evidence to quantify this in a universal implementation NHS setting.
- Criteria 14. The opportunity cost of the screening programme (including testing, diagnosis and treatment, administration, training, and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (value for money). Assessment against this criterion should have regard to evidence from cost benefit and/or cost effectiveness analyses and have regard to the effective use of available resource. The STARshiP economic evaluation will provide data on costs, benefits, and the probability of cost-effectiveness at particular thresholds.

Given the significant cost and logistical challenges of introducing the FMF screening test, an implementation evaluation with embedded cost effectiveness evaluation is essential and must include analysis of population subgroups in which cost effectiveness and acceptability may differ (e.g. multiparous pregnant women/people without prior pregnancy complications). Decisions regarding screening implementation in specific subgroups cannot be made until cost effectiveness data is available from a real-world implementation evaluation.

2.2 Design Justification

2.2.1 Choice of Screening Strategies

Other similar models exist [33-35] with varying degrees of applicability and validation [36-38]. However, such models generally lack external validation and have not demonstrated potential efficacy at preterm PE prevention when prospectively coupled to LDA prophylaxis in high-risk pregnant women/people, whereas the FMF screening test has such evidence [29].

2.2.2 Justification for Participant Population

There is existing precedence for a model of universal screening for the presence/risk of developing rare but serious conditions affecting pregnant women/people and their unborn babies. For example, opt-out screening for the maternal blood borne infections HIV, syphilis, and Hepatitis B (respective prevalences 0.01%, 0.16% and 0.07%), and the NHS fetal anomaly

screening programme provides universal opt-in screening for trisomies 13, 18 and 21 (combined trisomy prevalence 0.35%, lower than the prevalence of preterm PE, 0.8%). Indeed, targeted screening approaches based on maternal medical history/clinical characteristics alone fails to identify a significant proportion of individuals who will subsequently develop PE/preterm PE (~60% missed preterm PE) [26]. The pathophysiology of PE is poorly understood, multiple risk factors are known (and many likely remain unknown) and likely have complex interactions preventing easy identification of those at highest risk. Therefore, a universal screening approach is advocated. Current risk screening methods are known to perform particularly poorly in first time pregnant women/people and in individuals of Black and Minority Ethnic Heritage, who are disproportionately affected by preterm PE. There is preliminary evidence that use of the FMF screening test is associated with a reduction in perinatal deaths (particularly those related to PTB, SGA birth or hypertensive disorders of pregnancy) [28], although this evidence is underpowered and carries risk of bias; this can be confirmed or refuted in the STARshiP study. It is possible that multimodal screening (or individual elements of multimodal screening) for preterm PE risk will not be cost-effective in certain subgroups of the pregnant population, for example in parous individuals with no prior history of PE in whom the risk of early preterm PE (requiring delivery before 34 weeks) is 0.11%; embedded cost effectiveness evaluation in population subgroups within the STARshiP study will help to appraise this [39].

2.2.3 Justification for Primary Outcome

The intervention aims to reduce the number of pregnancies with preterm PE and FGR leading to iatrogenic PTB or stillbirth. PE is not accurately coded in the mandatory Maternity Services Dataset (MSDS, the core English maternity care routine data source) nor is it possible to derive a diagnosis from symptoms and measurements as relevant fields are not mandatory. The costs incurred by PE are predominantly dominated by the cost of prematurity, resulting largely from iatrogenic delivery of the infant in the interests of maternal and fetal health. The clinical consequences of prematurity are well documented. Gestation of birth and onset of labour are recorded in the mandatory MSDS data set and therefore iatrogenic (induced or caesarean) PTB is a reliable outcome from which an objective assessment of clinical and cost effectiveness can be measured. Decisions regarding timing of birth are also unlikely to be influenced by screening status, as the decision for iatrogenic PTB is made based on clinical factors present at the time of birth [40].

2.2.4 Justification for Design

An individually randomised study is unfeasible due to risk of contamination, and the potential for clinical confusion and mismanagement; a cluster randomised (CR) study is the appropriate design for an intervention that is implemented at maternity unit or Trust level. We have carefully considered the advantages and disadvantages of parallel and stepped wedge (SW) designs. The intervention being tested (FMF screening strategy) has been proven to be more accurate [26], however, whether this translates to improved clinical outcomes in an NHS antenatal care setting is unknown, hence the need for this study. Given the superior performance of the screening test, a SW-CR study design enables all NHS Trusts to implement the new screening strategy and is therefore attractive to sites and should facilitate recruitment. The controlled rollout of the intervention (whilst retaining a random element)

enables the study team to focus resources on supporting the implementation of the intervention in individual Trusts, ensuring maximal penetration and fidelity of the test in each site during the FMF period. With the SW-CR study design each cluster contributes data using both screening modalities, thereby accounting for within-cluster, as well as between-cluster, comparisons. Therefore, we consider the SW-CR study design to be the most efficient, practical design to address the study question [41].

The study period will be divided into 21-time blocks, each with a duration of 7 weeks. Each will start on a Monday, with two of the 16 Trusts moving into the transition phase at the end of each block. The roll-out of the FMF screening test will occur at the start of the transition phase and continue during the FMF phase (figure 2).

Figure 22 STARshiP Study Stepped Wedge Design

	Block 1	Block 2	Block 3	Block 4	Block 5	Block 6	Block 7	Block 8	Block 9	Block 10	Block 11	Block 12	Block 13	Block 14	Block 15	Block 16	Block 17	Block 18	Block 19	Block 20	Block 21
Site 1	NICE	NICE	FMF	FMF	FMF	FMF	FMF	FMF	FMF	FMF	FMF	FMF	FMF	FMF	FMF	FMF	FMF	FMF	FMF	FMF	FMF
Site 2	NICE	NICE	FMF	FMF	FMF	FMF	FMF	FMF	FMF	FMF	FMF	FMF	FMF	FMF	FMF	FMF	FMF	FMF	FMF	FMF	FMF
Site 3	NICE	NICE	NICE	NICE	FMF	FMF	FMF	FMF	FMF	FMF	FMF	FMF	FMF	FMF	FMF	FMF	FMF	FMF	FMF	FMF	FMF
Site 4	NICE	NICE	NICE	NICE	FMF	FMF	FMF	FMF	FMF	FMF	FMF	FMF	FMF	FMF	FMF	FMF	FMF	FMF	FMF	FMF	FMF
Site 5	NICE	NICE	NICE	NICE	NICE	NICE	FMF	FMF	FMF	FMF	FMF	FMF	FMF	FMF	FMF	FMF	FMF	FMF	FMF	FMF	FMF
Site 6	NICE	NICE	NICE	NICE	NICE	NICE	FMF	FMF	FMF	FMF	FMF	FMF	FMF	FMF	FMF	FMF	FMF	FMF	FMF	FMF	FMF
Site 7	NICE	NICE	NICE	NICE	NICE	NICE	NICE	NICE	NICE	FMF	FMF	FMF	FMF	FMF	FMF	FMF	FMF	FMF	FMF	FMF	FMF
Site 8	NICE	NICE	NICE	NICE	NICE	NICE	NICE	NICE	NICE	FMF	FMF	FMF	FMF	FMF	FMF	FMF	FMF	FMF	FMF	FMF	FMF
Site 9	NICE	NICE	NICE	NICE	NICE	NICE	NICE	NICE	NICE	NICE	NICE	FMF	FMF	FMF	FMF	FMF	FMF	FMF	FMF	FMF	FMF
Site 10	NICE	NICE	NICE	NICE	NICE	NICE	NICE	NICE	NICE	NICE	NICE	FMF	FMF	FMF	FMF	FMF	FMF	FMF	FMF	FMF	FMF
Site 11	NICE	NICE	NICE	NICE	NICE	NICE	NICE	NICE	NICE	NICE	NICE	NICE	NICE	NICE	FMF	FMF	FMF	FMF	FMF	FMF	FMF
Site 12	NICE	NICE	NICE	NICE	NICE	NICE	NICE	NICE	NICE	NICE	NICE	NICE	NICE	NICE	FMF	FMF	FMF	FMF	FMF	FMF	FMF
Site 13	NICE	NICE	NICE	NICE	NICE	NICE	NICE	NICE	NICE	NICE	NICE	NICE	NICE	NICE	NICE	NICE	FMF	FMF	FMF	FMF	FMF
Site 14	NICE	NICE	NICE	NICE	NICE	NICE	NICE	NICE	NICE	NICE	NICE	NICE	NICE	NICE	NICE	NICE	FMF	FMF	FMF	FMF	FMF
Site 15	NICE	NICE	NICE	NICE	NICE	NICE	NICE	NICE	NICE	NICE	NICE	NICE	NICE	NICE	NICE	NICE	NICE	NICE	FMF	FMF	FMF
Site 16	NICE	NICE	NICE	NICE	NICE	NICE	NICE	NICE	NICE	NICE	NICE	NICE	NICE	NICE	NICE	NICE	NICE	NICE	FMF	FMF	FMF

The pale grey cells represent the transition phase. Trusts will implement the FMF screening test at the start of this phase, pregnancies screened during the transition phase will not be included in analysis of the primary outcome. The blue and green cells represent the NICE screening phase and FMF screening phase respectively.

The SW-CR study will use a continuous recruitment design, as pregnant women/people will be receiving maternity care during their first trimester for several weeks, which may occur during the NICE phase, during the transition phase or afterwards, in the FMF phase or a combination of two phases.

The NHS Trusts and individuals receiving maternity care in those participating NHS Trusts will be aware of the screening strategy in place as part of routine maternity care at that time in that Trust, as recruitment of pregnant women/people in the first trimester of their pregnancy is inherently continuous. With a non-consent model, pregnant women/people may choose to opt-out of PE risk screening (in line with any aspect of maternity care), but all pregnant women/people should be offered the opportunity for PE risk screening, without clinician selection. We will also mitigate contamination by identifying those pregnant women/ people screened during the transition phases so that their outcomes are excluded from the primary analysis.

Using routine data at Trust level ensures that the primary outcome data is collected for all pregnant women/people who could be screened and reduces the potential for detection bias arising from knowledge of the testing strategy. Secondary outcome selections are limited by what is robustly reported in routine datasets. Not all aspects of the PE core outcome set, particularly maternal health outcomes [42], are reported, but STARshiP's secondary outcomes are adapted from PE and PTB prevention [43] and neonatal research [44] core outcome sets and can be extracted from routine datasets.

Time becomes a confounder in a SW-CR study design if secular changes (i.e., a natural tendency of sites or healthcare system to improve or worsen over time, making it difficult to separate the effect of the intervention from the effect of this trend) arise. It is also possible that PE is seasonal [45]. We will explore and report any trends in secular changes or period effects and adjust for time effects in our statistical analyses to provide confidence that reported effect sizes are as a result of the intervention alone.

Widespread adoption of an early pregnancy screen, and potential consequent improved targeting of (and compliance with) LDA prophylaxis, has the potential to offset the initial costs of FMF screening test and to dramatically reduce NHS costs relating to PE and PTB overall. This would be achieved through better targeting of LDA, potential impact on improved patient compliance with LDA and therefore prevention of preterm PE, leading to reduced requirement for maternal surveillance, hospital admission, operative birth and high dependency care consequent to preterm PE. However, the major cost savings will be achieved through reductions in neonatal unit admissions and length of stay, and health and social care costs for the infants (£2.9bn/year in England and Wales [46]) incurred through prematurity-related childhood hospital admissions, cerebral palsy, chronic lung disease and disability (estimated cost per severely or moderately disabled child of £72,000 and £18,000 per annum respectively [46, 47]). A small absolute reduction in PTB therefore has a huge potential impact on long term health and social care costs.

Our health economic analysis will assess the true opportunity cost of providing this enhanced screening test to all pregnant women/people, as well as to selected (pre-specified) sub-populations of pregnant women/people (determined in the statistical analysis plan). Additionally, if the study finds that the FMF screening test is no more effective than the

current NICE screening, this may prevent excess costs being incurred in the small number of NHS Trusts that have already implemented, or intend to implement, the FMF screening test.

