PregnAncy Risk assessmenT aNd dEcision suppoRt (PARTNER): A Clinical Decision Support Tool To Reduce Placental Disorders and Preterm birth in Pregnancy

Clinical Investigation Plan

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Protocol Amendment Summary of Changes

Protocol Amendment	Description of Change
Clinical Investigation Plan V2.0	The spelling of 'MHRA' has been corrected on page 7.
	Section 14.1 has been updated to reflect that the type 1 error rate of 5% is two-sided.
	Section 14.2 has been updated to justify the use of a complete case analysis approach. It is anticipated there will be a very small number of participants with missing outcome data.
	Section 14.3 has been added to make clear that all subjects will be accounted for in the final study report, and that the characteristics of subjects who withdraw or who are lost to follow-up will be described.
Clinical Investigation Plan V3.0	The spelling of 'recruited' has been corrected in section 11.6
	Section 19.3.1 has been updated to make clear that only one named individual and a backup from the research team will have access to study data for the purpose of linkage and analysis.
	Section 19.3.1 has been updated to make clear that only personal information and not identifiable data may be accessed by the digital developers and device manufacturers.
	Section 19.3.2 has been amended to reflect that identifiable study data will only be stored until the end of study and study documentation (site files and trial master file) will be archived for 5 years following end of study.
	'Anonymised data' has been replaced with 'pseudonymised data' in section 19.3.3.
Clinical Investigation Plan V4.0	Removed inclusion criteria b).
	Changed University of Bristol logo in the top right corner of every page.
	Contact email address replaced for 'Project Midwife for Implementation'
	'Health Economist' contact details updated
	Clarification Primary endpoint should be measured up to 2 weeks post birth
Clinical Investigation Plan V5.0	Updated trial design to feasibility design. Significant changes that effect multiple sections, relevant sections have been marked with original and revised design.
	Trial sites will no longer be randomised
	WS2 and WS3 are to be discontinued
	Trial aim is now feasibility

Details of Sponsor

Division of Research, Enterprise and Innovation
University of Bristol
2nd Floor, Augustine's Courtyard
Orchard Lane, Bristol, BS1 5DS
Email: research-governance@bristol.ac.uk

Chief Investigator & Key Research Team Contact Details

Chief Investigator (CI)
Dr Christy Burden
Academic Women's Health Unit
University of Bristol
Learning and Research Building
Southmead Hospital
Bristol BS10 5NB
Email: Christy.burden@bristol.ac.uk

Deputy CI
Professor Andrew Judge
Musculoskeletal Research Unit
University of Bristol
Learning and Research Building
Southmead Hospital
Bristol BS10 5NB
Email Andrew.Judge@bristol.ac.uk

Lecturer in Medical Statistics and Quantitative Epidemiology
Dr Erik Lenguerrand
Musculoskeletal Research Unit
University of Bristol
Learning and Research Building
Southmead Hospital
Bristol BS10 5NB
Email Erik.lenguerrand@bristol.ac.uk

Clinical Lead
Professor Basky Thilaganathan
Fetal Medicine Unit
St Georges
University Hospitals NHS Foundation Trust
Blackshaw Road
London SW17 0QT
Email Basky.thilaganathan@nhs.net

Implementation Science
Professor Jane Sandall
Department of Women and Children's Health
Faculty of Life Sciences and Medicine
King's College London
10th Floor, North wing
St Thomas Hospital
London SE1 7EH
Email: jane.sandall@kcl.ac.uk

Clinical Lead – Preterm birth
Professor Dilly Anumba
University of Sheffield, Department of Oncology and Metabolism, JW4/40, Level 4, Jessop Wing, Tree Root Walk,
Sheffield S10 2SF
Email: d.o.c.anumba@sheffield.ac.uk

Practical Implementation Lead
Professor Tim Draycott
Royal College of Obstetricians and Gynaecologists,
10-18 Union Street
London SE1 1SZ

Trial Portfolio Lead & Methodologist
Dr Sarah Baos
Bristol Trials Centre
Bristol Medical School
University of Bristol
Email: Sarah.Baos@bristol.ac.uk

Email: tdraycott@rcog.org.uk

Health Economist
Nyasha Mafirakureva
Division of Population Health
School of Medicine and Population Health
University of Sheffield
30 Regent Street
Sheffield
S1 4DA
Email: n.mafirakureva@sheffield.ac.uk

Implementation Science and Qualitative Methodologist
Dr Jenny Carter
Department of Women and Children's Health
Faculty of Life Sciences and Medicine
King's College London
10th Floor, North wing
St Thomas Hospital
London SE1 7EH
Email: jenny.carter@kcl.ac.uk

Senior Lecturer in Statistics
Dr Jessica Harris
Bristol Trials Centre
Bristol Medical School
University of Bristol
Email: Jessica.Harris@bristol.ac.uk

Patient and public involvement
Mrs Maria Viner
Chief Executive Office
Mothers for Mothers
New Fulford Family Centre, Gatehouse Avenue
Bristol BS13 9AQ
Email:maria.viner@mothersformothers.co.uk

Head of Bristol Trials Centre Operations
Jodi Taylor
Bristol Trials Centre
Bristol Medical School
University of Bristol
Email: j.taylor@bristol.ac.uk

Trial Manager
Stefan Lewandowski
Bristol Trials Centre
Bristol Medical School
University of Bristol
Email: s.lewandowski@bristol.ac.uk

Project Midwife for Implementation
Siobhán Gillespie
University of Sheffield
The Jessop Wing, Tree Root Walk
Sheffield S10 2SF
Email: sgillespie@rcog.org.uk

Trial Co-Ordinator
Ellen Clark
Bristol Trials Centre
Bristol Medical School
University of Bristol
Email: e.clark@bristol.ac.uk

Implementation Midwife
Jodi Carpenter
Bristol Trials Centre
Bristol Medical School
University of Bristol
Email: vm21470@bristol.ac.uk

Trial Administrator
Naura Choy
Bristol Trials Centre
Bristol Medical School
University of Bristol
Email: kv23669@bristol.ac.uk

A list of research sites and Principal Investigators are detailed in part C of the IRAS application (327559).

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Abbreviations

AE	Adverse Event
AI	Artificial Intelligence
CI	Chief Investigator
CFM	Change in Fetal Movement
CRF	Case Report Form
CRN	NIHR Clinical Research Network
DMC	Data Monitoring Committee
GCP	Good Clinical Practice
ISRCTN	International Standard Randomised Controlled Trials Number
MHRA	Medicines and Healthcare products Regulatory Agency
NIHR	National Institute for Health Research
PET	Preeclampsia
PIH	Pregnancy Induced Hypertension
PPI	Patient and Public Involvement
PPTL	Possible Preterm Labour
PTB	Preterm Birth
QALY	One quality-adjusted life year
RCM	The Royal College of Midwives
RCOG	The Royal College of Obstetricians and Gynaecologists
RCT	Randomised Control Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SGA	Small for Gestational Age
ToB	Timing of Birth Assessment
SOP	Standard Operating Procedure
TSC	Trial Steering Committee
The Clinical Decision Support Tool/ The Tool	Tommy's Pathway: a Clinical Decision Support Tool

1 Synopsis of the Clinical Investigation

Primary aim	To evaluate the effect of the 'real world' implementation of the Tommy's Pathway: a Clinical Decision Support Tool within the NHS.
Terminology used throughout this document	The terms "Original design (RCT)" and "Revised design (feasibility)" are used throughout this document to distinguish between the initial trial design and the amended design following the approved variation to contract.
Trial Design	**Original design (RCT):** Multi-centre, randomised controlled cluster trial with embedded implementation and health economic analysis. **Revised design (feasibility):** Multi-centre, non-randomised feasibility study
Setting	NHS Trusts in England which contain maternity units ('Maternity Trusts').
Target Population	All women and pregnant people booked in to participating NHS Trusts for maternity care.
Inclusion criteria	a) NHS Trust with active maternity unit b) IT system available for outcome data extraction c) Internet access in clinical areas (including community settings
Exclusion criteria	a) Trust unwilling to participate b) Trust using (or planning to use) Fetal Medicine Foundation algorithm as part of their formalised standard care pathway.
Randomisation	**Original design (RCT):** Maternity Trusts will be randomised 1:1 to provide either the Clinical Decision Support Tool ('The Tool') or standard care. Randomisation will be stratified by maternity unit size (number of births per annum) and blocked. **Revised design (feasibility):** Maternity trusts will self-select their allocation to either the Clinical Decision Support Tool ('The Tool') or standard care
Interventions	**Original design (RCT):** Maternity Trusts randomised to receive the Clinical Decision Support Tool will use the Tool to inform care pathway choices for women and pregnant people at those centres. The Clinical Decision Support Tool provides care pathway options based on best practice with evidence assimilated from all current

	national guidance available. It incorporates three algorithms for risk assessment and clinical decision support; one for placental disorders (preeclampsia, stillbirth) and two for the risk of preterm birth (one at the beginning of pregnancy and the other during pregnancy if women present with threatened preterm labour), and two rule engines for change in fetal movements and timing of birth. Maternity Trusts randomised to receive standard care will follow their usual care pathway protocols. **Revised design (feasibility):** Maternity Trusts will select whether to receive the Clinical Decision Support Tool will use the Tool to inform care pathway choices for women and pregnant people at those centres.
Primary outcome	Hypertensive disorders of pregnancy (pre-eclampsia or pregnancy induced hypertension).
Secondary outcomes include	**Original design (RCT):** <u>Work stream 1: The main trial</u> Stillbirth (fetal loss > 24 weeks gestation) Preterm birth (birth at < 34 and < 37 weeks of gestation) <u>Work stream 2: Implementation evaluation</u> Healthcare staff and women & pregnant people's experiences Fidelity/reach/acceptability of the intervention <u>Work stream 3: Health economic evaluation</u> Health effects of the mother and child, together with health service costs accruing to both. **Revised design (feasibility):** <u>Work stream 1: The main trial</u> To assess the feasibility of implementing Tommy's Pathway as a Clinical Decision Support Tool for personalised pregnancy risk assessment across NHS maternity units.
Data collection	**Original design (RCT):** <u>All sites</u>: Baseline data will be collected at 3 months post-randomisation. After this timepoint, data will be collected on all women and pregnant people from the booking appointment until 28 days after the end of their pregnancy. Data will be obtained from routinely collected hospital maternity records. <u>Intervention sites only</u>: Data will be collected on the Clinical Decision

	Support Tool and verified at the first 'booking' or antenatal visit with the midwife at the maternity unit. This will include routinely gathered data as well as information entered directly by women and pregnant users of the tool. The Clinical Decision Support Tool platform and its data are hosted by NHS England (NHSE) in the Cloud Centre for Excellence and serviced by the NHSE Infrastructure Team under agreement with The Royal College of Obstetricians and Gynaecologists (RCOG) as the device manufacturer. **Revised design (feasibility):** Data will be collected until the end of the study, any sites that change the arm of the study they are allocated to will continue to collect data throughout.
Sample Size	**Original design (RCT):** Work stream 1: National data shows that the incidence of hypertensive disorders of pregnancy is 5.8%. To detect an absolute reduction of 2% (relative reduction of approximately one third) in the intervention group, with 90% power, 5% significance, where the intra-cluster correlation is estimated at 0.005, we require each maternity unit to collect data on 2,400 participants, with a minimum of 13 maternity units in each group (31,200 women and pregnant people in the intervention group and 31,200 in the control group). Unavailability of data and women asking to withdraw their data is expected to be less than 1%. England Work stream 2 (intervention sites only): Total 1,950 online surveys: Healthcare Practitioners (HCPs) 50 per site x 13 = 650); Women and pregnant people,100 per site x 13 = 1300. Interviews and focus groups: Interview and focus group participants will be sampled from survey respondents. Interviews – 3 HCPs per site x 13 = 39; 4 women and pregnant people per site x 13 = 52) and 13 HCP focus groups with 6 participants per site = 78. **Revised design (feasibility):** Work Stream 1 As a feasibility study, a formal sample size calculation based on clinical outcome power is not required. A total of 10 NHS maternity sites will be recruited.

Duration of study	**Original design (RCT):** 36 months comprising 6-month set-up, 15-month recruitment (with 8-month internal pilot), 9-month follow-up, and 6-month reporting and closedown (subject to change). **Revised design (feasibility):** The study will continue until 13 months following the first baseline date.
Data analysis	**Original design (RCT): Work Stream 1** Statistical analyses will be performed at patient level. Analyses will be by intention to treat and will follow CONSORT reporting guidelines for cluster randomised controlled trials (RCT) and a pre-specified statistical analysis plan. Outcomes will be compared using multilevel generalised linear modelling, adjusting for maternity unit size and accounting for clustering at maternity unit level. Risk difference and relative risk reduction will be reported, with 95% confidence intervals. Baseline characteristics and outcome data will be presented for the two groups using descriptive statistics. **Work Stream 2** Qualitative data from interviews and focus groups: thematic framework analysis. Quantitative and qualitative from online surveys, local hospital systems and the Clinical Decision Support Tool: Descriptive and comparative statistical methods. Reach and fidelity: Descriptive and comparative statistical methods. **Work Stream 3** The economic evaluation will examine the health effects of the mother and child, together with health service costs accruing to both. The primary analysis will examine the costs to the NHS up to 28 days after the end of pregnancy. Secondary analyses will undertake cost-effectiveness modelling to incorporate external data sources that will generate costs and quality-adjusted life years (QALYs) for the mother and child over their expected lifetime (i.e. including potential maternal mortality associated with pre- eclampsia, and infant mortality associated preterm birth). **Revised design (feasibility):**

	Work Steam 1 No outcomes will be formally analysed. Primary outcome descriptive analyses will include summary statistics and details on data completeness. Data availability by site and outcome completeness will be described for all secondary outcomes. Secondary outcome summary statistics will be presented for secondary outcomes where possible. Summary statistics for continuous data will be described with either means and standard deviations or medians and inter-quartile ranges, depending on the underlying data distribution. Summary statistics for discrete and categorical data will be described as frequencies.

2 Plain English Summary

Background

Every year in the UK, there are 25,000 pregnancies complicated by pre-eclampsia, 3000 stillbirths and 60,000 preterm births. Pre-eclampsia is a complication of pregnancy that can lead to serious long-term health problems for women and pregnant people and their children. Severe pre-eclampsia can be fatal to both mother and baby. Stillbirth is the death of a baby after 24 weeks gestation before or during birth. Preterm birth is when a baby is born before 37 weeks of pregnancy. The number of complications that occur vary from hospital to hospital, which may be due to differences in care provided for women and pregnant people.

There are three reasons why these pregnancy problems remain so common:

- It is hard to identify which women are most likely to develop these complications, meaning that problems may develop unnoticed.
- Risk assessment is often based on previous pregnancy outcomes, meaning that many parents must experience complications before receiving specialist care.
- NHS maternity staff struggle with lack of resources and it is hard for them to ensure they are using the latest national guidelines to provide the best care.

The Tommy's National Centre for Maternity Improvement has developed the Tommy's Pathway: a Clinical Decision Support Tool for use by women and pregnant people, midwives and doctors. The Clinical Decision Support Tool is provided as a web application which means it is accessed via an internet browser just like any other website, using either a desktop computer, laptop, smart phone or tablet (any device with access to the internet).

We aim to investigate whether the tool will reduce pre-eclampsia, stillbirth, and preterm birth by improving how we identify those at risk of these problems and then providing healthcare professionals with current national guidance on the best care to offer women and pregnant people.
The Clinical Decision Support Tool accurately calculates the woman and pregnant person's risk of pregnancy problems at their first pregnancy visit with the aim of then providing "the right care at the right time, by the right healthcare professional". This will mean that some women and pregnant people will avoid having unnecessary assessments and treatments, whilst others will be offered the additional monitoring and intervention they need. Staff time and more hospital beds will be available for women and pregnant people who need them most.

This project includes a trial of The Tool, which is made up of a number of assessments which help to identify potential issues for women and pregnant people. These assessments have been demonstrated to be effective in other studies, but this trial will test the Tool as a whole package, in a number of NHS hospitals across England. We will compare the number of women and pregnant

people with pregnancy problems who have had care from hospitals using the Tool, with those not using the Tool. The results will help the NHS decide if the Tommy's Pathway: a Clinical Decision Support Tool reduces the number of pregnancy problems, and improves outcomes for mother and babies, and also if it saves the NHS money. If it does, its use will be recommended in all hospitals across the UK.