Implementation of the FMF screening test is potentially challenging, so a mixed methods implementation evaluation is needed. This is detailed within section 14 of the protocol. This evaluation will commence after the study sites have been randomised.

3 Aims, Objectives and Outcome Measures

STARshiP comprises of three inter-dependent studies:

- Stepped-wedge cluster randomised study.
- In-study economic evaluation, and subsequent decision analytic modelling.
- Mixed methods implementation evaluation.

3.1 Research question for the Stepped-Wedge Study

In pregnant women/people in the first trimester of pregnancy (population), does routine implementation of the FMF screening test for PE (intervention), compared to NICE screening (control), reduce iatrogenic PTB (outcome)?

3.2 Aims

3.2.1 Aims of the Stepped-wedge cluster randomised study

1. To determine whether universal implementation of the FMF screening test for PE reduces iatrogenic PTB.

3.2.2 Aims of the in-study economic evaluation

1. To assess the cost effectiveness of the FMF screening test for PE in the whole study population and in clinically relevant subgroups.

3.2.3 Aims of the mixed methods implementation evaluation

1. To assess patients and professionals' perceptions of impact of PE risk on subsequent antenatal care and birth choices.
2. To assess acceptability and identify barriers and facilitators of routine adoption of the FMF screening test.
3. To assess the impact on experience of FMF screening test implementation on professionals and pregnant women/people.

3.3 Objectives

1. To perform a SW-CR controlled study with implementation of the FMF screening test at 11^{+2} to 14^{+1} weeks gestational age as the primary screening test for prediction of PE.
2. To perform a health economic evaluation using observed event rates and modelled health economic data for both universal screening tests.
3. To perform a mixed methods evaluation of site staff and service users to understand factors that aid and impede universal implementation of the FMF screening test and how this affects those involved.
4. To identify practical issues relating to deployment of the FMF screening test intervention and how these are overcome.
5. To assess whether the use of the FMF screening test to *quantify* PE risk leads to greater readiness of professionals to recommend LDA adherence, and of maternity service users to adhere to that recommendation.

3.4 Primary Outcome

Primary outcome	Main data source*/definition
Iatrogenic (via induction of labour by any method or by caesarean [non-labour] delivery) preterm birth (birth at <37 weeks' gestational age).	The Maternity Services Data Set (MSDS) will provide both components of the primary outcome as follows: Iatrogenic labour: MSD301 Labourdelivery, LabourOnsetMethod coded as any Caesarean [2], surgical induction [3], medical induction [4] or combination of surgical and medical induction [5]. Preterm birth: MSD401 Babydemographics, GestationalLengthBirth is less than or equal to 259 days.

**Data missing will be potentially obtained from other routinely collected data sources.*

3.5 Secondary Outcomes

Secondary outcome selection is limited by what is robustly reported in routine datasets. Not all aspects of the PE core outcome set particularly maternal outcomes [42], are completely and consistently reported. Our secondary outcomes (Table 1) are adapted from PE and PTB prevention and neonatal research core outcome sets and can be extracted from routine datasets.

Table 1 Secondary Outcomes

Maternal	Data source/definition
Mortality	Office for National Statistics (ONS) Mortality
Postpartum haemorrhage	MSDS, BadgerNet Maternity, Hospital Episodes Statistics (HES) maternity or inpatients
Labour onset	MSDS
Mode of birth	MSDS

Caesarean section indication (Robson Group)	MSDS
Blood transfusion	MSDS, BadgerNet Maternity, HES maternity or inpatients
Admission to intensive/high dependency care	MSDS/National Neonatal Research Database (NNRD), BadgerNet Maternity, HES inpatients, critical care
Length of stay (postpartum)	MSDS, BadgerNet Maternity, HES inpatients
Length of stay (cumulative per pregnancy)	MSDS, HES inpatients
Readmission to hospital (within 42 days)	HES inpatients
Neonatal	
Stillbirth (death of baby after 24 completed weeks; occurring before or during birth or timing unknown)	MSDS, BadgerNet Maternity, HES maternity
Gestational age at birth	MSDS
Small for gestational age neonate (<10th centile for GA)	Derived
Fetal growth restriction (<3rd centile for GA or <10th centile if born under 34 weeks)	Derived
Birth weight (grams)	MSDS, NNRD, HES maternity
Early neonatal mortality (<7 days of age)	ONS Mortality, MSDS, NNRD
Extended neonatal mortality (<28 days of age)	ONS Mortality, NNRD
Admission to neonatal unit	MSDS, NNRD
Level of neonatal care (level 1, 2 or 3)	NNRD
Length of hospital stay (days)	NNRD
Readmission to hospital (within 42 days)	HES inpatient
Respiratory morbidity (as recorded): Respiratory distress syndrome mechanical ventilation chronic lung disease discharge on oxygen	NNRD
Neurological morbidity (as recorded): Seizures Hypoxic ischaemic encephalopathy Therapeutic hypothermia	NNRD

Retinopathy of prematurity Hearing impairment	
Gastrointestinal morbidity: Necrotising enterocolitis Laparotomy	NNRD

3.6 Process Outcomes

It is important to collect and analyse process outcomes for both screening strategies, as failure to detect differences in iatrogenic preterm birth may be due to poor compliance with the processes, rather than an intrinsic problem with the screening tests. It will also be important to measure any change in LDA provision arising from each strategy. These outcomes will be collected in a consecutive sample of 100 pregnant women/people per site. Key parameters (non-exhaustive) that will determine feasibility and overall effectiveness of the NICE screening and FMF screening tests are listed in Table 2. In addition, the number of pregnant women/people screened as a proportion of pregnant women/people booked at each hospital will be captured and reported as a process outcome.

Table 2 Process Outcomes

Outcome	Data source/definition
Number of pregnant women/people with clinical risk factors for PE and which risk factors they have.	Detailed Data Collection (REDCap)
Number of pregnant women/people having a blood test taken for PlGF (of all those eligible for this test).	Detailed Data Collection (REDCap)
Number of pregnant women/people having an ultrasound scan for UtA-PI (of all those eligible for this test).	Detailed Data Collection (REDCap)
Number of pregnant women/people with a PlGF result of all those having the test taken.	Detailed Data Collection (REDCap)
Number of pregnant women/people having a blood test for the FMF screening test within the time window (of all those eligible).	Detailed Data Collection (REDCap)
Number of pregnant women/people having a UtA-PI for the FMF screening test within the time window (of all those eligible).	Detailed Data Collection (REDCap)
Number of pregnant women/birthing people who decline trisomy screening.	Detailed Data Collection (REDCap)
Number of pregnant women/birthing people having a blood tests and UtA-PI uterine scan for the FMF screening test within the time window (of all those eligible).	Detailed Data Collection (REDCap)

Number of pregnant women/birthing people with a FMF risk assessment available before 16 weeks.	Detailed Data Collection (REDCap)
Number of pregnant women/bithing people with a high risk preterm PE risk screening result who are recommended LDA (or not)and accept LDA in line with high or low risk preterm PE risk screening result.	Detailed Data Collection (REDCap)
Number of pregnant women/people with a low risk test result or no documented risk factors who are recommended and accept LDA (and reasons).	Detailed Data Collection (REDCap)
The dose and duration of LDA recommended.	Detailed Data Collection (REDCap)
The gestation at which LDA is recommended.	Detailed Data Collection (REDCap)
Number of pregnant women/birthing people prescribed LDA if recommended.	Detailed Data Collection (REDCap)
Number of pregnant women/birthing people declining LDA when recommended and reason why.	Detailed Data Collection (REDCap)
Number of pregnant women/birthing people with evidence of continuing LDA adherence reporting until 36 weeks Gestational Age (GA)/ birth.	Detailed Data Collection (REDCap)
Number of pregnant women/ birthing people with a negative low risk test result or no documented risk factors who are recommended and accept LDA (and reasons).	Detailed Data Collection (REDCap)

4 Study Design

This study is a SW-CR study with NHS Trusts as the unit of randomisation, hereafter called a site. A site may contain more than one NHS Trust if their individual births per year are fewer than 2500. 16 NHS Trusts across England who are willing and potentially able to implement the FMF screening test will be recruited and randomised. Each site will transition from the control (NICE screening for PE) to the intervention (FMF screening test) at specified time points. Two sites will switch from the NICE phase to the FMF phase at each transition point.

5 Internal Pilot

Progression criteria will be assessed at month 15 and month 27. As standard progression criteria relating to recruitment are not appropriate for this study design, the below stop/go criteria will be used to assess study progression:

Table 3 - Progression Criteria

	Progression criteria		
	RED	**AMBER**	**GREEN**
15-month criteria:			
Ethics approval in place	Not submitted	Submitted and awaiting feedback	In place
Number of sites with all local approvals in place, staff appointed, and training plan completed	< 8 randomised NHS Trusts	8-15 randomised NHS Trusts	16 randomised NHS Trusts
Confidentiality Advisory Group (CAG) approval	Approval declined	Application under review	Approval in place
27-month criteria:			
Full transition to FMF first trimester algorithm	<5 NHS Trusts	N/A	≥5 NHS Trusts
Evidence of alternative PE risk assessment tool implemented (of cases undergoing pre/post implementation detailed notes review)	>10% of cases reviewed	5-10% of cases reviewed	<5% of cases reviewed
Implementation of full FMF first trimester algorithm*	<80%	80-90%	≥90%
Progression of funding (at either 15-month or 27-month assessment)	Trial feasibility doubtful – consider ending	Discuss issues with oversight committees/funder and address concerns	Continue

**Proportion of eligible and consenting participants screened during preceding 3-month period in units that have fully transitioned to the FMF algorithm for a minimum of 3 months.*

6 Eligibility

6.1 Trust level eligibility criteria

6.1.1 Trust level inclusion criteria

NHS Trusts with maternity units will be eligible to participate in the study if they are:

- Located within England;

- Have a minimum of 2500 births per year (latest full year data) in the participating maternity units of the NHS Trust.
- Committed to implementing the FMF screening algorithm at a specified time point following study commencement, including the measurement of Uterine artery Doppler Pulsatility Index (UtA-PI), where feasible.

NHS Trusts who have more than one maternity unit will be randomised as a NHS Trust to preserve fidelity of implementation across all maternity units within that Trust.

NHS Trusts with fewer than 2500 births per year may potentially be paired together to create a single site for the purpose of the study. This option will only be pursued if an insufficient number of larger NHS Trusts are eligible and can commit to STARshiP in a timely manner.

Whilst it is possible that NHS Trusts will choose to implement the test outside of our study, this decision would make them ineligible for participation. Importantly, it would also mean that the financial and training resource embedded within our study design would not be available. Moreover, the draft guidance from the NSC has not recommended implementation of universal screening.

Early discussions with Trusts has highlighted capacity pressure on their clinical services, specifically sonography services, that may affect the ability of Trusts to fully implement all aspects of the FMF screening test. The decision has been taken to allow inclusion of NHS Trusts that cannot commit to full implementation of the UtA element of the FMF screening test in order to not bias the study findings (in terms of feasibility and performance of the test in a real world NHS setting), which may occur if the study only runs in hospitals with above average access to maternity sonography (which may in turn impact on pregnancy outcomes in general). The STARshiP study will capture data regarding the uptake rates of all elements of the FMF screening test to provide an informed and realistic implementation and economic health evaluation of the FMF screening test implementation.

6.1.2 Trust level exclusion Criteria

NHS Trusts will be ineligible to participate in the study if they are:

- Already providing first trimester screening for pre-eclampsia (PE) as standard care, or participating in another study implementing care pathways which include first trimester screening for PE.
- Unable to commit to the implementation of the FMF screening test at the specified time point. Trusts may still participate where they are able to make a commitment to performing all elements of the FMF screening test where feasible. Trusts would be unable to participate if they are absolute in the knowledge that they would not be possible to perform any UtA-PI measurements following the specified transition time point.