Design and methods

For health professionals to provide the best care for patients, randomised studies are needed to find out if treatments work. A randomised study involves assigning patients by chance to the treatment of interest, or to usual care, so that the effect of the treatment can be compared fairly. In this study, the whole hospital is randomised (original design) or self-selected (revised design) to deliver one intervention whilst another hospital will deliver standard care, to reduce the likelihood of patients being treated with a mixture of both interventions.

This study will aim to involve 62,400 NHS women and pregnant people in maternity units in England. Half of the hospitals will use the Clinical Decision Support Tool to calculate the risk of pregnancy problems and provide associated care pathways, and half will carry on providing the care they offered before. All other aspects of care will be the same as the standard care provided by the hospital. Data will be collected on all women and pregnant people from the initial booking appointment until 28 days after the end of their pregnancy. Data will be collected from routinely collected hospital maternity records for both intervention and control units.

Patient and public involvement (PPI)

A specially gathered group of women, including those with lived experience of preterm birth, stillbirth and neonatal death and those without, have co-designed and developed the Tool from inception. To make sure the views of women are central to the way the study is done, PPI input involving women with lived experience and without will be sought through regular meetings during the set-up, delivery and dissemination of the results. Two patient representatives will sit on the Trial Steering Committee.

Dissemination

Our aim is to help make the UK the safest place in the world to give birth by improving women and pregnant people's access to best care and reducing the variations in care offered around the country. If the Clinical Decision Support Tool is effective it will be rolled out to other hospitals to reduce rates of pre-eclampsia, preterm birth and stillbirth across the UK. It will also be translated into non-English languages. We will make sure that the findings reach all the people who can benefit from them in a suitable format. This includes plain English summaries for the public and customised material for other people such as health professionals and NHS Trust managers. The Tommy's Centre for Maternity Improvement, with the support of the Royal Colleges, the Department of Health and Social Care and

NHS England will lead on developing plans for integrating the Clinical Decision Support Tool into all maternity care services. Details of the study results and publications will also be made available on the ISRCTN registry and the funder's website.

3 Background and rationale

There are 25,000 cases of pre-eclampsia, 3000 stillbirths and 60,000 preterm births per year in the UK [1-4]. There is wide variation between hospitals in rates of stillbirth and preterm birth [5]. This difference persists despite adjustment for population socio-economic and demographic characteristics, demonstrating that poor pregnancy outcomes are principally a consequence of local variations in risk assessment and inconsistency in delivery of maternity healthcare pathways. All recent national reports have identified that staff struggle with a lack of information, support and resources to provide best care [3,6]. In the Each Baby Counts report [6], in almost half (45%) of these affected babies, guidelines and best practice were not followed. Reasons for not following guidelines included gaps in training, lack of recognition of problems, heavy workload, staffing levels and local guidelines not being based on best available evidence.

Available interventions include: aspirin to prevent placental dysfunction and preterm pre-eclampsia; progesterone and cervical cerclage to prevent preterm birth; ultrasound to identify placental dysfunction and offer earlier birth to women and pregnant people with pregnancies at risk of stillbirth. These are all validated and effective clinical interventions [7-10]. Targeted use of these interventions relies on accurate identification of women and pregnant people with at-risk pregnancies which, at present, is undertaken using a checklist of risk factors first adopted into antenatal care 50-years ago [11]. The checklist does not weight risk factors, account for interaction between risk factors, or even include risk reduction for absence of any risks. With this in mind, Tommy's Pathway: a Clinical Decision Support Tool has been developed by the Tommy's National Centre for Maternity Improvement. The Clinical Decision Support Tool processes data already gathered at antenatal appointments as well as information directly entered by women and pregnant people themselves to automatically assess the risk of preterm birth and pregnancy complications that can cause fetal growth restriction and stillbirth.

Head-to-head studies have demonstrated the superior accuracy of artificial intelligence (AI) -based risk prediction models [12]. This advantage comes from the leveraging of 15-years of research involving data from more than 120,000 pregnancies to create regression models that assess the likelihood of placental dysfunction in pregnancy [12, 13]. The Clinical Decision Support Tool incorporates three algorithms for risk assessment and clinical decision support; one for placental disorders (preeclampsia, stillbirth) and two for the risk of preterm birth (one at the beginning of pregnancy and the other during pregnancy if women present with threatened preterm labour).

Estimates of diagnostic performance of the algorithm for placental disorder and pre-eclampsia at a fixed 10% false positive rate was 41% for the current routinely used checklist of risk factors compared to 82% using an AI-based model risk assessment [12]. Aspirin has been the most promising therapeutic option for the prevention of pre- eclampsia. A recent meta-analysis reported that taking daily low dose aspirin reduces the risk of preterm pre-eclampsia by 67%, provided that the daily dose of the drug is ≥100 mg and the gestational age at onset of therapy is <16 weeks [14]. In the randomised controlled ASPRE trial, use of aspirin (150 mg/day), based on risk assessment by the algorithm in the Clinical Decision Support Tool, starting from 11–14 weeks reduced the risk of preterm preeclampsia by 62% and a secondary analysis of the trial reported that the reduction was even greater (75%) if the compliance was ≥90.% [7]. A consequence of the superior diagnostic accuracy was to increase compliance with subsequent recommended interventions (aspirin) from 23% for checklist-based assessment to over 90% for AI-based assessment [7].

The use of a checklist to assess risk of preterm birth unreliably labels 25-30% of women and pregnant people as ‘high-risk’ at booking without being particularly good at identifying those whose pregnancies eventually result in preterm birth or stillbirth. The algorithms in the Clinical Decision Support Tool to assess preterm birth risk by screening at 11–13 weeks by maternal characteristics and obstetric history can identify women and pregnant people at risk of spontaneous preterm birth. This is superior to the current practice of only identifying those at high risk of preterm birth if they have experienced this in a previous pregnancy [15]. For women and pregnant people with threatened preterm labour during pregnancy, the algorithm in the Clinical Decision Support Tool combines risk factors with fetal fibronectin and/or cervical length assessments and calculates a simple percentage risk of spontaneous preterm birth. Validation has been undertaken in a cohort of women and pregnant people with symptoms of threatened preterm labour. Data demonstrated the ability of the algorithm to predict preterm birth with a sensitivity of 90.0%, specificity of 90.8%, positive likelihood ratio of 9.83, negative likelihood ratio of 0.11, Positive Predictive Value (PPV) of 27.3% and Negative Predictive Value (NPV) of 99.6% [16]. This AI technology will lead to better targeting of interventions to reduce preterm birth and associated morbidities whilst providing reassurance and avoiding unnecessary intervention in women and pregnant people at lower risk.

3.1 Potential benefits to women and pregnant people, the NHS and the wider population

Rates of stillbirth and preterm birth have not sustainably decreased in the past 30 years, because of failure to identify all high-risk women and pregnant people during routine prenatal care. Despite Government, commissioner, NHS management and NHS staff best efforts, health inequalities exist in the maternity care delivered across the NHS. A large meta-analysis demonstrated a two-fold increased likelihood of stillbirth in black women [17], and this health disparity is also reflected in other ethnic and socio-economically disadvantaged groups [3, 17]. Historically, ethnic health disparities

were thought to be due to socioeconomic factors and poorer access to healthcare services with possible language barriers [18]. However, these disparities persist even after taking account of socioeconomic factors and other demographic variables [5]. To date, these efforts have failed to address the impact of routine early pregnancy risk assessment, which forms the basis for personalising care pathways with the aim of reducing adverse outcomes. However, the recommended National Institute for Health and Care Excellence (NICE) checklist of risk factors does not take maternal ethnicity into consideration, and is known to have a high screen positive rate and a low detection rate [12]. The placental disorder algorithm in The Clinical Decision Support Tool incorporates maternal ethnicity and produces a numerical risk for the development of placental dysfunction leading to pre-eclampsia and/or small-for-gestational-age (SGA) birth.
A clinical effectiveness study in a single maternity unit, demonstrated that implementation of the AI-based algorithm in the Clinical Decision Support Tool to assess the risk of placental disorders resulted in a two-fold de-escalation of risk, doubling of pre-eclampsia detection, near total physician compliance with aspirin use and an 80% reduction in the prevalence of preterm pre-eclampsia, and a 45% reduction in SGA [19, 20].

This was achieved without increasing healthcare resources, but also with a significant reduction in perinatal deaths for women of black, Asian and minority ethnic background. Following the introduction of placental disorder algorithm in the Clinical Decision Support Tool, the perinatal death rate fell in the non-white group from 7.95 to 3.22/1000 births (OR 0.40, 95% CI 0.21 to 0.79), such that it was no longer significantly different from the perinatal mortality rate in the white group (3.22/1000 vs 2.55/1000 births, OR 1.26, 95% CI 0.64 to 2.48) [21]. In the single maternity unit, an estimated 21 perinatal deaths were avoided in 4349 non-white women during the two year study period. The reduction in perinatal death resulted from a 73% reduction in deaths linked to hypertensive disorders of pregnancy and SGA birth. The likely mechanism of action is through the early and accurate assessment of the risk of placental dysfunction, resulting in women being allocated to the correct care pathway depending on their personalised risk assessment.

The main advantage of the Clinical Decision Support Tool is that it calculates the risk of placental dysfunction and preterm birth in pregnancy and recommends care pathways based on best practice using evidence assimilated from all current national guidance. This will reduce unwarranted variation in pregnancy risk assessment and care by supporting midwives and clinicians and acting as a quality assurance and a Clinical Decision Support Tool. Women and pregnant people receiving maternity care in all settings across the NHS should receive the same accuracy in risk assessment and personalisation of care. The Tool will give women and pregnant people more control over their own health information and informed choice in the care they receive. It will also provide access to quality

information about their care pathway that may support them to raise concerns over their own or their baby's health.

Even when preterm and stillbirth risk assessments are performed appropriately in early pregnancy, the use of paper documentation and current digital maternity records preclude the presentation of the specific pregnancy risks and care information at critical patient interactions in later pregnancy. The lack of continuity of information and subsequent sub-optimal clinical action is a recurrent contributory factor for adverse pregnancy outcomes in National reviews such as Each Baby Counts (https://www.rcog.org.uk/eachbabycounts). The Clinical Decision Support Tool will highlight the pregnancy risk status and care pathway plan to any midwife or doctor at subsequent visits so that appropriately tailored clinical interventions can be planned.

The Clinical Decision Support Tool aligns with the government's ambitions to be a net zero health service by providing a more targeted approach to risk assessments, and therefore a subsequent reduced number of women who need interventions such as use of medication, alongside prevention of maternal and neonatal hospital attendance and admissions with reduced pregnancy complications.

3.2 Potential economic benefits

Pre-eclampsia is associated with increased utilization of healthcare resources, placing a large burden on the system, particularly when the condition necessitates preterm delivery and extended neonatal care. Liu et al. performed a population-based study assessing the utilization of healthcare services by pregnancies complicated by pre-eclampsia and found substantially increased costs associated with pre-eclampsia [21]. These costs included increased use of intrapartum care, maternal transfer, caesarean delivery and neonatal care. Additionally, the short- and long-term economic impact of caring for a preterm infant is substantial. The utilization of healthcare services include hospital and outpatient care, medication and rehabilitation. Prevention of preterm delivery either spontaneous or secondary to pre-eclampsia would therefore have a considerable impact on the healthcare system. For women and pregnant people with threatened preterm labour under 30 weeks' gestation, NICE recommends a 'treat all' strategy. The effect of this strategy was compared to using the threatened preterm birth algorithm in the Clinical Decision Support Tool, and found that 90% of hospital admissions could have been safely avoided if the algorithm and a threshold of 5% risk of birth within the 7 days had been used to guide clinical practice [22], demonstrating the preliminary potential cost effectiveness of the algorithm in the Tool. Using this algorithm for threatened preterm birth in the Clinical Decision Support Tool will lead to improved targeting and timing of interventions for reducing preterm birth and its associated morbidities, while limiting unnecessary interventions and women and pregnant people's anxiety.

For those who have a low-risk pregnancy, a more accurate risk assessment would avoid unnecessary additional visits and follow up investigations that expose women to additional risk and interventions.

Targeting health interventions towards those who will benefit most will tackle health inequalities due to poor access and engagement to care.

Adoption of the Clinical Decision Support Tool across the NHS may reduce the significant healthcare costs associated with preeclampsia, stillbirth and preterm birth, and importantly could de-escalate risk in women and pregnant people, reducing the need for unnecessary visits, scans and investigations, as well as the associated worry/concerns for the family unit. As only 10% of cases will screen as high-risk, this could mean considerable cost savings for the NHS. It is estimated an average maternity unit with 5,000 births per annum would undertake 2,000 fewer ultrasound assessments each year, whilst at the same time, delivering targeted clinical care in line with national guidelines and improving outcomes. Therefore, there could be a net saving to the NHS, as the majority of women and pregnant people would no longer require routine growth scans in later pregnancy.

Adoption of the Clinical Decision Support Tool across the NHS could lead to considerable NHS cost savings and better allocation of limited NHS resources, ensuring that inappropriate assessments and interventions are not routinely performed; freeing up scarce professional time and allowing resources to be reinvested into maternity care. Implementation of the Tool into clinical workflows has the potential to improve NHS productivity with digital technology and thereby reduce the burden on clinicians and other NHS staff, so they can focus on women and pregnant people's care in line with NHS priorities outlined by NHS England. It aligns with the NHS England clinical safety strategy to identify and promote the use of digital technologies as solutions to patient safety challenges. The NHS and all bodies who receive government funding have a responsibility to allocate resources in the most efficient way possible for the benefit of all – and technology such as the Clinical Decision Support Tool will support the NHS in achieving this goal.

3.3 How the Clinical Decision Support Tool will work in practice

The Clinical Decision Support Tool does not replace clinical decision-making; rather it is a tool to support clinical decision-making. It increases opportunity for effective early preventative intervention, additional monitoring through pregnancy, and appropriate response to warning signs and symptoms during pregnancy based on risk. Before meeting their midwife for the first time, women and pregnant people enter relevant health information into the Tool. At the first antenatal visit, their midwife will verify the accuracy of the data and run the risk assessment which will calculate the risk of preterm birth. Following initial blood tests and ultrasound scans, risk assessment for placental function will be carried out. To minimise digital exclusion, the midwife can enter all required information if the woman or pregnant person is unable or declines to do so. The Clinical Decision Support Tool provides care pathway advice, tailored to individual pregnancy risks, both to the midwife and woman/pregnant person and provides continuity of information throughout their pregnancy. The Tool is also utilised later in pregnancy, providing further risk assessment and evidence-based care pathway

recommendations, if the woman or pregnant person experiences changes in fetal movements and/or symptoms of possible preterm labour. Women and pregnant people can also access current validated information, such as what to do if they notice changes in fetal movements, through the “Information Hub” links within the Tool.

Please refer to the Investigators’ Brochure and Instructions for use documentation for detailed information regarding the identification and description of the investigational device.

3.4 Rationale

There are 25,000 cases of pre-eclampsia, 3,000 stillbirths and 60,000 preterm births per year in the UK [1]. There is currently wide variation between hospitals in rates of placental disorders, stillbirth, and preterm birth [5]. The Clinical Decision Support Tool uses clinically-validated AI-based algorithms to provide a more accurate and personalised pregnancy risk assessment for women and pregnant people during pregnancy allowing them to be allocated the correct targeted treatments, with the overarching aim of reducing pre-eclampsia, preterm birth and stillbirth, and reducing health inequalities. This cluster RCT will evaluate the effect of the ‘real world’ implementation of the Clinical Decision Support Tool within the NHS.

3.5 Background and rationale for feasibility study

The PARTNER study was originally designed as a multi-centre cluster randomised controlled trial (RCT) to evaluate the clinical and cost-effectiveness of the Clinical Decision Support Tool across NHS maternity units in England. This design formed the basis of the initial protocol, approvals, and funding award.

The original aim of the PARTNER trial was to assess the clinical and cost-effectiveness of Tommy's Pathway as a Clinical Decision Support Tool across maternity units in England. Following a variation to contract approved with the funder, the primary objectives of the study have been revised, with the focus now centred on the collection of feasibility and implementation data relating to delivery of the intervention at scale across NHS maternity services.