6.2 Individual level eligibility criteria

There will be two levels of eligibility for individual pregnant women/people:

- Testing level – eligible to be screened for PE.

- Dataset level – eligible to be included in the dataset for analysis, regardless of whether test performed.

There is no exclusion based on age of women/people, multiple births or comorbidities in the pregnant individual or baby.

Within participating maternity units, screening data and routinely collected data for all pregnant women/people in the first trimester of pregnancy receiving antenatal care at participating hospitals will be included in the final datasets, with the exception of those who choose to opt out of their data being used, either through the local study specific opt out process, or the NHS data-opt out discussed below.

6.2.1 Testing level inclusion criteria

All pregnant women/people receiving antenatal care at participating maternity units within randomised NHS Trusts prior to 16 weeks gestation will be eligible to be screened (to ensure timely prescription of aspirin) by either the NICE or FMF strategies. The window for FMF testing is 11^{+2} to 14^{+1} weeks (CRL 45-84mm). Eligibility is not dependent on participation in the NHS Fetal Anomaly trisomy screening programme.

6.2.2 Testing level exclusion criteria

- Known congenital anomaly incompatible with survival at birth, of a singleton or all multiple fetuses e.g. anencephaly.
- Fetal demise/miscarriage before PE risk assessment completed.

6.3 Dataset level eligibility criteria

6.3.1 Dataset level inclusion criteria

All pregnant women/people receiving antenatal care at participating maternity units within randomised NHS Trusts prior to 16 weeks gestation who have not opted out of their data being used for research purposes. Individuals may be included more than once if multiple early pregnancy screening episodes in different pregnancies are performed.

Women/people who experience a miscarriage or stillbirth after early pregnancy screening will be included as they may have had testing for PE and PE may be implicated in the aetiology of their pregnancy loss.

6.3.2 Dataset level exclusion criteria

Withdrawal of consent to use data, through either the local study specific opt out process or the NHS data-opt out.

Pregnancy outcome data for those screened during the transition phase for each maternity unit will be collected but excluded from the primary outcome analysis; it will be available for use in secondary analyses.

7 Recruitment

All maternity units in England will be invited to participate through the RDN and LMNS networks.

For a SW-CR study with a no consent model, participants will not be approached to join the study, making the traditional concept of recruitment redundant. Information about the study (videos/ posters/ leaflets) will be displayed in the relevant clinical areas e.g. waiting rooms, on participating NHS Trust websites and social media. These sources of information will direct women/people to the study website <www.starship.ac.uk> where they can select their hospital and be directed to information about the study, the screening test currently in use at that site, use of their data and how to opt out of use of their data for research (replacing a traditional participant information sheet, though screening information sheets may be provided by site staff on request). The information will be made available in a range of languages. At appropriate stages of the study, the study web pages for individual hospitals will be centrally updated at the Nottingham Clinical Trials Unit (NCTU) to display information about the screening test e.g. the hospital page will display information about the FMF test when in use at the trust.

Individuals will also be able to follow a link from this page to complete an optional online questionnaire to capture their experiences of PE screening. Further details of this section of the study are described in section 14.

7.1 Consent for the SW-CR Study

As is typical in many SW-CR studies, individual consent will not be obtained for involvement in the study. However, pregnant women/people will provide verbal consent for the UtA Doppler ultrasound measurement and PlGF blood test elements of the PE risk screening algorithm, in accordance with local clinical guidelines, and are able to opt out of any aspect of routine maternity care including screening for PE risk (entirely or elements of this).

7.2 Data Opt-Out

Permission will be sought from the Confidentiality Advisory Group (CAG) for the use of pregnant women/people's screening, detailed data collection (DDC) and routine data. Pregnant women/people will, however, be made aware that the study is taking place and of the use of their data (e.g. through study awareness posters/leaflets, study information videos and via the study website). Pregnant women/people will have the opportunity to opt out of their data being used in STARshiP via a study specific opt-out, available within two time-windows, or through the national NHS digital data opt-out. Opting out via the study specific option or the national opt-out would remove both screening and pregnancy outcome for an individual being included in the study analysis.

7.2.1 STARshiP specific data Opt-Out

The study will incorporate two study specific opt-out processes for pregnant women/people that do not wish for their data to be used in the STARshiP research study. This can be done through either a site-specific opt out form (to prevent transfer of data to the study team), or later through a REDCap database form (to enact deletion of data already received) depending on when the request is made following the date of their booking appointment. A pregnant women/person's decision to withdraw their consent for their data to be used in research will not affect the care that they receive.

Each pregnant woman/person who attends a first trimester booking appointment at a STARshiP site will first have a 1-week window from the date of the booking appointment to

inform their site or the study team of their wish to opt-out of their data being used through a site specific opt out form.

The pregnant woman/person will be able to scan a QR code on a poster (displayed at their hospital) which will direct them to their site-specific webpage on the study website. This page will contain information detailing how they can locally opt out of STARshiP. If their booking appointment was <1 week from the date of submission of the opt-out request, the pregnant woman/person will be asked to provide their identifiers (NHS number and date of birth) and to confirm they wish to opt out; this form and their details will be held by their site. Following this one-week period, the screening data for all pregnant women/people will be filtered by the site staff to remove data for all those who have notified the site of their wish to opt out. Their data will not be included in quality assurance or screening fidelity monitoring and no pregnancy outcome or other routine data (for themselves or their baby) will be requested. If no local request for study opt out is received within 1 week of the date of the booking appointment, all remaining individuals' screening data will be provided to the study team at NCTU through upload to the REDCap research database for use in real-time quality assurance and screening fidelity monitoring.

If their booking appointment was >1 week but <6 months prior to the date of submission of the opt-out request, they will be directed to complete a REDCap survey to opt out. Their NHS number, date of birth, and the name of the NHS hospital providing their care will be required and these details will be stored by the research team in a secure REDCap server for the study duration at the Nottingham Clinical Trials Unit, University of Nottingham. This information will then be used to periodically filter screening data received from sites into the research database to ensure that anyone who has opted out using this form has their data removed before statistical analysis for reporting study findings. Additionally, their pregnancy outcome and other routine data (for themselves or for their baby) will not be requested from routine data providers.

7.2.2 National Data Opt-Out

Individuals who wish to utilise the national data opt-out will need to register on https://www.nhs.uk/your-nhs-data-matters/, by phone, or by printing and completing a paper form. If they use the national data opt-out, pregnant women/people will be made aware that this decision will not affect their future care but that it will be applicable for all research and healthcare planning purposes and not solely for the STARshiP study.

Individuals with parental responsibility can set a national data opt-out on behalf of their child via the non-digital channel only and will need to complete a specific form which can be downloaded from the NHS England Digital data opt-out page (https://assets.nhs.uk/nhsuk-cms/documents/Make_and_manage_your_choice_or_your_childs_choice_PDF_159kb.pdf). The opt-out request would be applicable if the request is received before the routine data for that individual woman has been transferred to the Nottingham Trusted Research Environment (TRE) from the national routine data sources. Once the routine data has been received and processed by the NCTU data managers, data will be pseudonymised and therefore it will not be possible to omit the data from the analysis.

Individual's data cannot be withdrawn from the study at the request of the Investigator or clinical care team.

For anyone requiring assistance in opting out locally, or via the national data opt-out, site staff will be available to assist. Staff will be trained on where to direct women/people to find out more information about the study specific opt out processes, and they will also be available to assist women/people in completing the required forms.

7.3 Randomisation

The time period at which sites will transition to the FMF screening test will be randomly determined. Each site will be randomly allocated to one of 8 sequences representing the number of periods spent in the control phase and the number of periods in the intervention phase, with two sites initiating the intervention at the same time. Randomisation will be stratified by the size of the site (large vs small). An independent study statistician will generate the randomisation schedule. All sites will be randomised together, prior to the start of the study.

7.4 Blinding and concealment

Blinding of the pregnant women/people and professionals is not possible due to the nature of the strategies.

8 Study screening strategies

As this study is a SW-CR study, the NHS Trusts (sites) will transition from NICE screening for PE (NICE phase) to the FMF screening test (FMF phase). The components and impact on individual pregnant women/people are described below.

8.1 Intervention – FMF phase

8.1.1 FMF screening test

The FMF screening test will be universally implemented, where feasible in respect of UtA-PI measurement, as published up to (and including) 14^{+1} weeks gestation [30]; the screening test can be commenced prior to 11^{+2} weeks gestation but measurements of blood pressure, UtA-PI and PlGF concentration can be taken only between 11^{+2} to 14^{+1} gestation (equivalent to CRL 45-84mm), in line with the NHS Fetal Anomaly Screening programme combined screen for Trisomy 13, 18 and 21. No additional appointments, ultrasound scans or blood sampling episodes are required for FMF screening test implementation, if done alongside the first trimester trisomy screening.

A pregnant woman/person will attend their antenatal booking and scan appointments as per routine clinical care. At their first contact/booking appointment, their maternal and obstetric history details will be taken and recorded in their patient record. At their subsequent dating +/- nuchal scan appointment, where occurring between 11^{+2} to 14^{+1} gestation (equivalent to CRL 45-84mm) a blood pressure reading will be taken using a validated digital blood pressure machine and a blood sample obtained [48]. The UtA-PI will be measured alongside the dating +/- nuchal translucency ultrasound. Colour Doppler waveforms of blood flow through the left

and right uterine arteries will be obtained and a mean UtA-PI calculated and reported by the sonographer according to the standardised technique described by ISUOG <ISUOG Practice Guidelines (updated): use of Doppler velocimetry in obstetrics>. Assessment of the uterine arteries adds no more than an average of 5-10 minutes to the scan duration. For blood sample collection, up to one additional blood sample bottle (<5ml blood) will be taken alongside the blood sample taken for trisomy biomarkers (if consenting to trisomy risk assessment) and used to determine PlGF concentration via a regional screening laboratory with commercially available clinical grade PlGF assay (subject to the manufacturer's standard technique and quality control procedures).

Blood samples will be sent by the sites, alongside the clinical parameters required to calculate preterm PE risk score using the FMF algorithm, to the contracted regional screening laboratory as agreed with the study team and local maternity unit. The PlGF concentration within the blood sample will be calculated. Where no blood sample is obtained from an individual pregnant woman/person, the regional laboratories will still receive the required clinical information for calculation of preterm PE risk score according to the FMF algorithm. For all individuals who agree to PE risk screening through provision of clinical information with or without additional biophysical or biochemical biomarkers, all available relevant clinical data will be input into the appropriate laboratory software FMF module/calculator and an individuals' FMF PE risk score will be calculated. The personalised FMF risk score result will then be reported back to the NHS site in a timely manner where the pregnant woman/person is booked using a process agreed between the local maternity unit and the designated regional laboratory, along with the PlGF concentration (if available). This process is expected to utilise existing infrastructure for the reporting of fetal trisomy screening results between the regional laboratory and NHS Trust. It is the responsibility of the NHS Trust and their respective regional laboratories to ensure the data provided, and the reporting of a personalised preterm PE risk score is accurate and complete.

A version of the FMF screening test can be applied even if individuals decline UtA-PI and PlGF assessment or where gestation at scan is outside of the 11^{+2} – 14^{+1} gestation window (although it will be explained that more accurate results are obtained when all components of the test are provided for the algorithm). If the first trimester trisomy screening is declined (anticipated to be approximately 30% overall), the FMF screening test will be offered and performed alongside the routine first trimester dating scan and routine booking blood tests, or another convenient time within the screening window. Pregnant women/people who do not undergo antenatal booking assessment and/or an ultrasound/dating scan until >14^{+1} weeks' gestation (crown rump length >84mm) cannot have the FMF screening test performed and will be managed according to usual care (defaulting to NICE screening). The same processes will be used for those who book for antenatal care after 14 weeks' gestation or are found to have a multiple pregnancy or lethal congenital abnormality diagnosed at the time of the dating scan; no UtA-PI or PlGF will be measured on these pregnant women/people. The FMF algorithm for twin pregnancies will not be followed as the coefficients have not been published or externally validated.

The result reported by the regional laboratories (high or low risk, along with risk score where risk has been calculated by the FMF screening test) will be recorded in the pregnant

woman/person's patient record at site. A preterm PE risk of greater than 1 in 100 as determined by the FMF screening test will be considered a high-risk result (e.g. a risk of 1 in 75). Local clinicians will review the screening data and score and plan onward care, for example the suitability for LDA, according to their local Trust guidance. Clinical decisions for LDA prescription will not be dictated by the study protocol. Any LDA recommendation from local clinicians will be communicated to the individual by the NHS Trust according to local policies; high risk results will be communicated to the individual as soon as possible after screening, ideally before 16 weeks gestation so that LDA can be commenced by 16 weeks gestation, if clinically recommended. Participating sites will be required to have updated local policies/protocols in place at the required transition timepoint to confirm that FMF algorithm will be used for PE screening and specify locally agreed management pathways. Participating sites and regional laboratories should have policies in place to ensure that where screening by FMF screening test is incomplete by 16 weeks gestation, that a PE risk score is still generated and reported, and if high risk, it is communicated to the patient. In the unlikely situation that not all test results are available before 16 weeks the FMF test is flexible, allowing a risk score to be generated without one or more of UtA-PI, MAP or PlGF, albeit with reduced sensitivity.

It is anticipated 10-11% of the screened population, equivalent to nine pregnant women/people per week in a 4,500 births/annum Trust, will receive a high risk result and need to be contacted by the local maternity team and ongoing care discussed. The outcome of the screen should be documented in the clinical record, and ongoing care will continue in line with local hospital guidelines.

8.1.1 FMF phase training

Prior to the switch to the FMF screening test, all sites will have training meetings (virtually or face to face) with members of the study team, including a study midwife. The study team will deliver training on the FMF screening test, including the taking of blood samples, blood pressure readings and UtA-PI assessment, and the process by which all tests are requested and the results fed-back. The regional laboratories will not complete the FMF screening algorithm until sites enter the transition phase.

All sonographers who perform dating scans as part of their role will be trained in first trimester Uterine artery Doppler examination using adaptations of existing, freely available online International Society of Ultrasound in Obstetrics and Gynaecology resources. This is a minor extension of competencies already established through implementation of 2nd trimester UtA-PI assessment as part of the national Saving Babies Lives (SBL) v3 recommendation (mandated as part of the Clinical Negligence Scheme for Trusts scheme for Hospital Trusts [49]). Implementation of UtA-PI since SBL v2 has been successfully coordinated and resourced through the LMNS regional networks. For STARshiP, local midwife coordinators working with the LMNS will use these established networks to support implementation and sonographer training, in association with regional co-investigators. Site readiness for implementation of the FMF screening test will be ensured by training of clinical and administrative staff members in relation to the FMF screening test, gestational age requirements for aspects of the algorithm and the local arrangements for final calculation of

PE risk and communication of the results and any management recommendations (per local policies). Sonographer training will comprise (as a minimum) a study-specific online theoretical training package with local approval of practical competency by an appropriately competent senior clinician (lead sonographer or trained obstetrician, as appropriate for the individual site). Optional local or regional face-to-face training with the opportunity to practice on healthy volunteers will be provided as needed following local/regional skill assessment (e.g. where provision of UtA-PI assessment as part of SBL is not locally devolved to general sonography teams). This approach has been highly effective for SBL care bundle implementation. After the transition phase, it is anticipated that ongoing competency assessment of sonographers / training of new sonographers and midwives will be assured according to the established processes in already place in each participating maternity unit.

8.1.2 Quality control of the FMF screening test

Mean arterial blood pressure, UtA-PI and PlGF data submitted via the study REDCap database will be used to monitor fidelity of test implementation in the FMF phase. Where incomplete implementation of the FMF test is identified, the NCTU will work with local research and clinical teams to establish if there are any additional local training needs/barriers to implementation and how best these would be addressed. Biomarker distributions will be monitored within the software implemented in the screening laboratories using standard methods in place for trisomy screening.

8.2 Control (NICE phase)

8.2.1 NICE screening

The NICE guidelines incorporate midwife evaluation of maternal characteristics at the booking appointment. The pregnant women/people will be classified as high or low risk of PE, as per standard care NICE risk assessment. Participating hospitals will follow their usual process for communicating this result and LDA recommendation.

8.2.2 Initial site training and the NICE phase

When local research approvals are in place and authorisation provided by the NCTU, the NICE Phase will begin for all 16 Trusts.

The NICE Phase (with NICE PE screening) will continue at sites until the transition phase which will be followed directly by the FMF phase (with FMF PE risk assessment). The duration of the NICE and FMF phases will be determined by the randomisation schedule.

Prior to the study commencing, research teams (including but not limited to the principal investigator, coordinating midwife and any research midwives etc.) at each participating unit will have undertaken a site initiation visit and received study-specific training. They will also have ensured site readiness for study implementation including arrangement to display patient-facing study-related materials (e.g. study awareness videos and posters/leaflets) and training of clinical and administrative staff members in relation to the NICE phase of the study. The NICE risk assessment will be facilitated by the booking midwife using the standard maternity electronic patient record (e.g. BadgerNet, K2) or paper records; the exact process for each site will be determined during site set up. Standardised training regarding use of NICE

screening and recommendation for LDA (according to local guidance) for high-risk individuals will be provided by the study team. Clinical teams will also be made aware of the STARshiP local specific opt-out process and the NHS England Digital data opt-out (including that this would result in opting out of use of data for all purposes, not only for the study), where to direct pregnant women/people if they wish to opt out using either method and how to assist in completion of a valid opt out request if required.

8.3 All phases

8.3.1 Missed screening window

The benefits of LDA prophylaxis for preterm PE and severe PE are reduced if LDA is commenced after 16 weeks gestation and are limited where commenced after 20 weeks gestation[24]. Where PE risk assessment cannot occur before 20 weeks gestation (for example where gestation at commencement of antenatal care is already >20 weeks or where gestation at the time of dating scan is unexpectedly beyond 20 weeks) decisions to complete PE risk assessment (using maternal characteristics only), and any LDA initiation, should be guided by local maternity hospital policies.

8.3.2 Low dose aspirin (LDA)

The prescription of aspirin (minimum/maximum gestation at commencement, recommended dosage and recommended gestation at cessation) will follow the participating site's usual practice, following clinician review of the raw results/risk factors. Sites are requested not to change these factors related to LDA treatment between study phases. Data on formal policy changes affecting these factors nationally and at local maternity sites occurring during the conduct of the study will be collected and, if necessary, used to adjust/interpret the study analyses.

Site policies/protocols are to be updated to highlight the PE screening process being utilised at the site, e.g. to confirm that the FMF algorithm will be used for PE risk assessment for the duration of the FMF phase, but any onward pregnancy pathways and LDA prescription policies after a risk score is generated (and categorised as high or low risk) should remain unchanged as standard practice at site. LDA is already included within Patient Group Directions for pregnancy and is most commonly prescribed by midwives [50]. The process of prescription or recommended self-purchase of aspirin will follow the site's usual practice and should not be altered between treatment arms. Data on formal policy changes affecting this nationally and at local maternity sites occurring during the conduct of the study will be collected and, if necessary, used to adjust/interpret the study analyses.

It is advised that hospitals have policies in place throughout the period of the study (regardless of phase of implementation) to review and reinforce individuals' ongoing adherence to LDA prophylaxis where this has been recommended according to usual care policies at the maternity hospital.

8.3.3 Ongoing Antenatal Care

The ongoing antenatal care of pregnant women/people identified as having a higher risk of PE (irrespective of which screening test was applied) should follow current NICE/Saving Babies Lives (SBL) v3 guidelines [19, 49] and established local policies. Those who are determined as having a higher risk of PE often have risk factors which justify additional pregnancy surveillance. However, in the absence of evidence to support changes in antenatal care based solely on first trimester PE risk screening, antenatal surveillance will continue to follow current standard care guidelines during the study. Importantly, there is no recommendation that those who are 'FMF screen positive' will have additional surveillance and be managed on a 'high risk pregnancy' pathway or to be recommended additional ultrasound scans or iatrogenic delivery (unless this pathway was already indicated due to other maternal or obstetric risk factors). All pregnant women/people are offered second and third trimester antenatal care including ongoing screening for development of PE itself by measuring blood pressure and performing urinalysis at antenatal contacts. Decisions regarding the timing, mode and place of birth should not be impacted by the first trimester PE risk assessment in pregnant women/people who have no signs of PE or other pregnancy complications at the time of birth. It is important to ensure pregnant women/people are given choice in planning their birth and this will be emphasised in study training.

Data on formal policy changes affecting the ongoing antenatal care and delivery of individuals high risk for PE but without additional comorbidities/risk indicators nationally and at local maternity sites occurring during the conduct of the study will be collected and, if necessary, used to adjust/interpret the study analyses.

8.3.4 Assessment of compliance with screening strategy

During the NICE phase, the number of people with a completed NICE screening documented on the study REDCap database as a percentage of all those eligible for testing (using the number of bookings performed per hospital per month) will be monitored by the NCTU. Where data submission falls below 90% of individuals booked in that period, the NCTU will work with local research and clinical teams to identify and overcome local barriers to study implementation.

During the transition phase, the number of pregnant women/people with a completed FMF screening test performed as a percentage of those eligible for testing will be monitored by the NCTU. The study aspires to a fidelity of FMF test implementation of 80%. Cascaded training by site staff trained on all testing steps during this transition phase must ensure all midwifery teams involved in booking and screening are trained promptly and appropriately and all sonographers who perform dating scans as part of their role have completed the additional training for UtA-PI assessment.

Where sites have been unable to perform the UtA-PI measurement, it should be documented in the REDCap database via data extraction, upload or transcription from the patient record. Options to explain why this was not completed would include:

- *Declined - declined by the woman or pregnant person*
- *Unobtainable - where an attempt has been made to obtain the measurement, but it has not been possible*

- *Did not perform (clinical constraint) - where the measurement was not obtainable due to a clinical constraint*
- *Did not perform (organisational/financial constraint) – where the measurement was not obtainable due to financial or organisational constraints, including resourcing.*

If 80% coverage is not met (acknowledging the short lag between test and scans and completion of the FMF screening test), the site will need to intensify the training and implementation of the testing process. Support and additional training will be provided by the NCTU and co-investigators throughout the transition phase, working closely with local research and clinical teams throughout the transition phase to identify and overcome barriers to its implementation.

Sites will not be withdrawn if they fail to achieve the 80% test uptake rate. After completion of the transition phase, the site will be deemed to be transitioned to the FMF phase regardless of testing coverage and it will be included in the primary analysis. Ongoing monitoring and support of fidelity of implementation at sites will continue throughout the study.

The proportion of pregnant women/people who are unable to complete the FMF screening test due to late or delayed booking appointments, missing results or who decline screening elements will be captured.

The reasons for missed screening opportunities will be explored within an embedded implementation study.

Adherence to aspirin will not be directly measured. There are various models of providing aspirin to pregnant women/people at higher risk of PE, but generally the first few weeks are prescribed by the hospital and thereafter women/people are advised to buy the aspirin from a pharmacy or supermarket or obtain supplies from their general practitioner. This precludes accurate pill counting.

The intent to prescribe aspirin will be captured on the REDCAP database following a data extraction and upload by the site at the end of the NICE and FMF screening process.