To maximise the scientific value and learning generated within the constraints of the revised study aims, the design has been modified to enable all participating maternity units to implement the intervention. This approach substantially enhances the volume and diversity of impl
ementation data, supports assessment of feasibility across a wider range of organisational contexts, and strengthens conclusions regarding adoption and real-world use of the tool.

4 Aims and Objectives

The aim is to evaluate the effect of the 'real world' implementation of the Clinical Decision Support Tool within the NHS. The following research objectives will facilitate achievement of this aim.

4.1 Primary objective

To assess the effectiveness of the Clinical Decision Support Tool on reducing incidence of hypertensive disorders compared with standard care (Work stream (WS) 1).

4.2 Secondary objectives

Original design (RCT)

1. To assess the effectiveness of the Clinical Decision Support Tool on improving maternal and infant clinical outcomes compared with standard care (Work stream (WS1).
2.Determine whether the Clinical Decision Support Tool is acceptable to women, pregnant people and health care practitioners (HCP), and that it can be successfully adopted into routine clinical practice without excluding vulnerable or underserved groups. (WS2).
3. Evaluating health economic data on the cost-effectiveness of implementing the Clinical Decision Support Tool into NHS maternity units compared to standard care (WS3)

Revised design (feasibility)

1. To assess the feasibility of implementing Tommy's Pathway as a Clinical Decision Support Tool for personalised pregnancy risk assessment across NHS maternity units.

4.3 Primary and secondary outcomes

The primary and secondary clinical outcomes are based on the core outcome set in for studies in preeclampsia [23].

4.3.1 Primary outcome (RCT- WS1)

The primary outcome is incidence of hypertensive disorders of pregnancy (pre-eclampsia (PET) or pregnancy induced hypertension (PIH), defined by NICE guidance and measured at birth) [24].
PET is defined as new onset of hypertension (over 140 mmHg systolic or over 90 mmHg diastolic) after 20 weeks of pregnancy *and* the coexistence of 1 or more of the following new-onset conditions: proteinuria, maternal organ dysfunction – renal, haematological, uteroplacental dysfunction, neurological.
PIH is defined as new onset of hypertension (over 140 mmHg systolic or over 90 mmHg diastolic) after 20 weeks of pregnancy with no additional features.

Revised design (feasibility)

Table 1. Primary outcome and measures

Primary outcome	Collection Method	Time point measured
Incidence of hypertensive disorders of pregnancy (pre-eclampsia or pregnancy induced hypertension).	• The Tool (intervention sites) • Extracts from local hospital systems (intervention and control sites).	Birth or up to 2 weeks post-birth.

4.3.2 Secondary outcomes (WS1, 2 & 3)

Secondary outcomes for the three workstreams are detailed in the table below.

Table 2. Secondary outcomes and measures

Secondary outcomes	Collection method	Time point measured (if relevant)
Secondary objective 1 (WS1) – Original (RCT) and Revised (feasibility) designs		
Infant (per birth)		
Birth weight and birth centile, birthweight >4000g, LGA- birth centile >90th, and small for gestational age – SGA (birth centile <10th).	• The Tool (intervention sites) • Extracts from local hospital systems (intervention and control sites).	Birth
Miscarriage (up to 23+6 weeks gestation) and stillbirth[1] (death of baby after 24 weeks gestation before or during birth).	• The Tool (intervention sites) • Extracts from local hospital systems (intervention and control sites).	Booking appointment until birth
Neonatal death* (death ≤28 days of life)	• Extracts from local hospital systems (intervention and control sites).	Birth to 28 days of life
Preterm birth (< 34 and <37 weeks gestation of pregnancy)	• The Tool (intervention sites) • Extracts from local hospital systems (intervention and control sites).	Birth
Gestational age (weeks)	• The Tool (intervention sites) • Extracts from local hospital systems (intervention and control sites).	Birth
Neonatal complications: NICU	• Extracts from local hospital	Birth

[1] *Number of stillbirths and neonatal deaths will be crossed checked with aggregate hospital level data from the Perinatal Mortality Review Tool (PMRT). We will request aggregated data from the PMRT from sites to cross check the number of perinatal deaths recorded in the Tool/local hospital systems.*

admission; umbilical cord blood pH; Apgar score; birth injury clavicle/humeral/skull fractures; shoulder dystocia; hypoglycaemia requiring NICU treatment; respiratory distress; fetal hyperbilirubin anaemia.	systems (intervention and control sites).	
Maternal (per pregnancy)		
Antepartum haemorrhage	• Extracts from local hospital systems (intervention and control sites).	Booking appointment until birth
Gestational Diabetes	• The Tool (intervention sites) • Extracts from local hospital systems (intervention and control sites).	Booking appointment until birth
Mode of delivery (LSCS – emergency/elective/ID – forceps/ventouse/SVD)	• The Tool (intervention sites) • Extracts from local hospital systems (intervention and control sites).	Birth
Obstetric anal sphincter injury (OASIS)	• Extracts from local hospital systems (intervention and control sites).	Birth
Spontaneous labour	• The Tool (intervention sites) • Extracts from local hospital systems (intervention and control sites).	Birth
Induction of labour (gestation in weeks and days and reason including following ToB recommendation)	• Aggregate data for 12 months prior to baseline will be collected from all participating hospitals on a CRF. • The Tool (intervention sites) • Extracts from local hospital systems (intervention and control sites).	Birth
Elective and Emergency Caesarean section (and reason including following ToB recommendation)	• Aggregate data for 12 months prior to baseline will be collected from all participating hospitals on a CRF. • The Tool (intervention sites) • Extracts from local hospital systems (intervention and control sites).	Birth
Maternal death	• Extracts from local hospital systems (intervention and control sites).	Booking appointment until 28 days after birth
Eclampsia	• Extracts from local hospital systems (intervention and control sites).	Booking appointment until 28 days after birth
Stroke	• Extracts from local hospital systems (intervention and control sites).	Booking appointment until 28 days after birth

Pulmonary oedema	• Extracts from local hospital systems (intervention and control sites).	Booking appointment until 28 days after birth
Acute Kidney Injury - defined by AKIN [25]	• Extracts from local hospital systems (intervention and control sites).	Booking appointment until 28 days after birth
Liver haematoma/rupture	• Extracts from local hospital systems (intervention and control sites).	Booking appointment until 28 days after birth
Postpartum haemorrhage	• Extracts from local hospital systems (intervention and control sites).	Birth until 28 days after birth
Admission to ITU, intubation and ventilation	• Extracts from local hospital systems (intervention and control sites).	Booking appointment until 28 days after birth
Antenatal maternal hospital stay (days)	• Extracts from local hospital systems (intervention and control sites).	Booking appointment until delivery
Postnatal maternal hospital stay (days)	• Extracts from local hospital systems (intervention and control sites).	Birth until 28 days after birth
Admissions for possible preterm labour (Admission as inpatient. Does not include those observed on labour ward/ triage/ day care etc for a short period)	• Extracts from local hospital systems (intervention and control sites).	Booking appointment until birth
Preterm birth clinic appointments	• Aggregate data for 12 months prior to baseline will be collected from all participating hospitals on a CRF. • Extracts from local hospital systems (intervention and control sites).	Booking appointment until birth
Growth scans	• Aggregate data for 12 months prior to baseline will be collected from all participating hospitals on a CRF. • Extracts from local hospital systems (intervention and control sites).	Booking appointment until birth
Secondary objective 2 (WS2)	**Original design (RCT) only**	
Fidelity and reach		
Has the implementation been carried out as intended (fidelity)?: Number/proportion of staff trained (training records at each unit). Number/proportion of women registering on the Tool. Is the intervention working as intended (fidelity)? Proportion of women with a documented risk assessment, quality of care – scheduled assessments: preterm birth	• Extracts from the Tool and local hospital systems (intervention sites only) • Records on trial management training system.	N/A

and placental function risk assessments, aspirin prescribed, additional scans booked, referral to specialist preterm birth service, timing of birth appointment; unscheduled visits: possible preterm labour symptoms, PPTL assessment and management, changes in fetal movements.		
Are any groups disproportionately excluded? Demographic data compared to data on population served by each Trust. The proportion of eligible women risk stratified according to the Clinical Decision Tool in early pregnancy (risk of placental dysfunction and/or preterm birth) measured by tool data compared to data on population served by each Trust.	• Extracts from the Tool and local hospital systems (intervention sites)	N/A
Clinical practice (pre-trial and during trial recruitment phase) at intervention and control sites Clinical practice during the trial at intervention and control sites (e.g. number of growth scans, aspirin prescribed, number of specialist preterm clinic visits, rates of induction of labour, caesarean sections (planned and unplanned)).	• Aggregate data for 12 months prior to baseline will be collected from all participating hospitals on a CRF. This will include number of growth scans, preterm birth clinic appointments, inductions, planned and unplanned caesarean sections. • Investigation of trust guidelines. • Extracts from the Tool and local hospital systems (intervention and control sites).	N/A
Acceptability		
Acceptability, effect on informed decision-making, perceptions of safety anxiety, and confidence to voice concerns.	• Interviews, Focus groups and online surveys with users of the Tool.	N/A
Organisational/contextual factors: Barriers and facilitators to successful implementation.	• Interviews, Focus groups and online surveys with users of the Tool.	N/A
Secondary objective 3 (WS3)[2]	**Original design (RCT) only**	
Antenatal visits: Date of antenatal visits, type of visit (e.g.	• Extracts from local hospital systems (intervention and control	Booking appointment until birth

[2] In components of care that will be included will be clinic visits (by type), admissions (by type and reason), delivery (by type) and medications. For the purposes of the modelling lifetime costs and quality adjusted life years, gestation at birth and birthweight will be collected. Pre-existing studies will be used to link these to costs, quality of life and life expectancy.

consultant led, non-consultant led, type of scans and/or procedures/investigations given at visit)	sites).	
Antenatal admissions: Date of antenatal admissions and associated discharge date, type of admission (elective or non-elective), reason and any diagnoses. Type of scans and/or procedures/investigations given during admission.	• Extracts from local hospital systems (intervention and control sites).	Booking appointment until birth
Delivery and birth: Date of admission for delivery and associated discharge date, type of admission (elective or non-elective), type of delivery, use of epidural, use of induction, any post-partum surgical procedures. Gestation at birth in weeks and days Birth weight and birth centile	• The Tool (intervention sites) • Extracts from local hospital systems (intervention and control sites).	Birth
Treatments Medications prescribed	• Extracts from local hospital systems (intervention and control sites).	Booking appointment until 28 days after birth
Maternal deaths Miscarriages, still births and neonatal deaths	• Extracts from local hospital systems (intervention and control sites).	Booking appointment until 28 days after birth
Time and costs required for training, use of the Tool and implementation into clinical practice.	• Consultations with Tool developers • Discussion with PARTNER Trial Research Midwives who deliver training to sites.	N/A
Date of admission and discharge from neonatal care and type of care on admission (classified as intensive care, high dependency care, special care without external carer, special care with external carer or normal care)	• Extracts from local hospital systems (intervention and control sites).	Until 28 days after birth

5 Trial Design

Original design (RCT)

The study design is a pragmatic, parallel group, cluster RCT (WS1) with an embedded implementation evaluation (WS2) and health economic analysis (WS3. Participating NHS Maternity Trusts in England will be randomised to either utilise the Clinical Decision Support Tool to inform care pathway choices for women and pregnant people or to provide standard care following their usual care pathway protocols. A cluster trial design has been chosen to reduce the risk of contamination between groups. The Trial is split into three work streams, these are detailed below:

WS 1 – The Main Trial: A multicentre cluster RCT to assess the effectiveness of the Clinical Decision Support Tool on improving pregnancy outcomes compared with standard care. For details relating to previous clinical testing and evaluation of the Tool please refer to the Investigators' Brochure.

WS 2 - Implementation evaluation: A mixed methods implementation evaluation to assess fidelity, reach, and acceptability of the Clinical Decision Support Tool to staff and women, pregnant people and organisational impact. Data will be collected using online surveys, focus groups and interviews, data collected through the Clinical Decision Support Tool and routine clinical data.

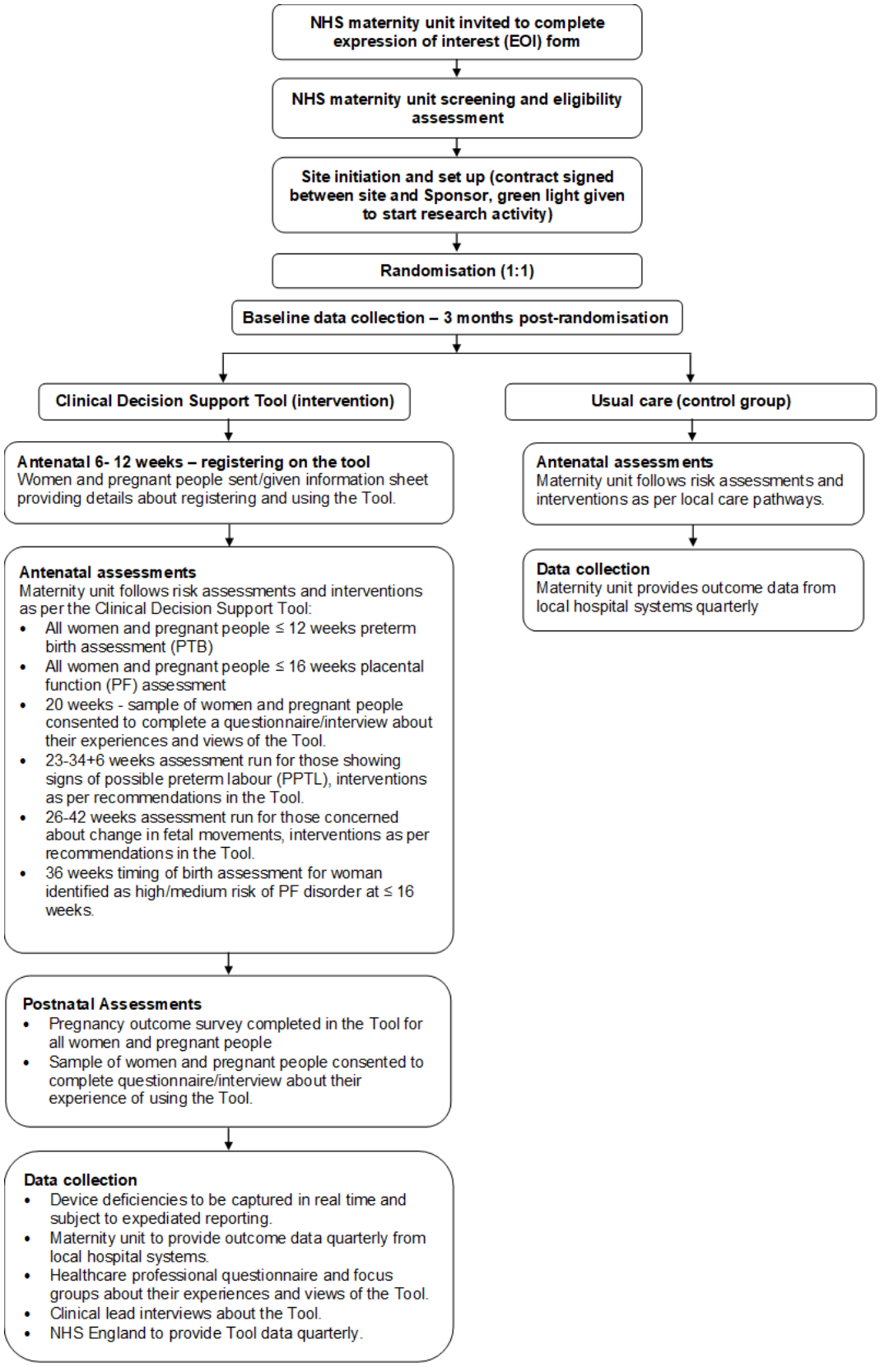
WS 3 – The Economic Evaluation: The primary health economic analysis will examine the costs to the NHS up to 28 days after the end of pregnancy. Secondary analyses will undertake cost-effectiveness modelling to incorporate external data sources that will generate costs and quality-adjusted life years (QALYs) for the mother and child over their expected lifetimes.