9 Data collection

Data items that contribute to either screening strategy will be collected at site (as appropriate for the participating site's phase of randomisation) on all pregnant women/people booked at a site, in a study specific, validated patient record form. This data will then be extracted and uploaded regularly into the REDCap study database. The upload/transcription into REDCap will be completed by sites regularly after filtering out data from any pregnant women/people who have locally opted out in the 1-week period post booking appointment. After receipt of data by the NCTU, data in REDCap will be regularly filtered to delete data pertaining to anyone who has subsequently opted out using the REDCap opt out form up to 6 months post booking as described in section 7.2.

Individual level data on process outcomes will be collected for a subset of pregnant women/people once during the NICE phase (up to 100 per site) and once during the FMF phase (up to 100 per site) after application of relevant opt-out requests.

Any additional data needed to conduct the primary and secondary analyses will be extracted from national sources of routinely collected data (following application of relevant opt-out requests) to which all maternity units routinely submit data.

9.1 Data Collected for Screening Algorithms

Following the completion of an individual's risk score calculation according to relevant local processes, and once the stage 1 study specific opt-out filter has been applied by the site, all screening data will be regularly sent to the research database REDCap for extraction and upload. These data exports should be completed by sites on a regular basis to ensure that the data can be imported into the database and the study team has sufficient data to complete the required quality control checks (e.g. fidelity of screening) for each site.

The study team will provide help and training on the upload of data to the University of Nottingham REDCap database as required to assist site staff.

9.2 Detailed data collection

For determining the process outcomes, individual level data, not reported in the routine data sources, is required. To collect data on all pregnant women/people would negate the advantages of routine data use, so detailed data collection (DDC) will be undertaken for a small subset of pregnant women/people at each site.

This will be retrospective source data collection using an online proforma designed for each screening strategy. At each site, individual data for a consecutive sample of at least 100 pregnant women/people per site in each phase of the study will be collected. A sample of 100 pregnant women/people in their first trimester in the final block of the NICE screening phase and then a second sample of 100 pregnant women/people in their first trimester in the second block after full implementation of the FMF screening test will be identified. These individuals will be retrospectively identified by local site research teams from booking appointment lists at participating hospitals.

This data will be extracted from the women/people's health care records and transcribed/uploaded by the local research teams at each site onto the STARshiP online database. The detailed data collection will provide individual-level data associated with the screening coverage, aspirin prescription, resource use and baby outcomes. The detailed data collection will capture whether the need to take aspirin has been reinforced/whether ongoing LDA compliance is recorded at subsequent antenatal appointments.

In order to avoid including women/people who have opted out of data collection through either the study specific opt out process or the national data opt service, sites will use both the study specific opt out list and the NHS MESH (Message Exchange for Social Care and Health) service to provide a list of the relevant NHS numbers to be checked against the national data opt-out repository on the Spine system.

Any pregnant women/person who has withdrawn consent for their data to be used for the study will not be selected. Site staff will generate a consecutive list of NHS numbers for individuals booking in their first trimester of pregnancy in both time periods, taking into account anyone who has opted out through method 1 (site specific form). This list will then be filtered by NCTU for anyone who has also locally opted out using the second method

(REDCap form). This list of NHS numbers will then be sent to the NHS MESH service for comparing against the National data opt out record. The MESH service will remove the information of those with current National opt-outs. The site will receive a list of NHS numbers for the records that can be disclosed for the detailed data collection. If any pregnant women/ people have opted out in the first sample, additional NHS numbers will be provided until the required number of records are reached.

To ensure a cross-sectional unbiased sample of process outcomes pertaining to routine testing at sites, it would not be feasible to operate a study consent process for series of 2x 100 consecutively screened pregnant women /people attending maternity care appointments at multiple antenatal clinics across a Trust. As the pregnant women/people themselves do not need to be present to enable a consecutive unbiased retrospective data collection (as no new data is collected purely for the purpose of the study), an informed consent process is impractical and could introduce bias Further it is not deemed feasible or practical to provide an additional study specific opt-out process specifically for the DDC element of the SW-CT study. However, the study is implementing two study specific opt out processes and national data opt-out for the study data as a whole, and these processes will also be applied to the DDC element of the study. It is considered that this provides adequate safeguards against the inclusion of data from individuals who do not wish their data to contribute to the research

9.3 Routine data sources

Most of the data needed to conduct the study primary and secondary analyses will be extracted from national sources of routinely collected data. Once the NICE phase has begun, the routine data from NHS databases will be requested on a regular basis. The data will only be used for analysis from the NICE and FMF phases, with data from the transition phase used to retrospectively assess the speed and completeness of implementation and secondary outcome analyses but will not contribute to the primary outcome analysis.

The routine data will be requested from the national dataset providers by the NCTU. Table 4 shows the datasets and variables needed for each relevant aim of the study, while Table 5 lists the datasets and data providers involved.

If no routine data is received from NHS England for an individual in the study database, their record in the study database will be deleted, no routine data will be received/requested and their data will not enter the TRE.

Table 4 Data collection sources for each aim of the study.

	Aims	**Dataset**	**Variables**
1	To determine whether (universal) implementation of the FMF screening test for PE reduces (iatrogenic) PTB.	MSDS	Gestation at birth. Mode of birth. Mode of labour onset.
2	To assess the cost effectiveness of the FMF screening test for PE in the whole study population and in clinically relevant subgroups.	MSDS BadgerNet NNRD HES ONS	As above, plus: Birthweight*. Neonatal/maternal admission/level/length of stay Neonatal/maternal secondary

			Outcomes. † Neonatal/maternal death.
3	To assess acceptability and identify barriers and facilitators to routine adoption of the FMF screening test.	Study data	Acceptance/completion of screening/each component of FMF screening test.
4	To assess the impact on experience of FMF screening test implementation on professionals and pregnant women/people.	MSDS Study data	Intended/actual place of birth. Questionnaire and interviews.

*HES = Hospital Episode Statistics. MSDS = Maternity Services Dataset. NNRD = National Neonatal Research Database. ONS = Office for National Statistics. * With gestation at birth allows FGR/SGA status calculation.*
† See Table 1 for details.

Table 5 Datasets and data providers

Information type	**Dataset type**	**Dataset**	**Data provider**
Maternity	Maternity services	BadgerNet Maternity	SystemC
		MSDS v2	NHS England
Hospital	Inpatients	APC	
	Outpatients	OP	
	A&E	ECDS	
	Critical Care	CC	
Mortality	Maternal/Neonatal Deaths	ONS	
	Miscarriage/ Stillbirth	MSDS/HES	
Neonatal	Neonatal service	NNRD	Imperial College
		BadgerNet Neonatal	SystemC

APC=Admitted Patients Care (Inpatients) for England
CC=Critical Care for England
ECDS= Emergency Care Data Set (England)
HES=Hospital Episode Statistics (England)
MSDS=Maternity Service Dataset for England
NNRD=National Neonatal Research Dataset (England)
ONS=Office for National Statistics for England
OP=Outpatient Appointments for England

Data sharing agreements between the sponsor and data provider will enable the University of Nottingham to receive routine data for the STARshiP study. The final datasets for analysis will be retained after the study has finished and safely stored at NCTU in a separate location from the identifiers. This will allow further follow up analyses to be conducted in the future following linkage to data on the children's health and development and maternal long-term outcomes, subject to further funding and all relevant approvals. New data providers and sources, such as educational records and GP records, may be required in the future.

For the whole length of the project, the routine data, once received, will be safely stored in the accredited Trusted Research Environment (TRE) located at University of Nottingham. The

TRE will receive all the routine datasets from each respective data provider and manually collected data from the NCTU database.

9.3.1 BadgerNet (Maternity and Neonatal)

BadgerNet Maternity is available in two versions: as a brief clinical summary record or a complete electronic health record system that captures all aspects of care and outcomes from booking, to discharge from postnatal care. All trusts in England use BadgerNet Neonatal (with the exception of Great Ormond Street Hospital). Around 40-50% of trusts in England are now using BadgerNet Maternity.

The providers, SystemC, under appropriate information security and governance standards, hold the data for all units centrally. Data from the system would enable babies not ill enough to be admitted to a Neonatal Unit (NNU), and who remain on the postnatal ward, to be added to the study dataset. This would enable the equivalent information as for those infants admitted to a NNU to be used to determine neonatal secondary outcomes and outcomes for the economic analysis.

Currently, BadgerNet Neonatal is the source of Neonatal Dataset for the NNRD, along with additional variables which can add richer data for the secondary neonatal outcomes and for the economic evaluation. SystemC may not be the sole provider of the core dataset indefinitely, if other electronic health record providers develop suitable systems that can meet the requirements of the NNRD. Therefore, we will not replace NNRD with the BadgerNet neonatal dataset: the latter will supplement the NNRD.

9.3.2 National Neonatal Research Database (NNRD)

All 200 neonatal units in England, Wales and Scotland form the United Kingdom Neonatal Collaborative (UKNC) and contribute electronic health record data to the National Neonatal Research Database (NNRD), currently hosted by Imperial College, London. The NNRD holds individual patient-level data on all infants admitted for National Health Service neonatal care in England, Scotland and Wales from 2014 to present. The NNRD is a national resource formed of the Neonatal Data Set (an NHS Information Standard), comprising 450 clearly defined variables [51], extracted at patient level from the commercial Electronic Health Record used by all UK neonatal units.

Information on secondary neonatal outcomes and further details for the economic assessment will be obtained from this database on a regular basis. Maternal obstetric information will be potentially extracted as well, if missing from Maternity datasets.

9.3.3 Maternity Data

Information needed to define the primary outcome (such as gestational age at birth, living status at birth and onset of labour) and other secondary maternal outcomes (such as mode of birth, birthweight to identify FGR) will be extracted from the English Maternity Services Dataset (MSDS).

MSDS is a patient-level dataset that captures key information at each stage of the maternity care pathway including the mother's demographics, booking appointments, admissions and re-admissions, screening tests, labour and delivery along with the baby's demographics, admissions, diagnoses and screening tests. Version 2.0 of the MSDS has been accepted as an

Information Standard and is mandated. The MSDS is accessible via the Data Access Request Service at NHS England.

9.3.4 Hospital Episode Statistics (HES)

Hospital Episode Statistics (HES) is an NHS England database containing details of all admissions, outpatient appointments and accident and emergency attendances at NHS hospitals in England.

Information relevant to the economic assessment and further clinical details on the study primary and secondary outcomes, which are missing from the maternity or neonatal data sources, will be extracted from the HES datasets.

9.3.5 Mortality data

Mortality data will be required to capture secondary maternal and neonatal outcomes other than economic outcomes. Although these events are rare, they need to be reported in the study and cannot be manually collected nor reliably obtained from hospital data because neonatal deaths at home might not be reported to the hospital. Data on all deaths is obtained from the Office for National Statistics (ONS) registers.

9.4 Source Data

Data management will be guided by the study-specific data management plan (DMP). Data obtained from NHS England, Imperial College and SystemC are obtained directly from electronic health records and as such, are the source data.

Completion of the screening test will contain the source data for screening strategy, and although some data items may be repeated in the maternal and neonatal health records, this will vary by site.

The source data for the detailed data collection is the maternal and neonatal health records at the site. There are no informed consent forms (ICF) for the SW-CR study. Informed consent will be obtained for questionnaire completion and qualitative interview; these are described in Section 14.

9.5 Data Management

NCTU will inform the site that the intervention and data collection periods at the site have ended. The site will be closed after completing all necessary close-out procedures, coordinated by the NCTU.

The monitoring of routine data import; data linkage; data storage and data transfer procedures back-up and disaster recovery of any local databases and validation of data manipulation will be detailed in the Data Management Plan.

9.6 Archiving

In compliance with the ICH/GCP guidelines and regulations, the Chief or local Principal Investigator will maintain all records and documents regarding the conduct of the study. These will be retained for 5 years. If the responsible investigator is no longer able to maintain the trials records, a second person will be nominated to take over this responsibility.

The Trial Master File (TMF) and study documents held by the CI on behalf of the sponsor shall be finally archived in the Microsoft cloud which has multiple redundant systems and backup services. This archive shall include all study databases and associated meta-data encryption codes. Access to filed once archived (e.g. for inspection purposes), will be managed by the NCTU archivist and will only be accepted on approval of the sponsor. This requirement will not include data that is required to be destroyed as part of the conditions of its' receipt from central data suppliers, such as NHS England.

9.7 Data Sharing

Requests for data collected for the STARshiP study from parties outside the Trial Management Group (TMG) will be considered by the NCTU Data Sharing review panel. For approved requests, the dataset will be prepared by the NCTU and will be provided as a summary at a site and study level only. A data sharing agreement will be required between the sponsor and the external party. Participant-level data will not be made available, as it is not permitted by the NHS England, NNRD, Paediatric Intensive Care Audit Network (PICANet), or BadgerNet under the terms and conditions under which NCTU receives the data.

10 Adverse Event Reporting

10.1 Adverse Events Arising from Screening

The occurrence of an adverse event as a result of participation within this study is not expected and no adverse event data will be collected/reported.

10.2 Adverse Events Arising from Aspirin use

LDA is the proven, preventative drug recommended for pregnant women/people at risk of PE and serious adverse events are rare and well known. Aspirin is not the intervention studied in this study, so adverse events relating to LDA will not be collected/reported.

The important consequences of PE, for the pregnant women/people and babies, will be captured as outcomes.

11 Quality control and quality assurance

11.1 Site Set-up and Initiation

All participating Principal Investigators will be asked to sign the necessary agreements and supply a current CV and GCP certificate to NCTU. Members of the site research teams (principal investigator, coordinating midwife, any research midwives and any other staff involved in study training/detailed data collection) will also be required to sign a site delegation and training log. Prior to commencing the study all sites will undergo a process of initiation and will have completed any necessary training. Key members of the site research team will be required to attend either a meeting or a teleconference covering aspects of the study design, protocol procedures, collection and reporting of study data and record keeping. Sites will be provided with an Investigator Site File and training material containing essential documents, instructions, and other documentation required for the conduct and reconstruction of the study. NCTU must be informed immediately of any change in the site research team.

11.2 Monitoring

Monitoring will be carried out as required following a risk assessment and as documented in the monitoring plan. NCTU will be in regular contact with the site research teams to check on progress and address any queries that they may have. In particular, monitoring of the quality and completeness of FMF screening test will be regularly reviewed throughout the transition phases with proactive provision of support.

Monitoring of study data will be outlined in the study monitoring plan. Monitoring of study data shall include routine data import; data linkage; data storage and data transfer procedures; local quality control checks and procedures, back-up and disaster recovery of any local databases and validation of data manipulation. The CI and Deputy CI, or where required, a nominated designee of the Sponsor, shall be responsible for monitoring of study data as an ongoing activity.

Study data and evidence of monitoring and systems audits will be made available for inspection by the Research Ethics Committee (REC) as required.

11.3 Audit and Inspection

Study conduct may be subject to a systems audit of study management activities and the wTMF for inclusion of essential documents; permissions to conduct the study; local document control procedures training logs, adherence to procedures defined in the protocol (e.g. UtA measurement protocol).

The Principal Investigator (PI) will permit study-related monitoring, quality checks, audits, ethical reviews, and regulatory inspection(s) at their site, providing direct access to source data/documents. The Principal Investigator will comply with these visits and any required follow up.

The TMF and evidence of audits will be made available upon request for regulatory inspections.

11.4 Notification of Serious Breaches

The Sponsor is responsible for notifying the REC of any serious breach of the conditions and principles of GCP in connection with that study or the protocol relating to that study. Sites are therefore requested to notify the NCTU of any suspected study-related serious breach of GCP and/or the study protocol. Where NCTU is investigating whether a serious breach has occurred, sites are also requested to assist NCTU in providing sufficient information to report the breach to the REC where required and in undertaking any corrective and/or preventive action.

Sites may be suspended from further recruitment in the event of serious and persistent non-compliance with the protocol and/or GCP. Any major problems identified during monitoring may be reported to TMG and the REC. This includes reporting serious breaches of GCP and/or the study protocol to the REC.

12 End of Study Definition

The end of study will be when the final dataset has been retrieved from the last site and/or routine data source and the database has been locked. This is anticipated to be approximately

60 weeks after the final screening allocation period has completed, reflecting a period of up to 30 weeks between screening and birth, a further four weeks until neonatal outcome is confirmed and 26 weeks to extract routine data. NCTU will notify the REC the study has ended, and a summary of the clinical study report will be provided within 12 months of the end of study.

Following the end of the study period, participating NHS Trusts will continue screening for PE risk among their patient populations according to their local policies.

13 Statistical Considerations

13.1 Sample size and justification

We used the Shiny CRT calculator [52] to compute the achieved power given a detectable difference and sample size. We plan to enrol 16 UK NHS Trusts (clusters). Using NHS Maternity statistics for deliveries for 2020/21 [51] we estimated routine data would be obtained from an average of 4,500 deliveries per maternity unit per year, after accounting for a 7% opt-out rate [53]. We propose an incomplete design (Figure 1) with 8 sequences (16 clusters- two Trusts switching in each of 8 transition timepoints) and 21 periods each of 7 weeks duration, leading to an average cluster-period (cell) size of 700 pregnancies. Sites will be active for 34 months: all will start with at least 14 weeks (depending upon sequence allocation) of the NICE screening phase. This will be followed by a 7-week transition phase where the FMF screening test will be introduced, before entering the FMF screening phase. Pregnancies screened during the transition phase will not contribute to the primary outcome; the total number of pregnancies included in the analysis will be ~224,000 with the overall total number screened to be approximately 235,200. The incomplete SW-CR Study design with transition period mitigates for the impact of delayed implementation of the intervention. We assume the proportion under control group (NICE) for primary outcome (iatrogenic PTB) to be 2.2% [54] and a significance level of 0.05.

We have modelled the expected power based on a range of potential absolute risk differences (0.3-0.4%) and a range of cluster auto-correlations (CAC) (0.4-0.9). Assuming a discrete-time decay intracluster correlation structure with within-period ICC of 0.0005 (estimated using the Northwest region routinely reported data for our primary outcome [55]) and a CAC of 0.4, we will have 82% power to detect an absolute difference in primary outcome of at least 0.3% (2.2% with NICE [54] to 1.9% with the FMF screening test), and 97% power to detect absolute differences of 0.4%. A power of >90% to detect an absolute difference of 0.4 is maintained assuming higher CACs ranging from 0.5 to 0.9.

An 0.3% absolute risk reduction in preterm PE is expected from the published performance of the FMF screening test in the international ASPRE study [29] and UK-based SPREE study [22].

13.2 Monitoring of recruitment

As the study design is based on universal implementation of the PE screening test in place in that NHS Trust (as determined by the randomly assigned transition date) and the study does

not rely on individual patient recruitment, "under recruitment" may arise in two ways; a lower than anticipated number of patients booking for maternity care at participating NHS Trusts during the study period, a low fidelity of test implementation or a higher than anticipated opt-out rate. Data on the number of individuals booking for pregnancy care at participating sites during the study period, the number of patient PE screening datasets returned and on the fidelity of screening implementation at participating sites will be monitored throughout the study. The study team will work with participating Trusts to optimise the number of individuals screened, how the study is explained to patients and the fidelity of that screening. Due to the nature of the SW-CR study design, and the clinical governance requirements for participating Trusts in coordinating transition to the FMF screening test, it will not be feasible to extend the study period in order to mitigate the smaller sample size.

13.3 Definition of populations analysed

Analysis of primary outcome will be according to intention-to-treat (ITT), where "treatment" indicates the PE screening test to be used, analysing sites according to their randomised crossover time irrespective of whether crossover was achieved at the desired time. The definition of the populations to be analysed will be clarified in the statistical analysis plan prior to database lock.

13.4 Analysis of Effectiveness

The analysis and reporting of the study will be in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines extension for stepped wedge studies [56]. A full statistical analysis plan (SAP) will be developed and agreed prior to database lock. All data will be analysed using Stata version 18 or later.

Primary outcome analysis will use a mixed-effect logistic regression model comparing iatrogenic PTB rates between clusters in the two phases. The model will adjust for secular trends with time (period) as a fixed effect and within-cluster correlations (clusters and cluster-by-period as random effects), excluding implementation period data. Cluster size will be adjusted for as fixed effect. The between group effect will be reported using an adjusted risk difference and adjusted risk ratio along with corresponding 95% confidence intervals for each. Point estimates and confidence intervals will be obtained using Stata's Margins command with standard errors computed using the delta method [57]. Should there be any non-compliance with some sites unable to implement the FMF screening test (or certain aspects of the test) then a sensitivity analysis will be performed using complier average causal effect (CACE) analysis to account for any non-compliance.

Secondary outcomes will be analysed using appropriate mixed-effects regression models depending on the type of outcome variable, with same adjustments as described for the primary outcome. The estimated treatment effect with 95% confidence interval and two-sided p-value will be presented.

13.4.1 Planned subgroup analysis

Subgroup analysis for the primary outcome will be conducted according to maternal ethnicity and parity by including appropriate interaction terms in the analysis model for the primary

outcome. Since the study is powered to detect overall differences between the groups rather than interactions of this kind, this subgroup analysis will be regarded as exploratory.

13.4.2 Exploratory analyses

In an additional exploratory analysis, the primary and secondary outcomes extracted from the MSDS data set will be analysed for all pregnant women/people (without current opt-out) who are recorded as having a booking appointment within in each hospital site participating in the study. This analysis may have limitations due to the accurate ascertainment of gestational age at booking from the routine data submitted to MSDS.

13.4.3 Planned Interim analysis

There is no planned formal interim statistical analysis of treatment effectiveness (pregnancy outcome and subsequent receipt of outcome data from routine data sources would not be received within a timeframe that could enable meaningful assessment and action). Screening data will be monitored at least monthly, compared with the number of booking appointments in participating Trusts to ensure all relevant screening data is being reported to the study. Fidelity of screening implementation during the FMF phase will be monitored frequently during the transition phase and monthly thereafter to ensure the screening test is implemented as intended.

13.5 Timing for final analyses

Final analyses will be performed once the database has been locked.

13.6 Procedures for missing, unused and spurious data

All risk assessment data (screening data) will be initially recorded in the site's patient record system. In the transition or FMF phase of the study this information will be shared with the regional screening laboratories for preterm PE risk calculation and the result returned to site and recorded in the patient record. Regional screening laboratories have established protocols for handling of incomplete or potentially spurious clinical data including in-built data validation within screening software systems; these processes will continue to be followed in the STARshiP study. PE risk screening data (including clinical factors and risk score) will then be entered into the study REDCap database via regular bulk file upload or transcription. During the NICE phase of the study, missing data from the screening elements will be treated as "risk factor not present". During the transition and FMF phase, missing data will be handled as specified by the FMF algorithm. Where individuals have opted out of data usage after receipt by the NCTU, their screening results will be removed from the study database before locking of the final dataset.

14 Health Economics

14.1 Aim

The economic evaluation will aim to identify, measure, value and compare the costs and consequences of FMF screening test versus NICE screening approaches, from a health sector perspective. The intervention aims to reduce the number of pregnancies with preterm PE and FGR leading to iatrogenic PTB or stillbirth.

14.2 Outcome

Economic outcomes will be expressed in terms of incremental cost per iatrogenic PTB avoided and incremental cost per QALY gained, reported separately and in combination for the woman/ person and infant.

14.3 Data sources

The STARshiP study will provide estimates of the incidence of PTB as well as mortality and other morbidity outcomes.

We will seek to match screened pregnant individuals and their babies' records to HES and NNRD data in order to profile each study participant's duration and intensity of antenatal, intrapartum, postnatal and neonatal care, based on standard criteria for level of care, as well as maternal and neonatal surgical procedures, complications and readmissions.