Revised design (feasibility):

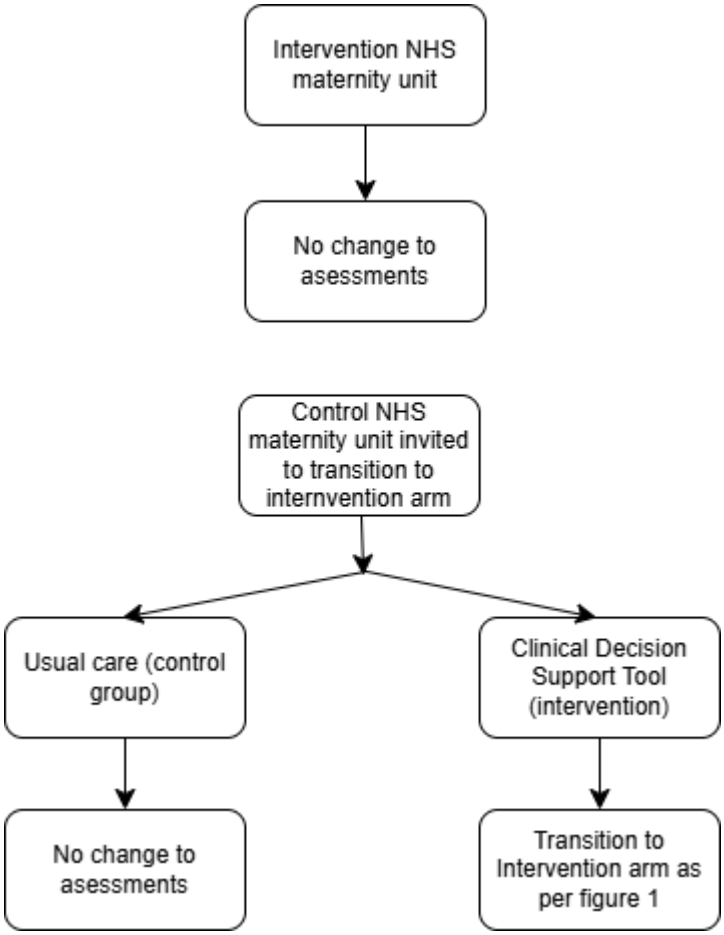
The study design is a pragmatic, multicentre feasibility study evaluating the real-world implementation of Tommy's Pathway: a Clinical Decision Support Tool across NHS maternity units in England. Participating maternity units will self-select whether to implement the Clinical Decision Support Tool as part of their standard maternity care pathway.

5.1 Figure 1: Trial schema

Original design (RCT)



Revised design (feasibility)



5.2 Project timeline

The study duration is expected to be 36 months comprising 6-month set-up, 15-month recruitment (with 8 months internal pilot), 10-month follow-up, and 5-month reporting and closedown (subject to change).

5.3 Internal Pilot

Original design (RCT) Only:

An internal pilot will be conducted. All participants in the internal pilot will continue with follow-up and be retained in the full analysis. The relevant progress report to the National Institute for Health Research (NIHR) will report on the progression criteria based on data up to 9 months of recruitment (month 18). We anticipate that the NIHR decision to progress to the main trial will be made by 10 months of recruitment to the trial.

5.4 Progression criteria

Original design (RCT) Only:

The success of the project relies on implementation of the Clinical Decision Support Tool into NHS sites and for staff and women seen at the sites to use the Tool. It also relies on the study team to be able to obtain the data from the Tool and from hospital records. The Funder have decided the following 'Go/No Go' criteria to be assessed after 8 months of recruitment (based on 26 sites).

Table 3: Progression criteria

Criteria	Red	Amber	Green
Sites open to recruitment	<3 (12%)	3-7 (12-27%)	≥8 (31%)
Women registered on the tool out of those expected (intervention group)	<75%	75 – 95%	>95 %
Health professional verified the woman's record and run the PTB assessment (intervention group)	<75%	75 – 95%	>95 %

5.5 Transition to non-randomised trial

Revised design (feasibility): From CIP v5.0 and the associated amendment, PARTNER operates as a pragmatic, parallel-group, non-randomised cluster-controlled study. NHS Maternity Trusts will select their own allocation to either the intervention or standard care arm, rather than being assigned by centralised randomisation. The cluster design is retained in full: the unit of allocation remains the NHS Maternity Trust, and the intervention and control conditions are unchanged from those described. Existing sites will make a formal, documented allocation choice at the point this CIP version and associated amendment is implemented at site level; new sites will select their allocation following greenlight activation, in place of the randomisation step.

Sites that transition between arms will continue data collection throughout the transition period without interruption. The BTC will record the transition point for each site, defined as the date on which Tool use formally commences or ceases in clinical practice. Data collected prior to a site's transition point will be attributed to the arm in which the site was operating at that time; data from the transition point onwards will be attributed to the new arm.

6 Methods, procedures and key design features to minimise bias

Original design (RCT) only:

Selection bias/allocation bias *(systematic differences between baseline characteristics of the groups that are compared)*.

The unit of randomisation is the hospital. It is expected that only a small number of women and pregnant people will decline to be risk assessed by the Tool/ask that their data is not shared with researchers. Therefore, we will have almost complete identification and inclusion of all women and pregnant people at participating hospitals. The two groups should therefore be similar at baseline except for chance imbalances.

Original design (RCT) and revised design (feasibility):

Performance bias *(systematic differences between groups in the care that is provided, or in exposure to factors other than the interventions of interest)*.

This bias will be minimised by defining procedures/protocols for participants and staff in the Clinical Decision Support Tool arm to follow and monitoring adherence with these protocols (see Section 11). Hospitals in the control arm will follow their usual care pathway protocols.

Detection bias *(systematic differences between groups in how outcomes are determined)*.

This bias will be minimised by having an objective and clearly defined primary outcome measure (see Section 4.3.1).

Attrition bias *(systematic differences in the availability of outcome data between groups)*.

This bias will be minimised by:

Providing ongoing training and support to sites to ensure all required outcome data extracts are received. Clinical Research Network (CRN) research midwives will be asked to visit postnatal wards to check primary outcome data is recorded in local hospital systems.

Reporting bias (systematic errors in the selection of the reported results)

This will be minimised by having pre-specified outcomes (see Section 4.3) and pre-specified Statistical, Qualitative and Health Economics Analysis Plans.

7 Trial Setting

Up to 30 English NHS Maternity Trusts which contain maternity units will be recruited to the study. We aim to collect data from 62,400 women and pregnant people across the participating Maternity trusts (original design (RCT)). The Maternity Trusts will be selected to provide a representative sample of maternity units across England according to geographical location, socioeconomic and ethnicity profile of the catchment area, hospital size, and number of births per year (original design (RCT) and revised design (feasibility)).

8 Eligibility criteria

8.1 Participant population

All women and pregnant people booked for maternity care in participating NHS Maternity Trusts.

8.2 NHS Maternity Trusts

8.2.1 Inclusion criteria for NHS Maternity Trusts

a) NHS Trust in England with active maternity unit
b) IT system available for outcome data extraction (e.g. BadgerNET or equivalent)
c) Internet access in clinical areas (including community settings)

8.2.2 Exclusion criteria for NHS Maternity Trusts

a) Trust using (or planning to use) Fetal Medicine Foundation algorithm as part of their formalised standard care pathway.
b) Trust taking part in another study that conflicts with the PARTNER study (will be assessed on a case-by-case basis)

Eligibility criteria for transitioning sites

Revised design (feasibility): There are no eligibility criteria to transition from one arm to the other during the non-randomised portion of the study, provided they are still enrolled in the study at the point of transition. All new sites must meet the above eligibility criteria.

8.3 Women and pregnant people

Pregnancy outcomes will be collected for all women and pregnant people at both intervention and control sites (except those who have opted out of research). In addition, women and pregnant people at intervention sites are offered access to the Tool (and its Information Hub). The risk assessment algorithms do not relate to all women and pregnant people in the same way. For example, those with multiple pregnancies are excluded from all assessments while those with pre-existing diabetes or pre-

existing hypertension are only offered the preterm birth assessments. For these women and pregnant people, care will be determined by specialist services within their Trust.

9 Trial intervention

9.1 The Clinical Decision Support Tool

The Clinical Decision Support Tool uses AI technology to process the data routinely gathered during antenatal appointments to assess each woman's individual chance of preterm birth and of developing complications of placental dysfunction during pregnancy. Placental dysfunction can lead to pre-eclampsia, fetal growth restriction and stillbirth. The Tool enables early identification and targeted intervention to ensure that each woman and pregnant person is offered the right care at the right time according to their individual needs and most importantly, to prevent these indications developing unnoticed and leading to potentially avoidable preterm birth and stillbirth.

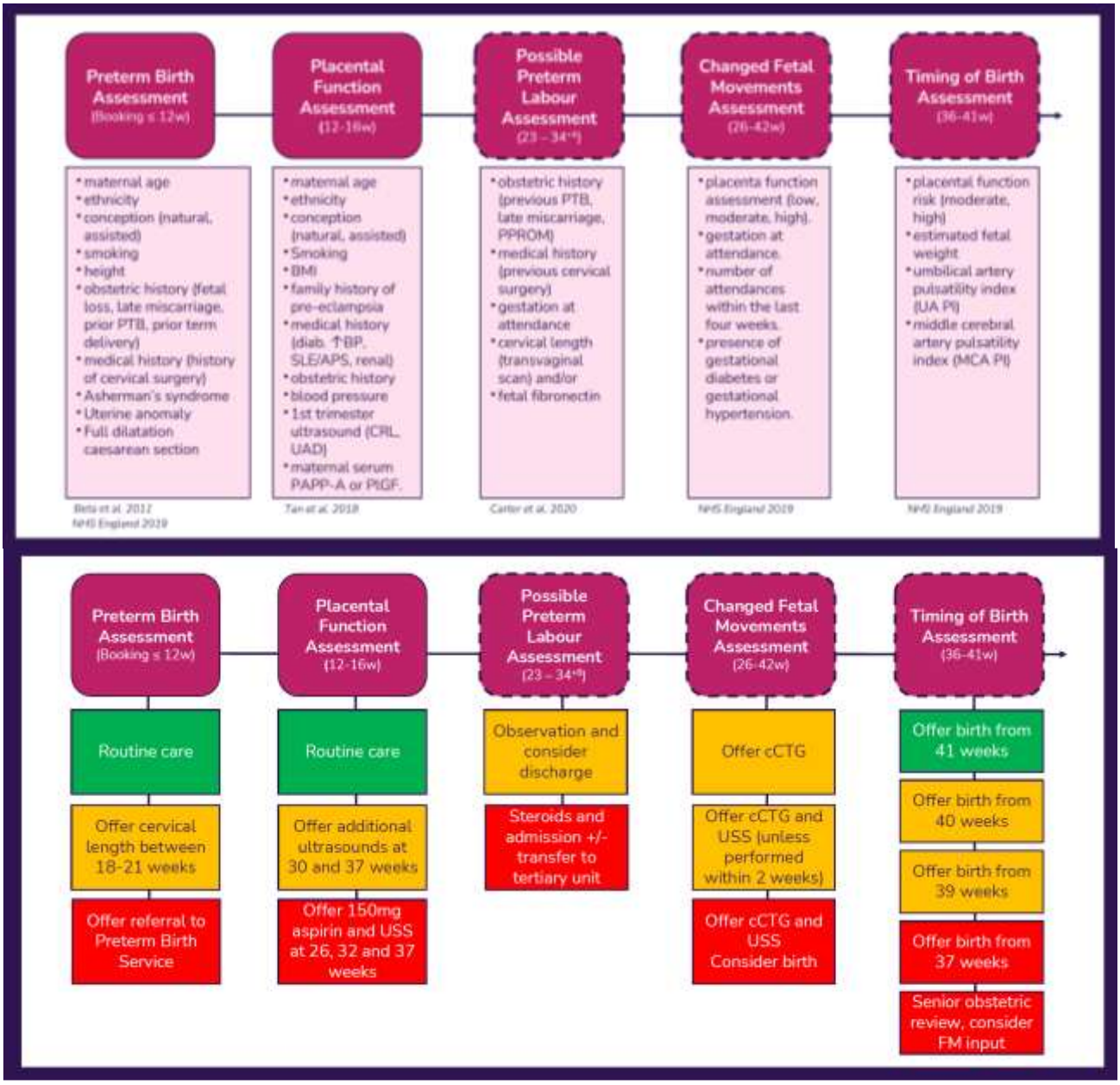
There are five key touchpoint assessments on the Tool which are completed by Healthcare Practitioners, two of which are offered to most women and pregnant people at (see figure 2 and Appendices A-E):

1. The early pregnancy booking appointment/first antenatal visit (≤ 12 weeks), at which a risk assessment is run for preterm birth (PTB).
2. Between 12 and 16 weeks of pregnancy, when the Placental Function Assessment (PF) is run, which looks at the risk of growth restriction and pre-eclampsia in conjunction with first trimester scan details, blood pressure (BP) and Pregnancy Associated Plasma Protein-A (PAPP-A) blood test result.

If the risk assessment results are low risk and the pregnancy is uncomplicated the Tool is not used again in that pregnancy. However, should a woman or pregnant person present with signs of possible preterm labour or changes in the baby's movements the healthcare professional will access their record on the Tool, note the key data already entered and results of previous assessments, and then run the possible preterm labour (PPTL) and/or changes in fetal movement (CFM) assessments.

Those who have been previously assessed as being at moderate or high risk of placental dysfunction will also be offered a timing of birth assessment, which follows the Saving Babies' Lives Care Bundle (SBLCB) guidance.

Figure 2: Clinical Decision Support Tool touchpoints



9.2 Access to the Tool

Maternity unit staff in units allocated to the intervention group will only be given access to the tool once all training has been completed and the BTC (and Sponsor) have agreed that the Tool can start being used at the site.

9.3 Use of the Tool in the main trial

Users of the tool will include local maternity unit staff (HCPs) and women and pregnant people at participating intervention sites. Women and pregnant people registered on the tool (or staff on their behalf) will be guided through the necessary forms to complete in addition to the assessments detailed in section 9.1. All assessments and related data collection in relation to the tool are detailed in table 4 below.

Table 4: Clinical Decision Support Tool assessments and related data collection

	Pre-booking appointment	**Booking appointment/ first midwife appointment**	**≤12 weeks**	**≤16 weeks**	**20 weeks**	**23-34+6 weeks**	**26-42 weeks**	**36 weeks**	**Postnatal**	**Throughout trial recruitment and follow up period**
Register with the Tool	✓	✓ (if not already completed)								
Demographics & medical history	✓	✓(if not already completed)								
PTB assessment			✓							
PF assessment				✓						
Sample of women & pregnant people – Online survey (see Section 12.3)					(✓)				(✓)	

	Pre-booking appointment	Booking appointment/ first midwife appointment	≤12 weeks	≤16 weeks	20 weeks	23-34+6 weeks	26-42 weeks	36 weeks	Postnatal	Throughout trial recruitment and follow up period
Sample of women & pregnant people – Interview (see Section 12.3)					(✓)				(✓)	
CFM assessment *(for women & pregnant people concerned about fetal movements)*							(✓)			
PPTL assessment *(for women & pregnant people showing signs of possible preterm labour)*						(✓)				
ToB assessment (for women &| pregnant people identified as high/medium risk of PF disorder)								(✓)		

	Pre-booking appointment	Booking appointment/ first midwife appointment	≤12 weeks	≤16 weeks	20 weeks	23-34+6 weeks	26-42 weeks	36 weeks	Postnatal	Throughout trial recruitment and follow up period
Pregnancy outcome survey									✓	
Adverse events – device deficiencies– see safety reporting see section 13	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Questionnaire and focus groups with sample of HCPs (see Section 12.3)										(✓)

10 Control

All maternity units allocated to the control group (original design (RCT) or self-selected to the control group (revised design (feasibility)) will be advised to follow antenatal risk assessments and interventions as per local care pathways. Data collected for control sites is detailed in section 11.9.

11 Trial Procedures

Original design (RCT):

Up to 30 maternity units will be recruited and randomised over a 15 month planned recruitment period. This section outlines the key trial procedures from identification of potential NHS Maternity Trusts and women and pregnant people, through to the end of the trial. An overview of the trial is shown in the Trial Schema (Figure 1).

Revised design (feasibility):

Up to 10 maternity units will be recruited over a 15 month planned recruitment period. This section outlines the key trial procedures from identification of potential NHS Maternity Trusts and women and pregnant people, through to the end of the trial. An overview of the trial is shown in the Trial Schema (Figure 1).

11.1 Identification of maternity units

All clinical directors in obstetrics and gynaecology departments and heads/directors of midwifery in English NHS trusts will be contacted about the study via email.

11.2 Maternity unit screening and recruitment

Interested maternity units will be asked to complete a site Expression of Interest (EOI) form, containing information required for the study team to carry out an eligibility assessment. Eligibility will be determined using the EOI form. Eligibility will be checked against the criterion in section 8.2. Any maternity units found to be ineligible will be informed of why they are not eligible to take part in the study. For those that are deemed eligible, the potential Principal Investigator (PI) will be invited to an initial meeting with the study team to discuss the study, answer any questions and check if the maternity unit is willing to take part. If they are willing to take part, then next steps will be discussed (see 11.3).

Informed consent for maternity unit participation will be formalised through contracts.

Please refer to the model agreement for non-commercial research for the PARTNER trial for information for details on responsibilities and financing for sites.

11.3 Maternity unit set up and initiation

Before research activity commences, sites will receive general training sessions delivered by the BTC and PARTNER Research Midwives. These sessions will ensure that personnel involved fully understand the clinical investigation plan, CRFs and the practical procedures for the study. Maternity units will have office hours access to team expertise, including study employed midwives. Completion of training modules will be prompted and monitored using an automated online system or similar equivalent.

Once the maternity unit research team have received the general site training and completed the set-up documents, the greenlight will be given to commence research activity.

11.4 Randomisation and allocation specific training

Original design (RCT):

Following green light activation, Maternity Trusts will be randomised 1:1 to either the Clinical Decision Support Tool or standard care (see section 9 and 10). randomisation will be stratified by maternity unit size (number of births per annum) and blocked. The randomisation list will be drawn up by a statistician at the Bristol Trials Centre (BTC). Where there is more than one maternity unit in a single NHS Trust, the decision to randomise these units together or separately will be made on a case-by-case basis. Factors influencing this decision include the extent to which women and pregnant people, and staff move between the units, as well as whether they adhere to the same policies. It will also be considered whether two maternity units within one hospital adhering to separate care pathways would signify a safety concern for women and pregnant people.

Following randomisation, Maternity Trusts will be informed of their allocation and complete allocation specific training. PARTNER Research Midwives will help sites to set up the study in accordance with local pathways. Intervention sites will commence training and implementation of the Clinical Decision Support Tool into standard practice. The implementation process will be tailored to each intervention site. Implementation will include being provided with a Clinical Decision Support Tool training toolkit. Local staff will be granted access to create personal accounts on the Tool. Data collection will begin following the baseline time point (see section 11.7)

Revised design (feasibility):

Following green light activation, Maternity Trusts will select their own allocation to either the Clinical Decision Support Tool or standard care (see sections 9 and 10). For sites already participating in the study at the point this amendment takes effect, allocation will be confirmed at the point of accepting the updated Clinical Investigation Plan. For new sites joining the study following this amendment,

allocation will be confirmed following greenlight activation, after which sites will undergo a three-month lead-in period before commencing research activity.

Where there is more than one maternity unit in a single NHS Trust, the decision as to whether these units should share an allocation or select independently will be made on a case-by-case basis. Factors informing this decision include the extent to which women and pregnant people, and staff move between the units, and whether they adhere to the same policies. It will also be considered whether two maternity units within one Trust operating under separate care pathways would signify a safety concern for women and pregnant people.

Following confirmation of allocation, Maternity Trusts will complete allocation-specific training. PARTNER Research Midwives will help sites to set up the study in accordance with local pathways. Sites selecting the Clinical Decision Support Tool will commence training and implementation of the tool into standard practice. The implementation process will be tailored to each site and will include provision of a Clinical Decision Support Tool training toolkit. Local staff will be granted access to create personal accounts on the tool. Data collection will begin following the baseline time point (see section 11.7).

11.5 Blinding

Blinding of patients and hospital staff is not possible as both will be either accessing the Clinical Decision Support Tool or following normal care pathways at their Trust. Blinding of trial statisticians/trial management staff is also not possible as they will be receiving/linking identifiable data from the Tool with outcome data provided by sites.

11.6 Recruitment of women and pregnant people

Due to the cluster design of the trial, allocation (original design (RCT)) or self-selection (revised design (feasibility)) will take place at the level of the maternity unit. Maternity units will follow their allocation (intervention and standard care) as standard practice to inform care pathway choices of the women and pregnant people within the unit. Therefore women and pregnant people attending the maternity units will not be approached for consent to take part in the study. Following the baseline timepoint, all women and pregnant people attending participating maternity units will be automatically enrolled ('recruited') to the trial (unless they opt out of their data being used in the trial), which means we will collect data from the Tool and local hospital systems throughout their pregnancy up until 28 days after birth (see sections 9 and 10). We will seek section 251 approval from the Health Research Authority Confidentiality Advisory Group (CAG) to obtain data from the Tool and electronically from hospital maternity records for women in both groups.

Trial specific posters will be displayed in appropriate places within all participating maternity units to explain that the unit is taking part in the trial, that we will be looking at data from the Clinical Decision Support Tool (if applicable), and pregnancy care and outcome information from local hospital systems. It will also include contact details to discuss the study with a member of the research team and the option to submit a request for their data not to be used in the study.

In the intervention group only, women and pregnant people will be sent/given an information sheet about the Tool prior to or at their first routine midwife 'booking' appointment inviting them to log on and familiarize themselves with the Tool.

11.7 Baseline: 3 months post-randomisation

Three months following randomisation baseline data will be collected. Maternity units will complete a CRF to collect aggregate data for 12 months prior to the baseline time point (see data outcome table 2).

11.8 Data collection (all sites)

Original design (RCT):

Data collection for all sites will begin at 3 months post-randomisation (baseline). Data collection will begin for all women and pregnant people newly booked into the maternity unit. Data will be collected from the booking appointment until 28 days after the end of their pregnancy.
Data will include whether the pregnancy is singleton or multiple, medical history (pre-existing diabetes and hypertension, parity, disability and mental health status), demographics (age, IMD decile, country of birth, ethnicity, primary language, level of education), and outcomes (see section 4.3). Data will be obtained retrospectively from routinely collected hospital maternity records on an approximately quarterly basis.

Revised design (feasibility):

Data collection will continue until the end of the study. Any site that changes the arm of the study they are allocated to, will continue to collect data throughout the entire period. The date of the change of allocation will be recorded.

11.9 Data collection (intervention sites only)

See section 9 for a detailed list of touchpoints relating to the Clinical Decision Support tool and section 4.3 for data items relating to the Tool. The Clinical Decision Support Tool will collect data that is

routinely gathered as well as information directly entered by women themselves. NHS England have agreed to support cloud hosting for storage of data on the Tool. Data will be retrieved from NHS England retrospectively on an approximately quarterly basis.

11.10 Discontinuation/withdrawal of participants

Posters will be displayed in maternity clinic/community areas explaining that the Trust is taking part in the PARTNER trial and will provide contact details for the local team. Women and pregnant people can contact the local team (PI, Lead Research Midwife) for further information or speak to their local midwifery team. For women and pregnant people at intervention sites, it will be explained that the Clinical Decision Support Tool has been introduced as part of routine care at their hospital for the duration of the trial. Women and pregnant people can request that their data is not used in the trial. They can still be risk assessed by the tool without engaging with it as all necessary data can be entered by HCPs. Withdrawal information for women who do not want their data to be used in the trial or decide during the trial they no longer want their data to be collected, will be captured and stored by local sites. From the point of withdrawal, no data will be extracted for women and pregnant people.

11.11 End of trial

The end of the trial is when all patient follow up has been completed, all data has been received, all data queries resolved and analyses completed. The trial may be terminated early or stopped at an individual site on the instruction of the data monitoring committee (DMC) for safety reasons or the results of another study supersede the necessity for completion of this study.

Although the study will end when all data analyses are completed, during the period before results are known, due to the Tool being embedded in intervention sites' patient pathways, Trusts may choose to continue to use the Tool unless there are safety concerns. If they wish to continue to use the Tool, they will be supported by The Tommy's National Centre for Maternity Improvement to complete an exceptional use request to the MHRA so that it can be continued to be used at the Trust outside of a valid UKCA mark.
Once results are known, if the Clinical Decision Tool is shown to improve pregnancy outcomes. The Tommy's National Centre for Maternity Improvement will apply for UKCA mark for a Class 2b device.

11.12 Transition to non-randomised study

Revised design (feasibility): From CIP v5.0, allocation of NHS Maternity Trusts to the intervention or standard care arm is determined by site selection rather than centralised randomisation. The BTC will facilitate and document the formal allocation process for all sites.

Existing sites — formal allocation choice

Existing NHS Maternity Trusts (those recruited and activated under CIP v4.0 and prior) will be contacted by the BTC alongside distribution of CIP v5.0. Each site will be asked to formally declare their allocation choice in writing to the BTC. Three options are available:

Option A — Continuation in current arm (no transition)

The site confirms it will continue operating in the arm to which it was originally randomised. No change to current clinical activities is required. No transition period applies. Data collection continues without interruption and will be attributed to the site's original arm throughout.

Option B — Transition to the intervention arm (de-novo implementation)

Available to sites originally allocated to the standard care arm that elect to adopt the Clinical Decision Support Tool. Following formal declaration and BTC acknowledgement, the site will commence the implementation process as described in Section 9.3, including completion of all required Tool training before use begins in clinical practice. The transition point is defined as the date on which Tool use formally commences in clinical practice at that site. Data collected prior to the transition point will be attributed to the standard care arm; data from the transition point onwards will be attributed to the intervention arm. Data collection will continue throughout the transition period without interruption.

New sites — allocation following greenlight

No new sites are planned. However, for NHS Maternity Trusts joining the trial from the effective date of CIP v5.0, allocation will take place following greenlight activation (Section 11.3). The BTC will acknowledge and record the allocation in writing.

Recording of allocation and transition points

The BTC will maintain a site allocation and transition log as a controlled document within the Trial Master File. For each site, this log will record: the original allocation (for previously randomised sites) or initial allocation (for sites joining under CIP v5.0); the amended allocation where a site has changed arm; the date of formal allocation confirmation; and, where applicable, the transition point date. This log will be used to ensure accurate attribution of data to the correct study arm and will be made available to the trial statistician, DMC, and TSC as required.

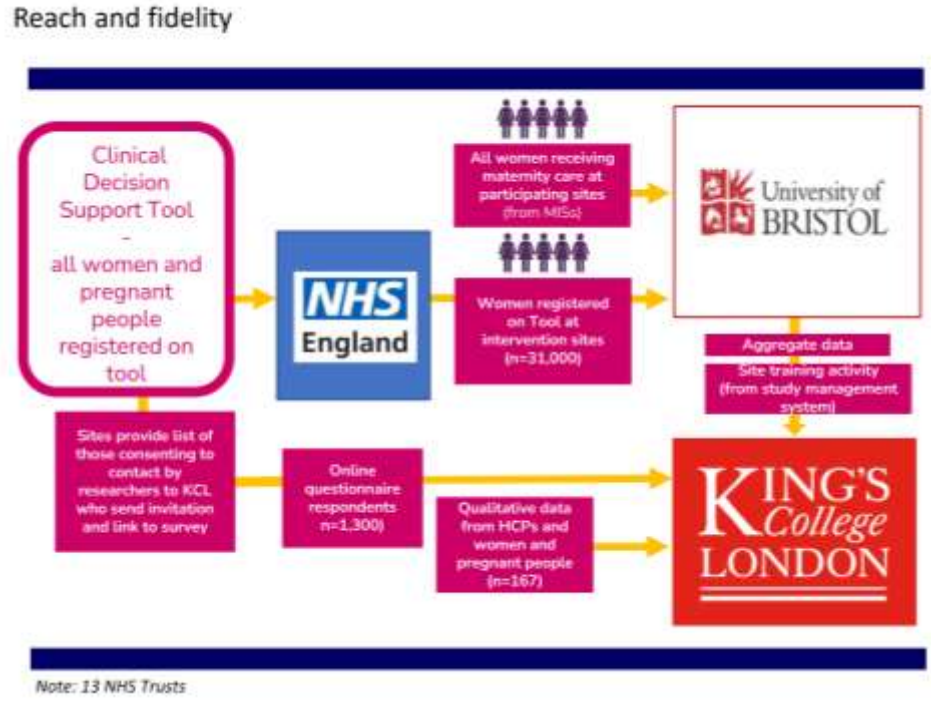
12 The Implementation Evaluation (WS 2)

Original Design (RCT)

The aim of WS2 is to conduct a process evaluation [26] to assess implementation processes [27] – fidelity to planned intervention, reach (in terms of access and use by different populations of women and pregnant people), acceptability to staff and women and pregnant people, and integration within current systems (e.g. organisational level use: integration with existing systems and processes; pathway processes (identification and management [28]), and unintended consequences).

12.1 Reach and Fidelity

Figure 3: Evaluation of reach and fidelity flow chart



12.1.1 Fidelity

Fidelity refers to the degree to which an intervention or programme is delivered as intended. Use of the Tool in management of care will be explored through a structured assessment of each of the main functions of the Tool, e.g., whether care recommendations were acted upon. This will be assessed using data collected through the tool itself and compared with data collected through Trust electronic maternity record and scan viewing systems. We will also evaluate and compare current clinical practice in both intervention and control sites by examining Trust guidelines, number of preterm clinic appointments, growth scans, inductions of labour and caesarean sections, and whether women

identified as high risk for placental dysfunction are prescribed aspirin. Investigating practice in both intervention and control sites is important, particularly in cluster trials, because it is possible that practice may be similar, whether the trial intervention is implemented or not. Staff training is an important element of successful implementation, and this will be evaluated by [training records recorded on the PARTNER Trial Management System].

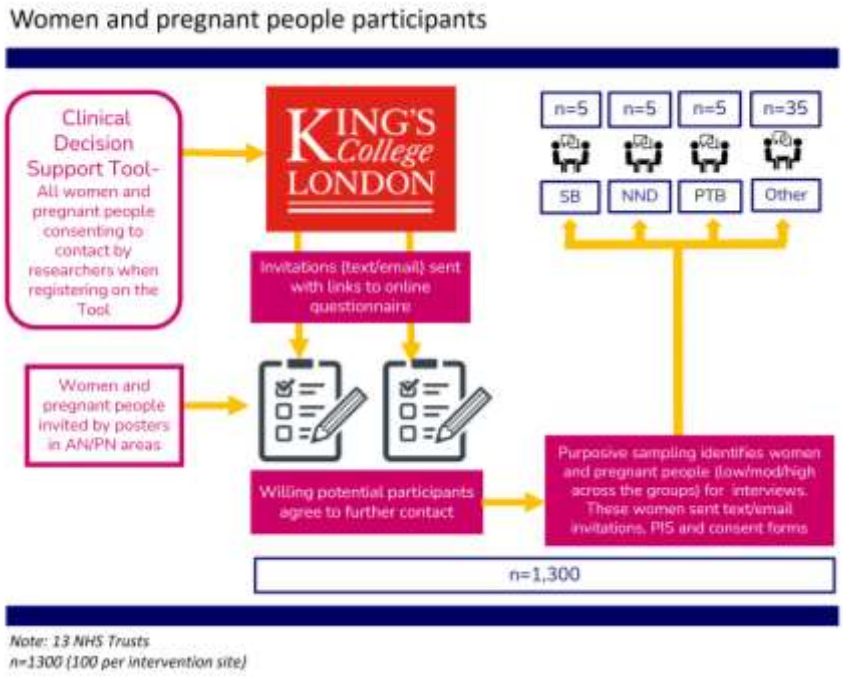
12.1.2 Reach

Reach refers to the extent to which the Tool is used within the population it is intended for, including whether particular groups have been under-represented, for example, those in certain age or ethnic groups, whether the maternity service user requires an interpreter or those from areas of greater social deprivation. We will compare proportions of those in each risk category (i.e. low, moderate and high) and those being offered interventions of interest (e.g. aspirin, steroids, growth scans, induction of labour, caesarean section) by different groups (e.g., hospital, age, ethnic group and IMD decile). We will use data from the Tool and local hospital records from both intervention and control sites, in order to investigate whether use of the Tool in the intervention sites leads to more appropriate targeting of care, compared to the control sites. We will also investigate the demographic characteristics and risk profiles of women using the Tool for pregnancy concerns, through the Information Hub, and compare these with the characteristic profiles of the populations served by each Trust.