To assess short-terms cost effectiveness, the following routine datasets will be linked and used; the MSDS will provide data regarding gestation at birth, mode of birth and birthweight. BadgerNet will provide resource use information regarding neonatal admissions, and related level and length of stay, and associated surgical procedures and high-cost interventions. These datasets will be linked to (HES, including data on maternal admissions, to inform resource use for the economic evaluation alongside the study. Healthcare resource use will be collected for all cause HES hospital admissions, all HES outpatient appointments and A&E contacts. Healthcare cost estimates will be calculated by applying tariff costs to the resources listed in primary outcomes over the period pregnant women/people are in the study. Inpatient stays will be categorised in line with NHS reference costs calculations. Secondary care encounters will be derived from HES inpatient and outpatient data and will include admitted care (inpatient and day case admissions) and outpatient attendances and procedures. Each admission will be assigned an appropriate reference cost using the national tariff prices, based on the national average unit service provision costs from the National Schedule of Reference Costs. For outpatient encounters, each encounter will be costed using treatment speciality average costs from the relevant NHS reference cost schedules.

In addition, targeted economic studies will be integrated into the STARshiP study to generate key resource use and economic cost parameter estimates for the model. Specifically, the DDC for 100 pregnant women/people within each study site, pre- and post-implementation of the FMF screening test, will provide a vehicle for estimating resource use and cost profiles associated with first trimester PE screening and associated impacts to the healthcare systems such as antenatal staffing, sonographer time, staff training, maternal and infant level/cumulative duration of care, and additional procedures (e.g. imaging, laboratory services and medical interventions) as well as test and LDA uptake rates. Data items will be captured in disaggregated units where possible, and micro-costing will be performed to capture variance in costing patterns. Unit costs for each resource input will largely be derived from national secondary sources, for example the Department of Health & Social Care's NHS Reference Costs but supplemented where necessary using primary research methods and discussions with suppliers. These costs will importantly enable an evaluation of the health

system resource consequences of FMF screening test roll out, in terms of estimating the additional and incremental costs of introducing a screening programme in the UK.

14.4 Analysis

A within-study analysis of cost-effectiveness will be conducted for PE risk screening using FMF screening test versus NICE screening, expressed in terms of incremental cost per iatrogenic PTB avoided. The time horizon for the within-study economic analysis will be from recruitment until six weeks post-partum. Sub-group analyses will mirror those undertaken for the main analysis. Summary statistics and cluster analysis may be used to determine data characteristics. Missing data will be imputed where appropriate to reduce the impact of missing data on regression results. Multi-parameter uncertainty will be addressed using probabilistic sensitivity analysis. These sensitivity analyses will be carried out for key costs and outcomes, specifically where they are highly sensitive to certain values or input variables. Principles of opportunity cost will underpin all calculations.

The short-term cost-effectiveness evidence will be extended by building a *de novo* cost-effectiveness model. Decision-analytic modelling will express incremental cost of the FMF screening test per quality-adjusted life year (QALY) gained. Cost effectiveness acceptability curves will be used to show the probability of cost-effectiveness for each evaluated strategy at alternative cost-effectiveness thresholds held by decision makers. Maternal and neonatal costs and outcomes will be reported separately using natural units for the estimation of cost-effectiveness, though the methodological and modelling related approaches that could combine the presentation of cost-effectiveness and/or cost-utility for a mother-baby dyad will be explored. The final decision-analytic model incorporating all components of the short-term primary and secondary cost-effectiveness analyses will enable an extrapolation of longer-term cost-effectiveness. The model structure will capture maternal and infant progression using health states that represent the important natural history and clinical-and event-related activity, the appropriate model type (e.g. Markov or discrete-event simulation approach) and enable integration of data from external studies. Translating the potential benefits of screening in terms of PTBs avoided into QALY metrics is currently constrained by lack of validated utility measures in perinatal and early childhood contexts [58]. The utility values placed on health states will be informed by research conducted by the same investigators leading GBS3 (ISRCTN49639731). This includes a systematic review of published utility values for childhood health states [59]. The modelling approach will further enable exploration of the likely benefit gained by pregnant women/people from the screening approach versus potential over-diagnosis of PE higher risk status, as a key recommendation from the UK NSC consultation on PE risk screening [60]. The economic evaluation will be conducted and reported in accordance with relevant guidance [58, 61, 62]. This includes a systematic review of published utility values for childhood health states [59]. It will additionally explore data linkage options for further research to identify whether preventing preterm PE may impact lifetime maternal and neonatal healthcare costs.

15 Implementation evaluation

15.1 Aims

The aims of the qualitative embedded mixed methods evaluation are:

1. To assess pregnant women/people and professionals' perceptions of impact of PE risk assessment on subsequent antenatal care and birth choices.
2. To assess acceptability and identify barriers and facilitators of routine adoption of the FMF screening test.
3. To assess the impact on experience of FMF screening test implementation on professionals and pregnant women/people.

15.2 Objectives and Outcome Measures

The primary objective of the embedded mixed methods evaluation is to assess acceptability of the two PE risk assessment methods and subsequent management recommendations to maternity patients and service providers.

Secondary objectives of the embedded mixed methods evaluation are to:

- Identify practical issues relating to the deployment of the FMF screening test intervention and how these are overcome.
- Assess whether the use of the FMF screening test to quantify PE risk leads to greater readiness of professionals to recommend LDA adherence, and of maternity service users to adhere to that recommendation.

15.3 Design and Setting

This is a mixed methods implementation evaluation (informed by the Consolidated Framework for Implementation Research (CFIR)) which is embedded within the wider SW-CR STARshiP study.

Of the >224,000 pregnant women/people who receive maternity care in NHS Trusts participating in the SW-CR study during the study period (both NICE and FMF phase), an unlimited number will be able to self-identify to complete an online questionnaire as part of the mixed methods implementation evaluation by following advertisement posters/leaflets/social media posts displayed within participating maternity units. Participant information and questionnaires will be provided in each of the 5 most commonly spoken/read languages in the participating regions. If the service user indicates that they are pregnant at the time of questionnaire completion, they will be invited to opt in to receiving a follow up invitation to complete the questionnaire (questions relating to later antenatal care and birth experience after their pregnancy has ended, regardless of outcome). Individuals will be able to self-initiate the follow up questionnaire completion through details provided at the time of antenatal response, or (if optional consent for a follow up questionnaire receipt is given) an automated invitation will be delivered six weeks following their reported estimated delivery date. Prior to delivery of the follow up questionnaire, an email reminder will be sent with option to revoke consent to receive the follow up questionnaire; this can also be done

at any time following instructions in the post- questionnaire completion email received after initial questionnaire completion. The follow up questionnaire will commence by establishing the nature of the pregnancy outcome (e.g. live birth vs. miscarriage, stillbirth, termination of pregnancy or neonatal death), and questions will be filtered/phrased appropriately to the pregnancy outcome. The study will be closed to new responses at the end of the wider SW-CR study period.

Professionals (including but not limited to healthcare providers and non-clinical managerial and administrative staff) will be invited to complete an online questionnaire as part of the same mixed methods implementation evaluation by following a link circulated to maternity services staff based within each participating unit at regular intervals following and implementation of the new screening test. The questionnaire invitation email text will be standardised and pre-approved by the REC.

Each questionnaire will invite respondents to participate in a follow up semi-structured interviews. Of these, up to 50 respondents (across service users and professionals) will be interviewed.

15.3.1 Professional Questionnaires

Professionals (including but not limited to healthcare providers and non-clinical managerial and administrative staff) will be recruited from each of the NHS Trusts taking part in this evaluation. There is no minimum or maximum number of questionnaire responses from professionals to be included within the evaluation.

Designated members of staff at each site will be responsible for sending all relevant professionals (including midwives, midwifery support workers, doctors, sonographers and health care administrators) within the maternity unit the necessary questionnaire link and a summary of the study and purpose of the questionnaires. This email will be pre-formatted and approved by the REC to ensure that the voluntary nature of the questionnaire is enforced with the reassurance that there will be no professional repercussions for any staff who do not wish to complete the questionnaire. This information will be re-circulated across the Trust at least 3 times in each phase of the study (NICE and FMF).

During the questionnaire, respondents will be asked to (optionally) indicate contextual factors that may influence their experience of their involvement in PE risk assessment.

Respondents will be invited to provide their consent (optional) to be contacted to take part in a qualitative research interview about their experiences. The evaluation aims to recruit 50 participants to complete the interview. This includes professionals and service users. As such, there is no guarantee that everyone who opts-in for the interview will be selected (see section 15.3.3).

15.3.2 Service User Questionnaires

Study information will be provided to pregnant women/people via posters/leaflets displayed within the NHS Trusts (including birth centres and community midwifery services). Additional information and questionnaire link will also be displayed on the study website. Posters/leaflets/websites/social media posts will contain REC-approved study overview information relating to the implementation study and information on how to take part.

Pregnant women/people will be eligible to participate from all participating NHS sites throughout the study period. There is no minimum or maximum number of questionnaire responses from service users to be included in the evaluation.

Participants will be able to read the study PIS at their own volition prior to the completion of the questionnaire, which begins with initial screening for eligibility (participant declaration of current/recent pregnancy and care in a participating hospital during the study period) followed by participant declaration of consent to participate.

Pregnant women/people who are pregnant during the completion of initial questionnaire will be allowed to opt-in for a follow-up questionnaire. They will be contacted by email, provided with the opportunity to opt out of receiving the follow up questionnaire, and the questionnaire design will ensure that all wording is suitable for those women/birthing people who may have experienced an adverse perinatal event.

During the questionnaire, respondents will be asked to (optionally) indicate contextual factors that may influence their experience of PE risk assessment and subsequent care during the pregnancy. Respondents will be invited to provide their consent (optional) to be contacted to take part in a qualitative research interview about their experiences. The evaluation aims to recruit 50 participants to complete the interview. This includes professionals and service users. As such, there is no guarantee that everyone who opts-in for the interview will be selected (see section 15.3.3).

15.3.3 Interviews

Following receipt of consent to contact from within completed questionnaires, participant responses will be reviewed, and purposive sampling will be used based on reported relevant contextual factors (including service user vs. professional status, NHS Trust, primiparity and self-reported high/low risk status, healthcare profession) and up to 50 participants recruited/interviewed in order to maximise diversity of sampling. Sampling will also be influenced by available resources, previous experiences with similar evaluations and data saturation. Those not selected for interview will receive an email/letter informing them that they were not chosen for interview but also thanking them for taking the time to opt in to be contacted.

Selected participants will be invited to participate in a semi-structured qualitative research interview by an appropriately trained and qualified University of Nottingham research assistant according to the specified preferred method of contact after consent to contact is granted through the evaluation questionnaire. A copy of the interview study PIS will be provided and an appropriate date/method of follow up contact will be agreed (participant/researcher-initiated) in order to arrange a mutually convenient date, time and method (telephone or video call) of interview. Prior to the time of interview, the research assistant will provide the participant with a digital e-consent form or written consent form via post for completion prior to the interview commencing.

A maximum of 3 attempts to contact the potential interview participant will be made by the research team at any time point in this process, if unsuccessful no further researcher-initiated contacts will be made. However, where possible research team contact details will be

provided and the potential participant can self-initiate further contact if desired (maximum 3 further attempts to contact after any participant indication of enduring consent to contact).

Interviews with pregnant women/people will not be scheduled until at least 6 weeks postpartum.

The interview will be guided by a topic guide. This may be a video or telephone interview, according to participant preference. Interpretation will be provided where required. In the interviews, the trained researcher will follow a distress protocol to assess at any point, whether the participant is in distress and if they show signs of this, the steps to take.

15.4 Eligibility

15.4.1 Inclusion Criteria

Questionnaires

Professionals who:

1. Are working in an NHS Trust taking part in the study at least 7 weeks after the FMF screening test has been implemented at site (clinical and non-clinical staff).
2. Have the ability to complete an online questionnaire through access of a URL or QR code.
3. Have completed the declaration of consent to participate in the questionnaire.