12.1.3 Acceptability, integration within current systems and unintended consequences

Acceptability to staff and women and pregnant people will be assessed through online survey and qualitative methods (figure 4). Qualitative methods will allow participants to respond using their own words and will permit exploration of issues that are most important and salient to the participant and the subjective meaning they attach to utilising the Tool in delivering care within the NHS. This will allow for a rich, detailed understanding of experiences in this context and identification of any barriers and facilitators to uptake of the Tool into NHS workflows and care pathways. Participants will be recruited from across intervention sites.

Figure 4: Maternity service user participation flow chart



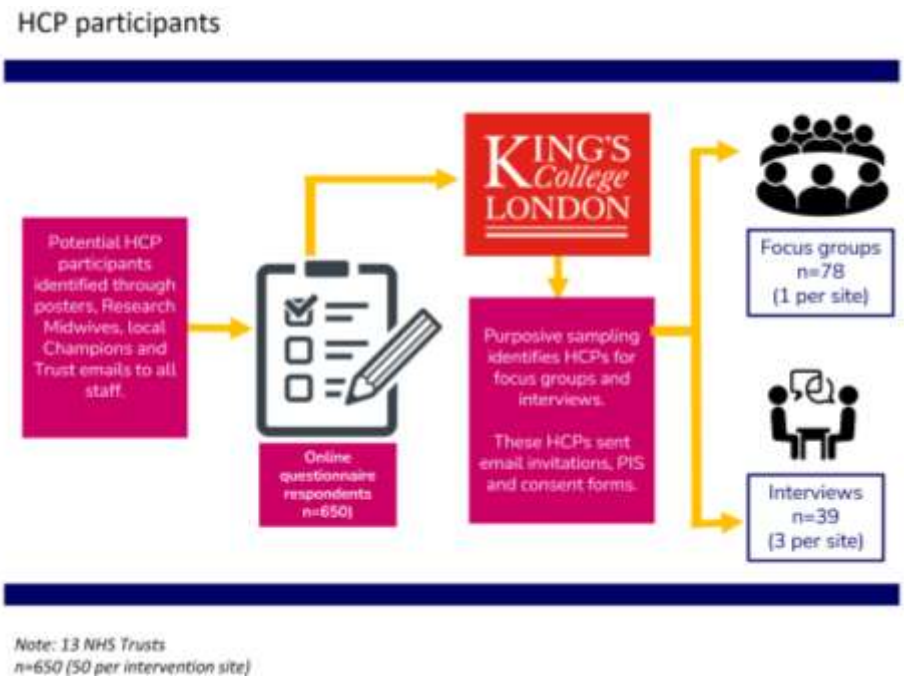
12.1.4 Maternity service user online questionnaires and interviews

The impact of the Clinical Decision Support Tool on women and pregnant people's experience of pregnancy will be assessed using an online survey and one-to one interviews (figure 4). Women and pregnant people registered on the Tool will be asked to indicate whether they agree to contact from researchers. Maternity service users from intervention sites who have agreed to contact by researchers when they register on the Tool will be invited by the Kings College London qualitative research team (by email or text message) to complete an online questionnaire about their views and whether they would be happy to participate further, if selected for interview. Up to five women and pregnant people per site will be sampled for interview from the survey respondents and others identified by local research midwives. Purposive sampling will be used to ensure diversity of participants. Women and pregnant people's experiences of using the Tool throughout the care pathway paying particular attention to those affected by digital exclusion and those who find services hard to access. In addition to exploring women and pregnant people's views and experiences of the Tool for risk assessment, we will also include their experiences of different touchpoints of using the Tool, for example, CFM and the tool's ToB assessment.

12.2 Health care professional online questionnaires, focus groups and interviews

Healthcare professionals at intervention sites will be invited (through posters and email by local site research team members) to complete an online questionnaire about their views and whether they would be happy to participate further, if selected for interview or focus groups (figure 5). Healthcare staff will be recruited to one focus group per intervention site (n≈13). Participants will include midwives, clinicians, stakeholders and governance specialists. In addition, semi-structured interviews with clinical leads in each study site (n≈3) (1 x Head of Midwifery; 1 x clinical obstetric lead; 1 manager). This will result in approximately 39 interviews addressing integration with existing systems and processes, potential barriers to the uptake of the Tool in the NHS maternity care pathway, how the Tool is used to inform clinical decision making, organisational impact**.** These interviews and focus groups will be conducted the qualitative research team at Kings College London.

Figure 5: HCP participation flow chart



Revised Design (Feasibility)

Work Stream 2 (WS2), which was originally designed to undertake an implementation and process evaluation alongside the trial, has been discontinued. As a result, no aggregate quantitative data relating to implementation outcomes (including reach, fidelity, acceptability, or integration within existing systems) will be collected or analysed for the purposes of this study.

However, limited qualitative data were collected during the period in which WS2 was active. These data will be retained and reported, where appropriate, to provide contextual insights into early experiences of the intervention.

13 Safety Reporting

13.1 Overview

The three algorithms used in the Tool: PTB-A, PF-A and PPTL-A, have been selected based on National Institute for Health and Care Excellence (NICE) evidence standards framework for digital health technology (DHT) for the use of AI technology (https://www.nice.org.uk/about/what-we- do/our programmes/ evidence-standards-framework-for-digital-health-technologies). They were selected for use by a Community of Practice consensus – women, Midwives and Obstetricians working together. As described above, these algorithms have already been externally validated and/or are evidenced in clinical trials and all comply with current national guidance.

PARTNER is adopting a risk-adapted and pragmatic approach to adverse event reporting whereby only device deficiencies will be reported. This approach is not in line with requirements in MEDDEV 2.7/3 to record and report all serious adverse events (SAEs). In this trial it is not possible to collect and report all SAEs as women and pregnant people are not actively followed up during the trial. Women and pregnant people are seen in accordance with relevant risk pathways as determined by the Tool (for intervention sites) or by their local pathway guidelines (control sites). Outcome data will be obtained retrospectively approximately quarterly from data extracts provide from the Tool (intervention sites only) and local hospital information systems (intervention and control sites). SAEs captured in these data extracts will already have been identified and managed within the NHS.

13.2 Recording and Reporting of Device Deficiencies

A Device Deficiency is an inadequacy related to the device identity, quality, durability, reliability, safety or performance. This may include malfunctions, use error, or inadequacy in the information supplied by the manufacturer.

The Tool is low risk from a safety perspective with there being no identifiable deficiencies directly related to its use. Therefore, all device deficiencies will be classed as unexpected.

The following events must be recorded within the CRF as soon as possible for the monitoring of device deficiencies occurring within the study. All device deficiencies need to be reported to the NHS England service desk and Trials Team (BTC).

a) Any malfunctions of the investigational device;

b) Any user errors that resulted in the device not working as intended;

c) Any inadequacy in the information supplied by the manufacturer resulting in the device not working as intended.

In addition, the following specific events must be recorded as device deficiencies on the CRF as soon as possible for the purposes of monitoring the acquisition and transfer of data to ensure that processes are working as per the device specifications.

a) Any failure of the investigational device to capture useable data;
b) Any failure of data transfer between the investigational device and the NHS England servers;
Any device deficiency that is observed by the investigator or reported by the participant must be assessed to determine whether the deficiency may have caused, or potentially caused harm to the participant.
All device deficiencies that resulted in an SAE or may have potentially resulted in a SAE if action had not been taken, an intervention had not been made, or if circumstances had been less fortunate will be reported to the Sponsor and manufacturer via the relevant paper device deficiency form CRF within 24 hours of the investigators becoming aware of such an event. Participating sites will be provided with contact details of the Sponsor, the Bristol Trials Centre (BTC) and NHS England service desk for the purposes of reporting device deficiencies. The NHS England service desk will triage queries that come through and pass on to the manufacturer as required.
The subject will be actively followed up, and the investigator (or delegated person) will provide information missing from the initial report within five working days of the initial report. The first follow-up report will be provided within 5 days of the initial report and subsequent information will be provided each time new information is available until the SAE has resolved, unless a different reporting period is agreed with the Sponsor on a case by case basis, or a decision for no further follow-up has been taken. All device deficiencies that resulted in SAEs will be reported to the REC, MHRA and Chair of the DMC.
All device deficiencies will be summarised and reported to the DMC and TSC.

13.3 Recording of non-device deficiencies

Adverse events which form part of our outcome data set will be recorded based on approximately quarterly outcome data extracts from sites/the tool. These will be summarised and reported to the DMC, TSC and Sponsor.

13.4 Reporting to the MHRA

The Sponsor is responsible for reporting to the MHRA. The following events are considered reportable.

Any device deficiency that might have led to an SAE or might have if:

- suitable action had not been taken or
- intervention had not been made or
- if circumstances had been less fortunate
- New findings/updates in relation to already reported events.

13.5 Reporting to the REC

All device deficiencies that resulted in an SAE shall be submitted by the BTC to the REC.

13.6 Reporting timelines

Device deficiencies resulting in death or were life threatening will be reported to regulatory bodies no later than 7 days of the BTC becoming aware and any additional information within 8 days of the submission of the initial report. All other serious device deficiencies will be reported no later than 15 days after the Sponsor/BTC has become aware of the event.

14 Statistics and health economics analysis

14.1 Sample size calculation (WS 1)

Original design (RCT):

National data shows that the incidence of hypertensive disorders of pregnancy is 5.8% [29]. To detect an absolute reduction of 2% (relative reduction of approximately one third) in the intervention group, with 90% power, 5% significance (two-sided), where the intra-cluster correlation is estimated at 0.005 [30], we require each maternity unit to recruit 2,400 participants, with a minimum of 13 maternity units in each group (a minimum of 26 units in total with 31,200 women in the intervention group and 31,200 in the control group). Unavailability of data and women and pregnant people asking to withdraw their data is expected to be less than 1% [30].

Revised design (feasibility)

As a feasibility study, a formal sample size calculation based on clinical outcome power is not required or appropriate. A total of 10 NHS maternity sites will be recruited.

14.2 Statistical analysis (WS 1)

Original design (RCT):

Analyses will be performed at patient level. Analyses will follow CONSORT reporting guidelines for cluster RCTs and be conducted on an intention to treat basis. We anticipate the outcome data to be missing in a very small number of instances; this will be monitored and if missing outcomes are higher than anticipated we will investigate approaches such as multiple imputation. Analyses will follow a pre-specified statistical analysis plan. Outcomes will be compared using multilevel generalised linear modelling, adjusting for maternity unit size and accounting for clustering at maternity unit level. Risk difference and relative risk reduction will be reported, with 95% confidence intervals. Baseline characteristics and outcome data will be presented for the two groups using descriptive statistics. Use of the Clinical Decision Support Tool by women and healthcare professionals in the intervention sites will be described (e.g., usage information, how many women and pregnant people and midwives used it etc.). As outcomes will be determined from routine data and they are clinical events that are recorded for all women and pregnant people, missing outcome data is expected to be very low. Alongside the intention to treat analysis, a sensitivity analysis will be undertaken as an as-treated analysis, excluding women who do not have access to all components of the Clinical Decision Support Tool due to multiple births or pre-existing hypertension or diabetes.

Revised design (feasibility):

No outcomes will be formally analysed. Primary outcome descriptive analyses will include summary statistics and details on data completeness.

Data availability by site and outcome completeness will be described for all secondary outcomes. Secondary outcome summary statistics will be presented for secondary outcomes where possible.

Summary statistics for continuous data will be described with either means and standard deviations or medians and inter-quartile ranges, depending on the underlying data distribution. Summary statistics for discrete and categorical data will be described as frequencies.

14.3 Missing data

Original design (RCT):

Missing data may occur if women or pregnant people are transferred in to or out of the Trusts during maternity care. We anticipate this frequency will be small and all subjects will be accounted for in the final study report. The characteristics of subjects who withdraw or who are lost to follow-up will be described.

Revised design (feasibility):

No description of the characteristics or frequency of women or pregnant people who transfer in or out of trusts, or who withdraw from the study, will be performed.

14.4 Implementation Evaluation (WS 2)

Original design (RCT):

Online questionnaires: Statistical software will be used to explore and analyse the quantitative data gathered through the questionnaires. Participant characteristics will be explored using descriptive statistics (i.e., frequencies and percentages) and groups will be compared using Pearson's Chi-squared tests and multilevel logistic regression models. Differences between groups will be considered statistically significant if the p value is ≤0.05. Qualitative data gathered through free text boxes, (e.g., answers to the question: "Is there anything else you would like to tell us about your experience of using the Tool?") will be analysed using qualitative thematic analysis.

Qualitative data will be managed through NVivo qualitative data software and analysed using a thematic framework approach. The Framework approach [31] is a method of qualitative data analysis designed to generate findings that can inform practice and policy and the steps used within this approach lend themselves well to the data likely to be generated in this study. Data analysis will be informed by the NASSS (Non-adoption or Abandonment of technology by individuals and difficulties

achieving Scale-up, Spread and Sustainability) framework [32] in addition to inductive analysis (where the researcher is open to new themes emerging from the data). This framework was chosen because it is an evidence-based, theory-informed, and pragmatic framework to help predict and evaluate the success of a technology-supported health or social care program. A proportion of transcripts and identification of themes will be reviewed by another experienced researcher to increase validity. Data reporting and analysis will be guided by reporting standards for implementation research [33].

Revised design (feasibility)

There will be no planned online questionnaires or interviews. Participant characteristics will be described as detailed in WS 1 statistical analysis (14.2) from maternity system and Tool data.

14.5 Economic evaluation (WS 3)

14.5.1 Original design (RCT): **Within trial cost analysis**

The cost of the Tool and its incorporation within clinical systems will be determined in consultation with the developers, then discussions with PARTNER Trial Research Midwives to estimate the time required for training in its use and the actual use of the Tool in clinical practice.

Data will be collected relating to all antenatal visits, associated investigations, treatments, hospitalisations (including for delivery) and neonatal costs up to 28 days post-delivery. Unit costs relating to each of these will be identified from the most recent NHS Reference Costs. For drug treatments, prices from the British National Formulary will be used.

Differences in the number of visits and hospitalisations between trial arms will be calculated. NHS costs for each individual patient will then be calculated and mean costs between trial arms will be estimated using multivariable regression methods that account for prognostic factors at baseline and the clustered nature of the data [34]. From these analyses, we will estimate the probability that the intervention is cost-saving.

14.5.2 Modelled cost-effectiveness analysis

The within trial analysis will form the major component of a model for Tommy's Pathway: a Clinical Decision Support Tool, but this will be combined with other sources of information to capture costs and QALYs relating to the mother and infant based on epidemiological data that will allow us to estimate years of life lost for maternal deaths and which links birthweight to health care costs, QoL and mortality of the infant [35]. The final parameterisation of these aspects of the model will be based on literature searches undertaken in the final year of the project in order to ensure the best possible data are available [36].

The modelling will include a probabilistic sensitivity analysis, with the generation of a cost-effectiveness acceptability curve for the Clinical Decision Support Tool, which will show the probability that the Tool is cost-effective at funding thresholds used by NICE in its Medical Technology Evaluation and Technology Appraisal programmes.
In addition, a value of information analysis will be undertaken in order to identify the value of further research for each parameter [37]. Finally, a value of implementation analysis will be undertaken, which will estimate the potential cost-effectiveness of investing in initiatives to increase the uptake of the Tool among healthcare professionals [38].

Revised design (feasibility)

There will be no planned formal cost-effectiveness analysis.

15 Trial management

15.1 Trial oversight

15.1.1 Day to day management

University of Bristol will act as Sponsor. The trial will be managed on a day-to-day basis by the BTC, a fully registered UK Clinical Research Collaboration (UKCRC) Unit (registration number 70). BTC will prepare all the trial documentation and data collection forms, specify the randomisation scheme, check data quality as the trial progresses, monitor recruitment and carry out trial analyses in collaboration with the investigators. BTC will be the primary point of contact for participating sites.

15.1.2 Trial Management Group

The study will be overseen by the Chief Investigator (CI), clinical leads and BTC staff, and will be managed by a Trial Management Group (TMG) that will meet on a 4-6 weekly basis (face to face or by teleconference). The TMG will be attended by the Chief Investigator, co-lead, representatives from the BTC, clinical leads, co-applicants and any other staff responsible for the delivery of the trial, as required. The TMG will monitor all aspects of the conduct and progress of the trial, ensure that the clinical investigation plan is adhered to and take appropriate action to safeguard participants and the quality of the trial.