Women/people who:

1. Have commenced maternity care in a participating NHS Trust during the study period.
2. Have the ability to complete an online questionnaire through access of a URL or QR code.
3. Have completed the declaration of consent to participate in the questionnaire.
4. Women/people who were unable or unwilling to undergo PE screening will not be excluded.

Interviews

Professionals who:

1. Are working in an NHS Trust taking part in the study and have experience with implemented FMF (clinical and non-clinical).
2. Have completed the online questionnaire and indicated consent to be contacted for a follow up qualitative interview.

Women/people who:

1. Have commenced maternity care in a participating NHS Trust during the study period.
2. Are >6 weeks and <6 months postpartum at the time of interview.
3. Have completed the online questionnaire and indicated consent to be contacted for a follow up qualitative interview.
4. Are able to take part in a telephone or video interview, with or without provision of interpretation.
5. Women/people who were unable or unwilling to undergo PE screening will not be excluded.

15.4.2 Exclusion Criteria

Questionnaires

Women/people who:

1. Lack capacity to give informed consent.
2. Are more than 6 months postnatal at the time of questionnaire entry.

Interviews

Women/people who:

1. Have not completed the online questionnaire or who decline consent to contact for the interview.
2. Lack capacity to give informed consent.
3. Have not experienced maternity care in one of the NHS Trusts taking part in the study.
    a. Those who were unable or unwilling to undergo PE screening will not be excluded.
4. Who are less than 6 weeks, or more than 6 months postnatal at the time of interview.

Professionals who:

1. Have not completed the online questionnaire or who decline consent to contact for the interview.

15.5 Consent and Withdrawal

15.5.1 Consent

Questionnaires

Women/people will have access to posters/leaflets within the NHS Trust that contains the study information and two QR codes. Women/people will scan each of the QR codes and one will direct them to the study website containing further information and the second will direct them to the questionnaire. The questionnaire will contain an embedded information sheet.

All individuals (women/people and professionals) will be required to confirm that they have read the 'information sheet' embedded within the questionnaire before being able to indicate consent to participate in the questionnaire evaluation overall and complete the questionnaire. This will ensure that all individuals have a complete understanding of the purpose of the questionnaire and how their data will be used.

Due to the nature of the questionnaire, individual informed consent will be demonstrated by individuals agreeing to standard consent clause questions and to overall questionnaire evaluation participation. The completion of the questionnaire, following the review of the 'information sheet' will count as individual consent for the data provided within the questionnaire to be utilised for the specified research purpose.

Women/people who self-declare that they are still pregnant at the time of completion will be able to opt-in for an additional follow-up questionnaire. By opting in for this, they will be consenting to their provided details (name and personal email address, estimated delivery

date) being stored by the research team within the study database with the purpose of providing an automated invitation to complete a second questionnaire (regarding later pregnancy and birth experience) and linking the two questionnaire responses together. If no response is received to the follow up questionnaire by a date 6 months after the reported estimated delivery date, the pregnant women/ people will not be contacted again, and the data will be anonymised.

In order to minimise the potential for a woman's/person's distress e.g. in the case of a negative pregnancy outcome, a pre-questionnaire email reminder will be sent in advance and will contain details of how to opt out of follow up questionnaire invitation receipt. Individuals will also be able to self-initiate opting out of further contact through details provided in the original questionnaire completion email. This approach is favoured by the study-specific PPI group.

Interviews

At the end of the questionnaire, there will be the option to opt-in for the semi-structured interview. By opting in for this the women/people or professionals will be consenting to their details (name, preferred method and time of contact) being stored with the purpose of contacting them with additional information and for holding the interview itself.

All those selected for interview will receive a copy of the participant information sheet for the interview and the researcher will ensure they have sufficient time to read the document before consent is obtained for interview. Prior to that start of the interview, the researcher will confirm that the woman/person or professional has understood everything fully, at which point the woman/person or professional will be provided with an e-consent form for completion.

15.5.2 Withdrawal

Table 6 - Description of the withdrawal procedures for data processing.

Withdrawal type	Withdrawal procedure	Use of data
Withdrawal from questionnaire and follow-up questionnaire where applicable	Any woman/person that requests to discontinue from the evaluation questionnaires will be marked as withdrawn from questionnaire collection on the study database and no further contact will be made with the women/person for the purpose of obtaining questionnaire follow-up data. Similarly, if women/people do not complete the questionnaires they will be counted as having withdrawn their consent to continue.	Women/people who complete the questionnaire postnatally or those pregnant women/people who complete the questionnaire whilst pregnant and do not opt-in for the follow-up questionnaire or interview will not be able to request their data be removed as this is anonymous and cannot be linked back to the individual participants. Professionals who do not opt-in for interview will similarly be unable to request that their data be removed for the same reason.

		Pregnant women/people or professionals who opt-in for (a follow-up questionnaire – service users only) or interview will remain identifiable. If requesting withdrawal they will be provided with the option to receive no further contact and/or for their data to be removed.
Withdrawal from the interview and request to remove data	Any women/person or professional that requests to withdraw from the evaluation interview will be marked as withdrawn and no further contact will be made with the individual for the purpose of obtaining interview data.	Any interview data of women/people or professionals who do not withdraw prior to 14 days post -interview deadline cannot be removed as the interview transcript will have been anonymised.

15.6 Data Collection

Questionnaires

The online questionnaires will aim to collect information on the views and impacts of PE risk screening from the perspective of both the pregnant women/people receiving the tests and the professionals responsible for providing these.

All data input will be by the participants, anonymised before use (where necessary), and stored within the secure online database held by the University of Nottingham. This will be the source data for both questionnaires.

Interviews

The interviews will be held over the phone or via video link (MS Teams) and a transcript will be created of the interview. This will be stored with identifiable details for 2 weeks after the interview, until the transcript will be reviewed, anonymised and stored securely within the University of Nottingham systems. This transcript will be counted as the source data for all interviews. Once the transcript has been anonymised and stored securely, the audio recording of the interview will be deleted.

16 Study Organisational Structure

The roles and responsibilities for each organisation are documented in the Collaboration Agreement and the responsibilities of the (Sponsor/CI/NCTU) specifically are detailed in the Delegation of Responsibilities.

16.1 Sponsor

The University of Manchester will act as sponsor for the study.

16.2 Coordinating Centre

The study is co-ordinated by the NCTU.

16.3 Trial Management Group

The TMG includes individuals responsible for the day-to-day management of the study, including the Chief Investigator, Deputy Chief Investigator, leads for the NCTU, economic, and mixed methods evaluations, the Senior and Trial Statisticians, Trial Manager, Data Manager. The role of the group is to ensure high quality study conduct, to time and within budget, to monitor all aspects of the conduct and progress of the study, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the study itself.

16.4 Trial Oversight Committee

The role of the Trial Oversight Committee (TOC) is to maintain oversight of the study. The TOC includes members who are independent of the Investigators, their employing organisations, and the Sponsor. The TOC should monitor study progress and conduct.

The design of the study means that there will not be outcome data available for analysis as the study progresses. The protocol does not contain any planned interim analyses, as in a SW design there will always be more control group data, compared to intervention group, until the end of the study, making interim analyses less efficient. There are no anticipated adverse effects of the screening tests, the study is assessing the effectiveness of implementing the FMF screening test, not its accuracy, and it will become standard practice at the study sites during the intervention period. Under these circumstances a Data Monitoring Committee (DMC) has very little scope for monitoring the effectiveness of the FMF screening test. The role of the DMC will be subsumed into the TOC, although the latter will retain the option to convene a DMC from within its membership should the necessity arise. In addition, as there are no planned interim analyses, no anticipated adverse effects, the trial has a TOC in place of a Trial Steering Committee.

Reports will be supplied in confidence to the TOC, which will be asked to give advice on whether the accumulated data from the study, together with the results from other relevant research, justifies the continuing recruitment of further participants. The TOC will operate in accordance with a study specific charter based upon the template created by the Damocles Group. The TOC will meet at least annually unless there is a specific reason to amend the schedule.

16.5 Finance

This study/project is funded by the NIHR HTA Programme (project reference NIHR152762). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

The study has been adopted on the NIHR Clinical Research Network portfolio.

Neither the investigators nor pregnant women/people will receive payments or reimbursement of expenses for participation in STARshiP.

17 Ethical Considerations

The study will be performed in accordance with the recommendations guiding physicians in biomedical research involving human participants, adopted by the 18th World Medical Association General Assembly, Helsinki, Finland, June 1964, amended at the 75th WMA General Assembly, Helsinki, Finland, October 2024 (website: https://www.wma.net/policies-post/wma-declaration-of-helsinki/). Additional consideration will be given to the Ottawa Statement on the Ethical Design and Conduct of Cluster Randomised Trials [63].

The study will be conducted in accordance with the Research Governance Framework for Health and Social Care, and the Data Protection Act 2018 and Guidelines GCP. The protocol will be submitted to and approved by the REC prior to circulation.

18 Confidentiality and Data Protection

Personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the Data Protection Act 2018.

Individuals whose data contribute to the detailed data collection (see section 9.2) will always be identified using only their NHS number, and date of birth on the Case Report Form and in correspondence between the NCTU and the participating site.

The local investigators must maintain documents not for submission to NCTU (e.g. Participant Identification Logs for detailed data collection) in strict confidence. In the case of specific issues and/or queries from the regulatory authorities, it will be necessary to have access to the complete study records, provided that participant confidentiality is protected.

NCTU will maintain the confidentiality of all participant's data and will not disclose information by which participants may be identified to any third party.

Section 251 approval will be obtained from the CAG to use locally recorded clinical data and routinely collected data without individual consent for the cluster randomised study. The NHS number and date of birth, will be used to identify women/people and their baby in the received datasets and to link datasets.

Due to the use of pseudonymised (main study) and anonymised (implementation evaluation) record identifiers, in the unlikely event that information is disclosed during the study, it is highly unlikely that it could pose a risk of harm to the participant or others. Any data breaches from the NCTU or University of Manchester, will be discussed with the Chief Investigator, the Sponsor and where appropriate, reported accordingly.

Data generated as a result of this study will be available for inspection on request by the participating investigators, the University of Manchester's Sponsor's representatives, the REC and local R&D Departments.

19 Insurance and Indemnity

The University of Manchester will act as sponsor for the study. Delegated responsibilities will be assigned to the NHS Trusts taking part, and the University of Nottingham. Insurance and

indemnity for study participants and NHS study staff is covered within the NHS Indemnity Arrangements for clinical negligence claims in the NHS, issued under cover of HSG (96) 48. There are no special compensation arrangements, but study participants may have recourse to the NHS complaints procedure.

The University of Manchester have appropriate and typical insurance coverage in place (including, but not limited to Clinical Trials, Professional Indemnity, Employer's Liability and Public Liability policies) in relation to the Institution's Legal Liabilities arising from the University's activities and those of its staff, whilst conducting University business and research activity.

The University of Manchester is independent of any pharmaceutical company, and as such it is not covered by the Association of the British Pharmaceutical Industry (ABPI) guidelines for participant compensation.

20 Publication Policy

Results of this study and economic evaluation will be submitted for publication in peer reviewed journals. The manuscripts will be prepared by the TMG, and authorship will be determined by mutual agreement. The requirements of the NIHR for open research and transparency will be met.

Any secondary publications and presentations prepared by Site Investigators must be reviewed by the TMG. No data related to the study primary objectives can be published by site investigators before the main study publication. Manuscripts must be submitted to the TMG in a timely fashion and in advance of being submitted for publication, to allow time for review and resolution of any outstanding issues. All authors must acknowledge that the study was performed with the support of the NIHR.

An anonymised dataset (site and study level only) will be made available after the publication of all papers relating to the primary and secondary outcomes, subject to the prevailing requirements of any data sharing agreements signed by the sponsor and/or NCTU.

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