15.1.3 Investigator meetings

Investigator meetings will be held approximately every 6-12 months to review study progress and address any issues that arise. All team members, including all study applicants, local PIs, midwives, and study champions will be invited to these meetings.

15.1.4 Site monitoring

BTC will carry out central monitoring and audit of compliance of sites with the principles of GCP and data collection procedures. The TMG will review the completeness and consistency of the data from the Clinical Decision Support Tool and outcome data extracts from the sites' medical records throughout the trial.

15.2 Trial Steering Committee and Data Monitoring and Safety Committee

The Trial Steering Committee (TSC) will provide independent supervision of the trial and oversee trial progress. The TSC will consist of an independent chair and three other independent members including a clinical trialist, a statistician, a Patient and Public Involvement (PPI) representative and the CI. The TSC will develop terms of reference outlining their responsibilities and operational details. The TSC will meet regularly (at intervals to be agreed with the Committee) during the course of the trial.

A Data Monitoring Committee (DMC) monitors patient safety and trial data efficacy and consists of an independent chair, and at least two other independent members. The BTC will develop a charter outlining their responsibilities and operational details which will be reviewed and agreed by the DMC. The DMC will meet before the trial begins and they will meet regularly thereafter (at intervals to be agreed with the Committee) to review safety data during the course of the study.

16 Patient and Public Involvement

The study team is led jointly by The Royal College of Obstetricians and Gynaecologists (RCOG) and The Royal College of Midwives (RCM), who represent the entire UK maternity workforce and involves the largest UK PPI network, the Women's Voices Involvement Panel, as equal stakeholders (nearly 700 members of the public with experience of women's health services). Our PPI lead is a member of the Women's Voices Involvement Panel, the CEO of a grass roots, patient led charity, run by women with lived experience and has previously been a member of the Women's Network. A PPI group, formed specifically, includes black and Asian women; women with lived experience of preterm birth, stillbirth and neonatal death; women with usual pregnancy/birth experiences representing those not immediately considered high risk, and women with no maternity experience representing the views of first-time mothers.

The group has been involved in the design and development from inception, and is central to the project, attending workshops and Community of Practice events, informing on design, language, user experience, functionality, patient information and implementation plans. The design of the 'patient facing' Tool and the communication of risk are based on input from the group.

Pregnant women/people who have given birth, report lack of signposting and uncertainty of where to source reliable, accurate information relating to their pregnancy can lead to anxiety. Not being aware of how and where to seek reliable information can lead to poor outcomes. Women's access to the Clinical Decision Support Tool will overcome these issues.

The assessment of risk is personalised to each individual woman and pregnant person. This removes poor predictions and bias of the current checklist and variations in care therefore reducing inequalities and disparities in maternity care for all women and pregnant people.

For a woman or pregnant person who does not access the Clinical Decision Support Tool the risk assessments will be activated by the maternity care provider, producing an accurate risk assessment and allocation to a best practice care pathway. They will still be able to use this information to make informed choices and decisions in their care.

We are in discussions with other women and pregnant people's groups to understand potential barriers and how these can be removed to ensure that the Clinical Decision Support Tool is accessible to the groups of women and pregnant people who need it the most.

The PPI group has inputted into the training materials for Maternity Care Providers and the information to be shared with Maternity Care Providers, women and pregnant people and their families, explaining the AI technology and the language around risk. The Maternity Voices Partnership Chairs of the early adopter sites joined the group and will participate in the preparation of both training and information videos, ensuring the content is easily accessible to women and pregnant people.

The Tool includes evidence-based information support for women and pregnant people relating to concerns they may have during their pregnancy. The information we obtain from users of the Tool will

allow us to ascertain what additional and specific information women and pregnant people would like to access.

PPI members will join the Study Steering Committee. The Women's Voices Panel, has a large online presence, diverse representation, supported participation of members with additional needs and encourages participation by under-represented groups. Our PPI network will engage the wider community through support groups and the charitable organisations many of them represent. They will use focus groups, questionnaires, and social media to engage widely. Views regarding transparency of AI technology and communication with women concerning safety and the measures taken to protect wellbeing and confidentiality will be key. PPI members will be remunerated for their work in line with INVOLVE recommendations. Travel costs, meeting attendance, and refreshments will be covered, with occasional donations to groups considered. The PPI lead within the project team will be available to answer questions and offer support for PPI members. Training will be provided where necessary.

17 Ethical Considerations

17.1 NHS Research Ethics Committee (REC), Health Research Authority (HRA) and CAG approval

The research will be performed subject to a favourable opinion from an NHS REC, HRA and CAG. REC review of the clinical investigation plan for the trial and other trial related essential documents will be carried out by a UK NHS REC. Any subsequent amendments to these documents will be submitted to the REC, HRA and CAG for approval prior to implementation.

17.2 Risk and anticipated benefits

By taking part the trial maternity units allocated the intervention will have a better knowledge of the impact of using the Clinical Decision Support Tool on their service provision. They will also understand the challenges associated with implementation, barriers to adoption and understand the process of evaluation.

Individual women and pregnant people will have no additional benefits except the potential of improved risk assessment for hypertensive disorders and preterm birth and consequently appropriate management if the Tool proves successful.

Risk management and benefit-risk analysis information can be found in the Investigators' Brochure.

18 Research governance

This study will be conducted in accordance with:

- Ethical principles that have their origin in the Declaration of Helsinki
- The Medicine for Human Use (Clinical Trial) Regulations 2004
- GCP guidelines
- Research Governance Framework for Health and Social Care
- EU MDR Medical Devices Regulation 2017/745
- Data Protection Act (DPA) 2018
- General Data Protection Regulation UK (GDPR UK)

18.1 Sponsor approval

Any amendments to the trial documents must be approved by the Sponsor prior to submission to the REC, HRA, CAG and MHRA.

18.2 NHS approval

Agreement from the local NHS Trust is required prior to the start of the study at each site, including any provisions of local site capacity and capability confirmation.

Any amendments to the study documents approved by the HRA/REC/CAG/MHRA will be submitted to the Trust for information or approval as required, including confirmation of continued capacity and capability.

18.3 Investigators' responsibilities

Investigators will be required to ensure that local research approvals have been obtained and that any contractual agreements required have been signed off by all parties before recruitment begins. Investigators will be required to ensure compliance to the clinical investigation plan and study training materials and with completion of the CRFs. Investigators will be required to allow access to study documentation or source data on request for monitoring visits and audits performed by the Sponsor or BTC or any regulatory authorities. Investigators will be required to read, acknowledge and inform their trial team of any amendments to the trial documents approved by the REC/HRA/CAG/MHRA that they receive and ensure that the changes are complied with.

18.4 Monitoring, Audit and Inspection

18.4.1 Monitoring

The trial will be monitored and audited in accordance with the Sponsor's policy, which is consistent with the UK Policy Framework for Health and Social Care Research. The Sponsor has a Service Level Agreement with University Hospitals Bristol and Weston NHS Foundation Trust (UHBW), whereby the Trust monitors 10% of the University's sponsored studies. All trial related documents will be made

available on request for monitoring and audit by the UHBW, the relevant Research Ethics Committee (REC) and for inspection by the MHRA.

A Trial Monitoring Plan will be developed by the Sponsors and agreed by the TMG and CI based on the trial risk assessment. This will be dependent on a documented risk assessment of the trial.

The sponsor usually delegates some of the monitoring to the central research team (BTC). The following checks would be typical:

- That data collected are consistent with adherence to the clinical investigation plan
- That CRFs are only being completed by authorised persons
- That SAE recording and reporting procedures are being followed correctly
- That no key data are missing
- Review of number of users registered on the Tool (intervention sites)

18.4.2 Clinical investigation plan compliance

There will be no prospective, planned deviations or waivers to the clinical investigation plan. Any deviations will be documented and reported to the Trial Manager, CI and Sponsor immediately (see Key Trial Contact for contact details). Examples of deviations include outcome data not being sent by sites as planned and assessments not being followed as scheduled at intervention sites. Deviations will be documented on the Sponsor's Corrective and Preventative Action Form. Information about clinical investigation plan deviations will also be included in routine reports to the DMC and TSC. Any breaches identified by the central research team will be reported to Sponsor as soon as possible. The Sponsor will determine the seriousness of the breach.

In the event of systematic clinical investigation plan deviations, investigation and remedial action will be taken in liaison with the CI, DMC and the TMG.

18.4.3 Notification of serious breaches to GCP and/or the clinical investigation plan

A "serious breach" is a breach which is likely to effect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial; or
- the scientific value of the trial

The Sponsor will be notified immediately of any case where the above definition applies during trial conduct; they will determine the seriousness of the breach.

18.5 Indemnity

This is a University of Bristol-sponsored research study. If there is negligent harm during the clinical trial when the NHS body owes a duty of care to the person harmed, NHS Indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial. NHS Indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm. Ex-gratia payments may be considered in the case of a claim.

18.6 MHRA

The MHRA have confirmed that the trial comes under the clinical investigation for a medical device MHRA notification process. The Tool is as non-CE marked class 2b device.

19 Data management

19.1 Source data

Source data will be the patient's medical records, the Clinical Decision Support Tool records, online questionnaires, audio recordings and transcripts of interviews and focus groups and the CRFs.

19.2 Data protection

Data will be collected and retained in accordance with the UK Data Protection Act 2018.

19.3 Data handling, storage and sharing

19.3.1 Data handling

Original design (RCT):

Study data will be entered onto the Clinical Decision Support Tool and stored on an NHS England Cloud storage facility. Data extracts will be sent to BTC researchers with honorary NHS contracts securely via the NHS network. Trusts will have access to download data for their site to check for data completeness and to send details of participants who have consented to future contact from researchers to the Kings College London qualitative research team.

Study data will be extracted/downloaded from NHS data sources (electronic maternity records and scan viewing systems) at local Trusts and sent to BTC researchers with honorary NHS contracts securely via the NHS email. The data will then be transferred to a secure, restricted access University of Bristol (UoB) encapsulated virtual machine where data sets will be linked and analysed with access limited to one named individual and a backup from the research team.

Details of patients who consent to be contacted by researchers, consent forms, data from online surveys, audio recordings and transcripts from interviews and focus groups will be stored securely on secure King's College London SharePoint site. Aggregate demographic and outcome data about women and pregnant people across both intervention and control sites will be sent to King's College London from UoB to be included in user and reach analysis. This will also stored be securely on a secure King's College London SharePoint site.

Individual pseudonymised data (see Table 2) will be sent from UoB to the health economics team at the University of Sheffield. This data will be provided in an encrypted and password protected file, with the password communicated separately to the data file. Data will be stored on systems that are approved by the University of Sheffield. Access to the data will be restricted to University of Sheffield research staff who need access for the purpose of completing analysis for the project.

For the purpose of investigating any errors/issues/bugs that arise in relation to use of the device by an HCP user or a pregnant user and therefore for the purpose of direct care, there may instances where

the device Digital Developers (Apadmi) and the device manufacturer (RCOG) require access to individual level patient personal information (i.e. a specific user name and email address) to investigate and resolve the error/issue/bug.
The Sponsor (UoB) contract monitoring and safety reporting to, University of Bristol and Weston NHS Trust (UHBW). The research team at the University of Bristol will allow UHWB access to data for these purposes. The data is identifiable health information i.e. confidential, so a legal avenue is required. The legal avenue will be Section 251.

Revised design (feasbility):
Study data will be entered onto the Clinical Decision Support Tool and stored on an NHS England Cloud storage facility. Data extracts will be sent to BTC researchers with honorary NHS contracts securely via the NHS network. Trusts will have access to download data for their site to check for data completeness.
Study data will be extracted/downloaded from NHS data sources (electronic maternity records and scan viewing systems) at local Trusts and sent to BTC researchers with honorary NHS contracts securely via the NHS email. The data will then be transferred to a secure, restricted access University of Bristol (UoB) encapsulated virtual machine where data sets will be linked and analysed with access limited to one named individual and a backup from the research team..
For the purpose of investigating any errors/issues/bugs that arise in relation to use of the device by an HCP user or a pregnant user and therefore for the purpose of direct care, there may instances where the device Digital Developers (Apadmi) and the device manufacturer (RCOG) require access to individual level patient personal information (i.e. a specific user name and email address) to investigate and resolve the error/issue/bug.
The Sponsor (UoB) contract monitoring and safety reporting to, University of Bristol and Weston NHS Trust (UHBW). The research team at the University of Bristol will allow UHWB access to data for these purposes. The data is identifiable health information i.e. confidential, so a legal avenue is required. The legal avenue will be Section 251.
No participant details or data, pseudonymised or otherwise, will be sent to King's College London (KCL) or University of Sheffield (UoS).

19.3.2 Data storage

Original design (RCT):
Workstream 1: Identifiable data will be stored securely for as limited time as possible for its intended use, this will be until the end of the study once the results of the study have been analysed. Study documentation (trial master files and site files) will be archived for 5 years following the end of the

study. Identifiable data will be stored on a UoB encapsulated virtual machine (see 19.3.1). The trial master and site files will be stored on a UoB SharePoint.
Workstream 2: The audio recordings from interviews and focus groups will be deleted when analysis and publication are complete, no later than two years after the end of the study. Email addresses will be kept by researchers at King's College London for 3 months, after the trial has finished, unless a participant consented to be contacted about future research, in which case it will be retained until deletion is requested. Consent forms will be kept for until the youngest child born during the recruitment period turns 25. All interview extracts and survey responses will be disguised with a code number. Data will be stored on a secure Kings College London SharePoint site.
Workstream 3: Pseudonymised data will store on University of Sheffield approved systems and will be restricted to University of Sheffield research staff who need access for the purpose of completing analysis for the project.

Revised design (feasibility):
Workstream 1: Identifiable data will be stored securely for as limited time as possible for its intended use, this will be until the end of the study once the results of the study have been analysed. Study documentation (trial master files and site files) will be archived for 5 years following the end of the study. Identifiable data will be stored on a UoB encapsulated virtual machine (see 19.3.1). The trial master and site files will be stored on a UoB SharePoint.
Workstream 2 and Workstream 3 have been discontinued.

19.3.3 Data sharing

Original design (RCT):
Data will not be made available for sharing until after publication of the main results of the study. Thereafter data will be shared as below:
WS1 & WS3 - pseudonymised individual patient data will be made available for secondary research, conditional on assurance from the secondary researcher that the proposed use of the data is compliant with the MRC Policy on Data Sharing regarding scientific quality, ethical requirements and value for money. A minimum requirement with respect to scientific quality will be a publicly available pre-specified protocol describing the purpose, methods and analysis of the secondary research, e.g. a protocol for a Cochrane systematic review.
WS2 - pseudonymised individual patient data will be made available for secondary research, conditional on assurance from the secondary researcher that the proposed use of the data is compliant with the MRC Policy on Data Sharing regarding scientific quality, ethical requirements and value for money. A minimum requirement with respect to scientific quality will be a publicly available

pre-specified protocol describing the purpose, methods and analysis of the secondary research, e.g. a protocol for a Cochrane systematic review.

Revised design (feasbility):

Data will not be made available for sharing until after publication of the main results of the study. Thereafter data will be shared as below.

WS1 - pseudonymised individual patient data will be made available for secondary research, conditional on assurance from the secondary researcher that the proposed use of the data is compliant with the MRC Policy on Data Sharing regarding scientific quality, ethical requirements and value for money. A minimum requirement with respect to scientific quality will be a publicly available pre-specified protocol describing the purpose, methods and analysis of the secondary research, e.g. a protocol for a Cochrane systematic review.

20 Dissemination of findings

The collaborative approach between Tommy's, the RCOG, the RCM and its academic and charitable partners is key to the success of the study in achieving its aims. The weight of the combined clinical and academic expertise, their combined patient and public involvement networks and reputational reach across the UK maternity landscape sees this partnership ideally placed to ensure the Centre reaches the full potential of its aims.

Our established team has extensive multidisciplinary expertise and experience and are directly involved in many of the current national initiatives in maternity care improvement. The RCOG and RCM have significant traction and are both involved in all national policy initiatives in maternity care. The RCOG and RCM understand the needs of the health systems and are well placed to translate innovative solutions into clinical practice by collaborating with the entire maternity workforce across England to take what works best and quickly spread it nationally. The Tommy's National Centre for Maternity Improvement, led by the Royal Colleges and supported by DHSE will lead on development of a roadmap for integration of the Clinical Decision Support Tool into current maternity pathways incorporating stakeholder requirements, value proposition, business case and overcoming barriers to implementation.

The Tommy's Centre will develop the value proposition by defining clinical impact and incorporating health economic modelling to produce a strategy to roll out the product, produce an implementation pack and disseminate wider across the NHS. If this trial confirms the efficacy and cost effectiveness of the Tool, the team will proceed with a phase 4 application for national roll out.

The results of the RCT and other work streams will be shared with hospital trusts, submitted for publication in peer review journals and presented at conferences.

To facilitate the national roll out, the team and collaborators are currently working with the Department of Health and Social Care, in partnership with the NHS England national maternity safety champions to incorporate the use of the Clinical Decision Support Tool into national practice in line with the national maternity safety strategy.

Finally, NHS Resolution who manage all litigation in NHS England have committed to work with the research group to financially incentivise the adoption of the Tommy's Clinical Decision Support Tool at Trust/maternity unit level through their maternity incentive scheme which supports the delivery of safer maternity care in maternity units. This will provide a platform for National roll out across all maternity Units in NHS England. The Central Legal Office in Scotland, NI Health and Welsh risk pool have also expressed an interest in the results of this AI device with a view to facilitating implementation across the devolved nations.

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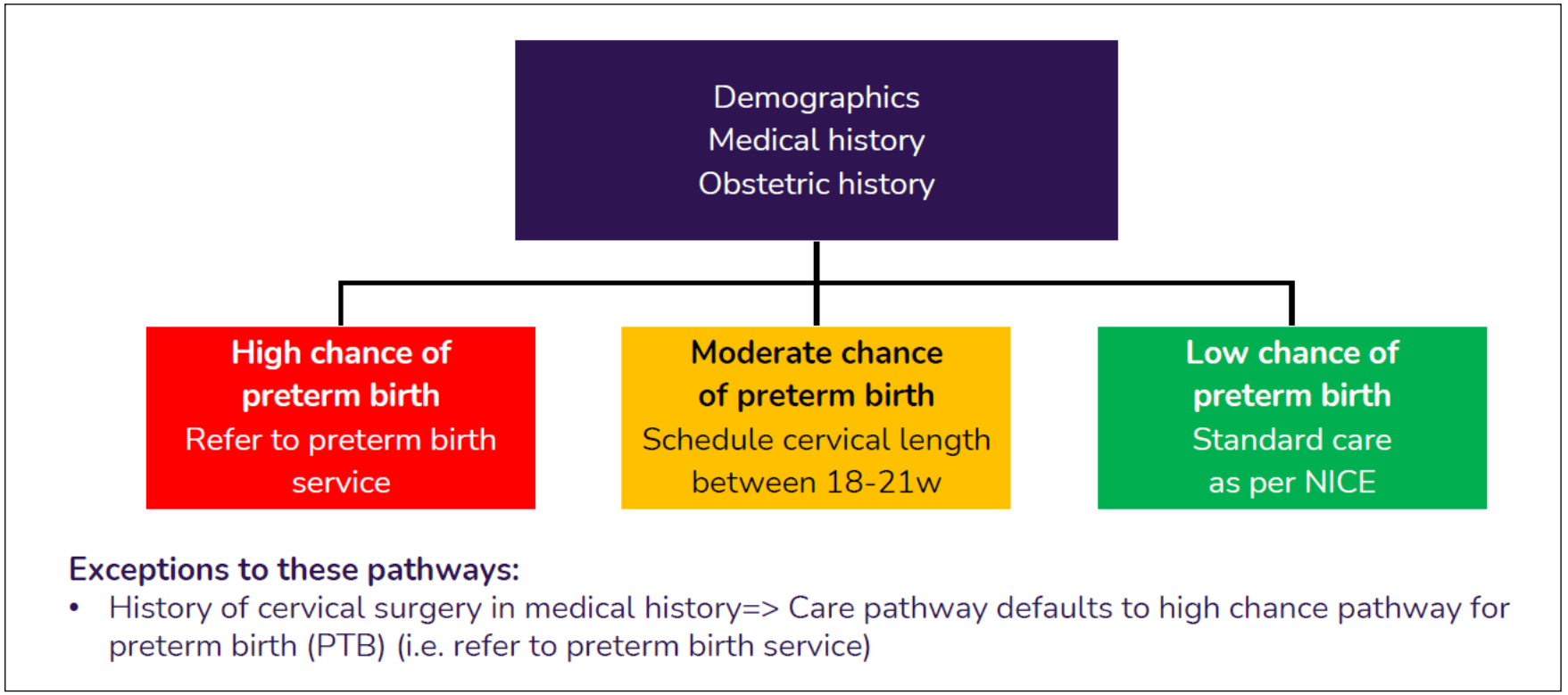
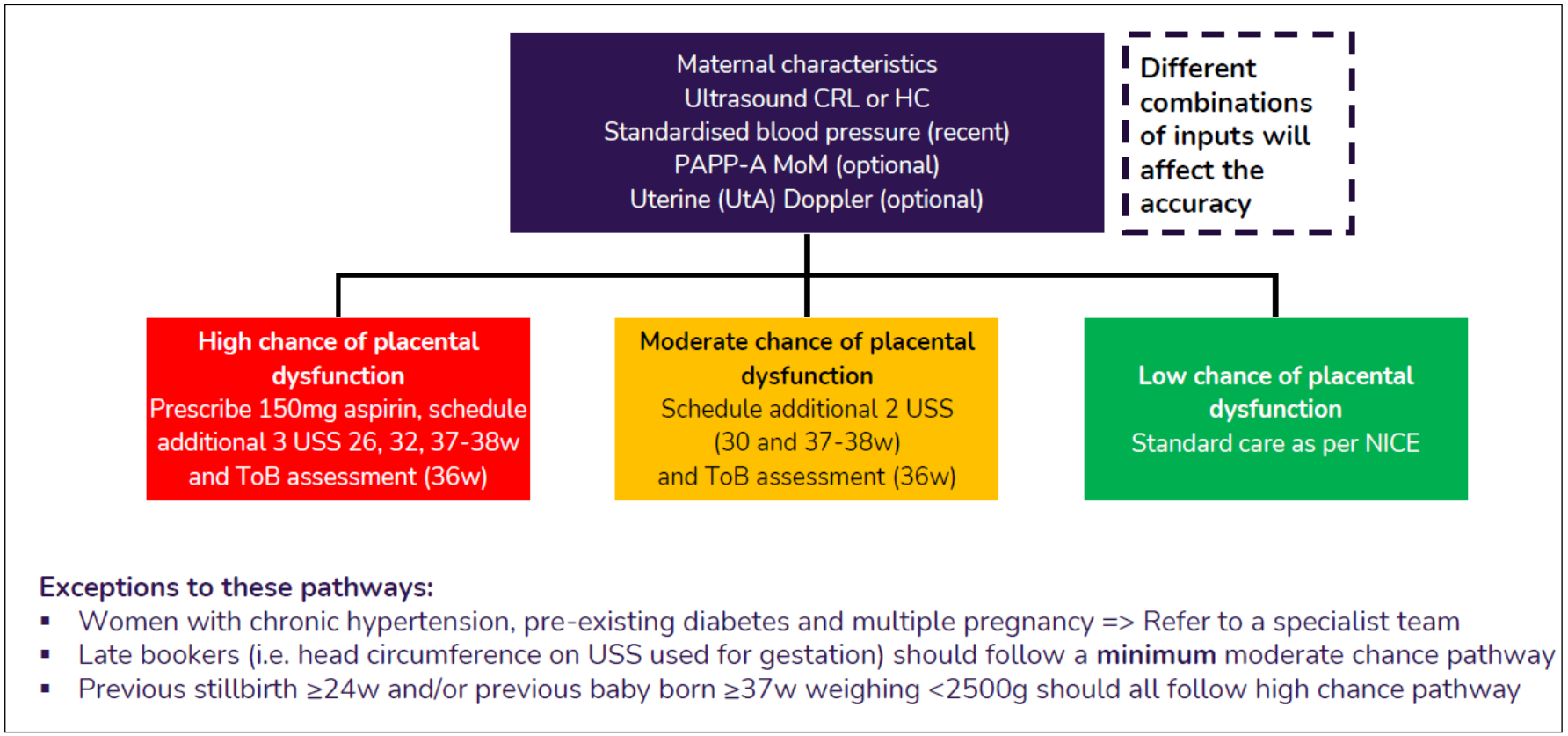
22 Appendices

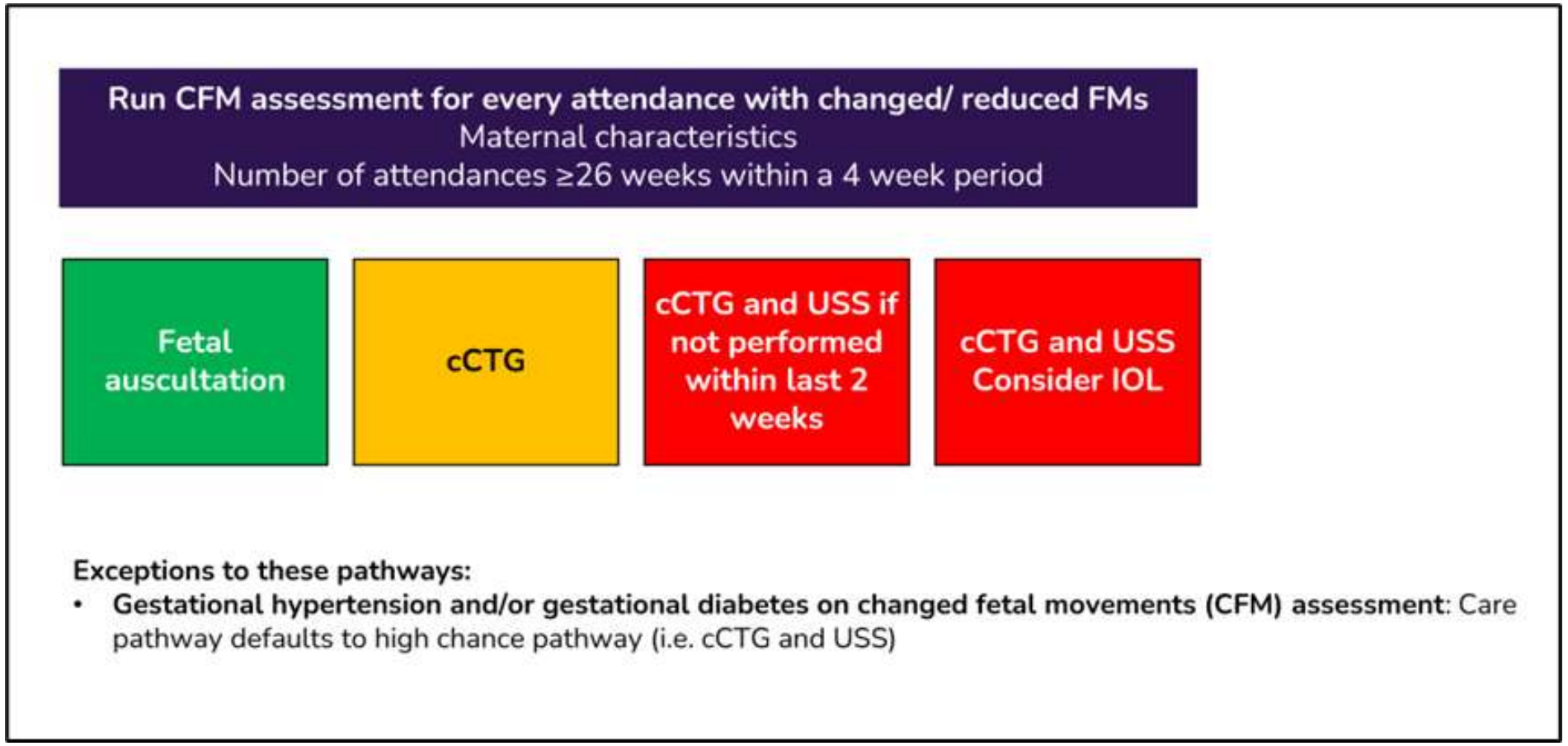
Appendix A- Preterm birth (PTB) assessment ≤12 weeks



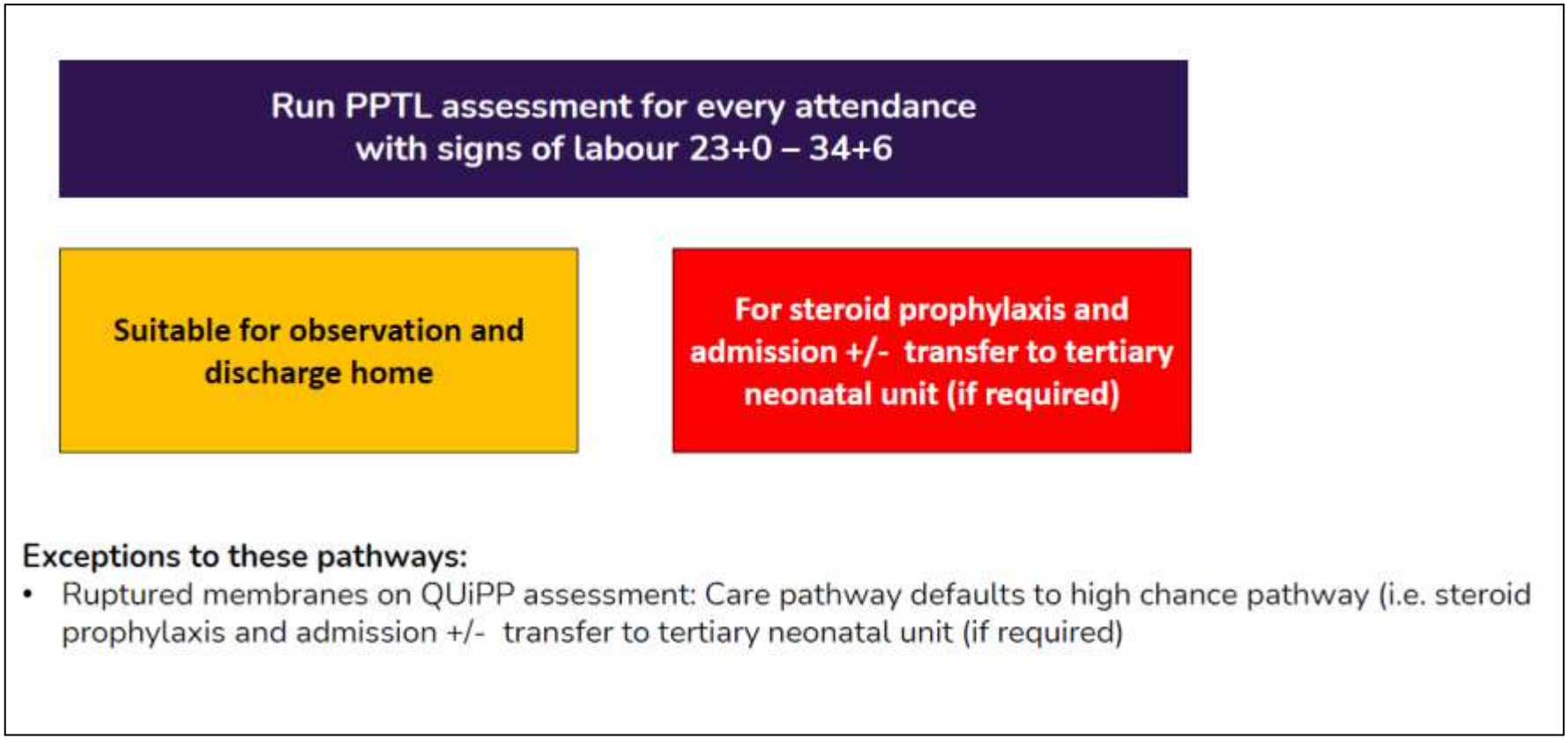
Appendix B - Placental function (PF) assessment ≤16 weeks



Appendix C – Changed fetal movements (CFM) assessment from 26 weeks onwards



Appendix D – Possible preterm labour (PPTL) assessment: 23+0-34+6



Appendix E – Timing of Birth (ToB) assessment around 36 weeks

This should be routinely completed for women who are moderate or high chance of placental dysfunction ≤16w or who are late bookers:

