PravastatIn tO preveNt prEtErm biRth (PIONEER): a parallel group randomised placebo-controlled trial

PIONEER
PRAVASTATIN TO PREVENT PRETERM BIRTH

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Contents

GLOSSARY OF ABBREVIATIONS

AE	Adverse Event
AESI	Adverse events of special interest
ALT	Alanine aminotransferase
AR	Adverse Reaction
ASA	Acetylsalicylic acid
AST	Aspartate aminotransferase
AUC	Area under the curve
BTC	Bristol Trials Centre
CARE	Cholesterol and Recurrent Events
CHD	Coronary Heart Disease
CI	Chief Investigator
CK	Creatine Kinase
CMW	Community Midwife
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of an Investigational Medicinal Product
CTU	Clinical Trials Unit
DIBD	Developmental International Birth Date
DMSC	Data Monitoring and Safety Committee
DSA	Data Sharing Agreement
DSUR	Development Safety Update Report
EDTA	Ethylenediaminetetraacetic acid
EME	Efficacy and Mechanism Evaluation
EU	European Union
GA	Gestational Age
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GRIPP2	Guidance for Reporting Involvement of Patients and the Public-2
HCP	Healthcare Professional
HDL	High-density lipoprotein
HMG CoA	3-hydroxy-3-methylglutaryl coenzyme A
HRA	Health Research Authority
IB	Investigator's Brochure

ICH-GCP	International Conference on Harmonisation for Good Clinical Practice
IDL	Intermediate-density lipoprotein
IL	Interleukin
IMD	Index of Multiple Deprivation
IMNM	Immune-mediated necrotizing myopathy
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Produce Dossier
INR	International Normalised Ratio
IQR	Inter-quartile range
ISRCTN	International Standard Randomised Controlled Trials Number
ISF	Investigator Site File
ITT	Intention to Treat
LDL	Low-density lipoprotein
LFT	Liver Function Tests
LIPID	Long-Term Intervention with Pravastatin in Ischemic Disease
LLETZ	Large Loop Excision of Transformation Zone
MBL	Mannose Binding Lectin
MHRA	Medicines and Healthcare Products Regulatory Agency
MI	Myocardial Infarction
MRC	Medical Research Council
MSU	Mid-Stream Urine
NICE	National Institute for Health and Care Excellence
NICU	Neonatal Intensive Care Unit
NIHR CRN	National Institute of Health Research Clinical Research Networks
NMR	Nuclear magnetic resonance
PARCA-R	Parent Report of Children's Abilities-Revised
PI	Principal Investigator
PIS	Participant Information Sheet
PND	Postnatal Days
PPI	Patient and Public Involvement
PPROM	Preterm Pre-labour Rupture of Membranes
PTB	Preterm Birth
PTBPC	Preterm Birth Prevention Clinics
QALY	Quality Adjusted Life Years
QP	Qualified Person

QRI	QuinteT Recruitment Intervention
RCT	Randomised Control Trial
RDSF	Research Data Facility Storage
REC	Research Ethics Committee
ROCK	Rho-associated protein kinase
RRR	Relative Risk Reduction
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SEAR	Screened, Eligible, Approached to take part, Randomised
SBLCB	Saving Babies' Lives Care Bundle
SBLCBV3	Saving Babies' Lives Care Bundle Version 3
SFH	Symphysis Fundal Height
SLA	Service Level Agreement
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SSAR	Suspected Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
UHBW	University Hospitals Bristol and Weston NHS Foundation Trust
UKPTBCN	UK Preterm Birth Clinical Network
ULN	Upper Limit of Normal
USM	Urgent Safety Measures
VLDL	Very-low-density lipoprotein
WOSCOPS	West of Scotland Coronary Prevention Study

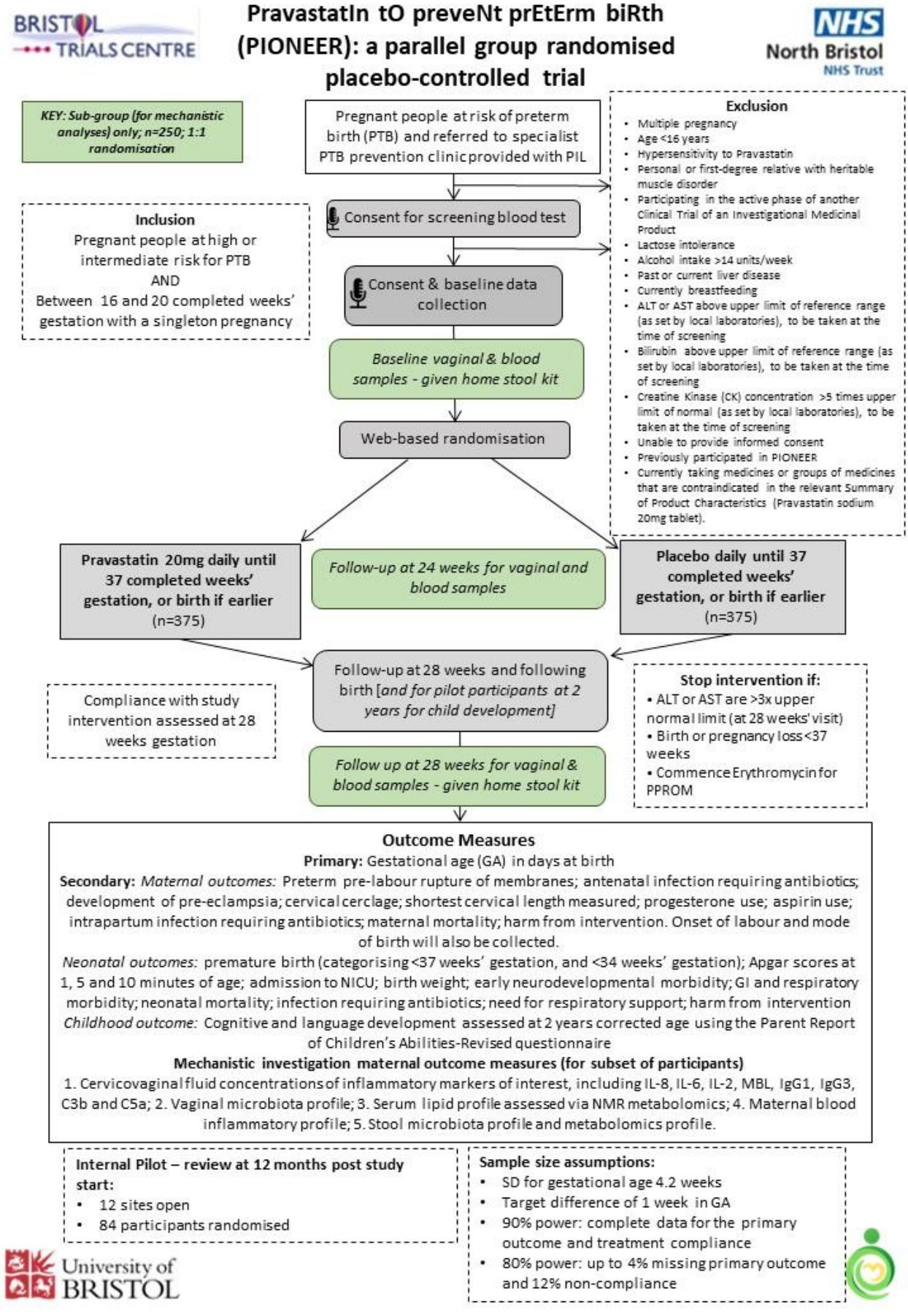
TRIAL SUMMARY

Trial Title	Pravastatin to prevent preterm birth: a parallel group randomised placebo-controlled trial
Short title	PIONEER
Chief Investigator	Dr Katherine Birchenall
Sponsor	University Hospitals Bristol and Weston NHS Foundation Trust
Funder	NIHR Efficacy and Mechanism Evaluation
Trial Design	Multi-site parallel group placebo-controlled RCT with blinding and an internal pilot, with integrated monitoring and feedback to maximise recruitment and adherence to trial medication, and an embedded mechanistic investigation, and embedded QuinteT Recruitment Intervention (QRI)
Trial Participants	Pregnant people referred to preterm birth (PTB) prevention clinics (PTBPC) across the UK, having been identified as being at intermediate or high risk for preterm birth according to the NHS England Saving Babies Lives Care Bundle Version 3 (SBLCBV3)[1]
Sample size	750
Number of trial sites	25
Intervention	20mg Pravastatin taken orally once daily
Treatment duration	Commenced between 16^{+0} and 20^{+0} weeks' gestation, until 37^{+0} weeks' gestation (maximum duration 21 weeks). Treatment may complete earlier for the following reasons: birth or pregnancy loss before 37^{+0}; commencement of Erythromycin for Preterm Prelabour Rupture of Membranes (PPROM); or if maternal liver transaminase (Alanine Transaminase (ALT) or Aspartate Aminotransferase (AST)) measurement at 28^{+0} weeks is over three times the locally-set upper limit of normal.
Inclusion criteria	Pregnant people with a singleton pregnancy at high or intermediate risk for PTB according to the Element 5 criteria as detailed in the NHS England SBLCBV3[1], where: • High risk factors are previous mid-trimester loss >16weeks' gestation; previous PTB <34 weeks' gestation; previous PPROM <34 weeks' gestation; previous use of cervical cerclage; known uterine structural variant, intrauterine adhesions, and history of trachelectomy. • Intermediate risk factors are previous birth by caesarean section at full dilatation and history of significant excision of abnormal cervical cells (i.e., Large Loop Excision of the Transformation Zone (LLETZ) where >15mm depth removed or >1 LLETZ procedure carried out, or cone biopsy performed).
Exclusion criteria	Multiple pregnancy; under 16 years of age at randomisation; hypersensitivity to Pravastatin (active substance or any of the excipients); personal or first-degree relative with heritable muscle disorder; participating in the active phase of another Clinical Trial of an Investigational Medicinal Product (CTIMP); lactose intolerance; drinking over 14-units of alcohol per week; past or current liver disease; ALT or AST above upper limit of normal at screening (as set by local

	laboratories); Bilirubin above upper limit of normal at screening (as set by local laboratories); Creatine Kinase (CK) concentration >5 times upper limit of normal at screening (as set by local laboratories); currently breastfeeding; unable to provide informed consent; previously participated in PIONEER; currently taking medicines or groups of medicines that are contraindicated for concomitant use with pravastatin.
Primary objective	To evaluate the efficacy of Pravastatin versus placebo, administered from between 16^{+0} and 20^{+0} weeks' gestation until 37^{+0} weeks' gestation (or until birth, or commencement of Erythromycin for PPROM, or if maternal liver transaminase level (ALT or AST) at 28^{+0} weeks is above three times the upper limit of normal, whichever occurs sooner) in reducing PTB in pregnant people identified as being at intermediate or high risk of PTB according the SBLCBV3[1].
Primary outcome	Difference between groups in mean gestational age (GA) in days at birth
Secondary outcomes	1. To estimate the difference between groups with respect to those outcomes defined in the core outcome set for evaluation of interventions to prevent PTB[3]: • Maternal secondary outcomes: maternal mortality; antenatal infection requiring antibiotics; intrapartum infection requiring antibiotics; development of pre-eclampsia; PPROM; harm to mother from intervention; cervical cerclage; progesterone use; shortest cervical length measured. Onset of labour and mode of birth will also be collected. • Neonatal: premature birth (categorising <37 weeks' gestation, and <34 weeks' gestation. Apgar scores at 1, 5, and 10 minutes of age; admission to Neonatal Intensive Care Unit (NICU); birthweight; early neurodevelopmental morbidity; gastrointestinal and respiratory morbidity; neonatal mortality; infection requiring antibiotics; need for respiratory support; harm to offspring from intervention. 2. *For the mechanistic sub-study participants only,* to investigate the mechanism or mechanisms via which Pravastatin may prevent PTB by assessing: • The maternal cervicovaginal and blood inflammatory profile, including assessment of: o Cervicovaginal fluid concentrations of Interleukin (IL)-8, IL-6, IL-2, Mannose Binding Lectin (MBL), IgG1, IgG3, C3b and C5a. • The maternal vaginal and gut microbiota, including assessment of: o Vaginal microbiota profile o Stool microbiota profile and metabolomics. • The maternal serum lipid profile: very-low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), low-density lipoprotein (LDL) and high-density lipoprotein (HDL), assessed using nuclear magnetic resonance (NMR) metabolomics. 3. *For the offspring of pregnancies for those participants recruited during the first 18 months of the trial only,* childhood outcome assessment of cognitive and language development at 2 years corrected age using the Parent Report of Children's Abilities-Revised

	(PARCA-R) questionnaire (late neurodevelopmental morbidity assessment)[4].
Internal pilot	Review after 12 months of participant recruitment: Projected that 12 sites will be recruiting with 84 participants recruited

TRIAL FLOWCHART



1. BACKGROUND AND RATIONALE

1.1 Evidence explaining why this research is needed now

Health problem to be addressed

Preterm birth (PTB) is birth before 37 completed weeks' gestation[5]. While infection is implicated in some cases, for many no cause is found and management options are limited[6]. Globally, in 2019 it is estimated that one million babies died due to PTB complications, comprising 16% of deaths in under-fives[5 7-10]. The rate of PTB has not changed over recent decades in England and Wales, affecting 7.4% of livebirths in 2020[11].

Impact on families and health and care services

This matters as, in the year to March 2020, of the 2,102 infants who died before their first birthday in England, 69% were born preterm. Risk for poor neonatal outcome is inversely proportional to gestational age (GA) at birth[9], and approximately 35% of babies born preterm are diagnosed with cerebral palsy[12 13], with an incidence in those born <28 weeks of 82.3 per 1000 live births[12], compared with 2-3.5 per 1000 live births in the UK overall[13]. There is socio-economic inequality in the distribution of PTB, where those in the most deprived decile by income are twice as likely to have a PTB as those in the least deprived decile[14]. PTB can have a significant personal cost to affected families, and the monetary cost to the UK public sector of PTB during the first 18 years of life (2006 prices) is estimated at £2.946 billion per year[15]. The national Maternity Safety Ambition aims to reduce PTB to 6% of livebirths by 2025[14 16].

Care for pregnant people at risk of PTB varies across the NHS[17], with limited treatment options. The NHS England SBLCBV3[1] recommends that all pregnant people are screened for PTB risk before 12 weeks' gestation. Those identified to be at high or intermediate risk of PTB are referred to specialist PTB prevention clinics (PTBPC) for secondary screening[16 18 19]. Progesterone and/or cervical cerclage are offered to pregnant people with both a history of spontaneous pregnancy loss >16 and <34 weeks' gestation and a short cervix (cervical length ≤25 mm), or Progesterone alone if only one factor[5]. The National Institute for Health and Care Excellence (NICE) recommends that Aspirin reduces the risk of pregnancy complications that are related to placental dysfunction, particularly pre-eclampsia[1]. Aspirin reduces the risk of PTB associated with pre-eclampsia and may reduce spontaneous PTB <34 weeks' gestation[20]. NHS England states the importance of identifying whether placental dysfunction was a contributory factor for pregnant people with a history of PTB, to recommend Aspirin for those at high risk of pre-eclampsia, and to consider Aspirin for those with two or more moderate risk factors for pre-eclampsia. High risk factors for pre-eclampsia include hypertensive disease in previous pregnancy, chronic kidney disease, autoimmune disease, Type 1 or 2 diabetes, chronic hypertension, and placental histological confirmation of placental dysfunction in a previous pregnancy; moderate risk factors are first pregnancy, age 40 years or older, pregnancy interval of more than ten years, BMI of 35kg/m^2 or higher at booking, family history of pre-eclampsia in a first degree relative, and multiple pregnancy[1]. In a recent individual participant data meta-analysis (3,769 women), vaginal Progesterone reduced risk of PTB <34 weeks' gestation by 22% (RR 0.78,95%CI 0.68-0.90), with greater efficacy for women with a cervical length <25mm and no benefit in twin pregnancies[21]. Cervical cerclage has been shown to reduce PTB risk by 23% (RR 0.77,95%CI 0.97-1.06), however cervical cerclage is an invasive procedure with risk of PPROM, miscarriage and PTB[22]. Importantly, most pregnant people who experience PTB do not have a history of a short cervix, with estimates that only 0.85% have a cervical length <20mm[23 24]. To improve outcomes and reduce health service costs associated with PTB, there is need for new preventative options. Ideally these options will be effective in women with a "normal" cervical length and will enhance the efficacy of progesterone and cervical cerclage for women with a short cervix.

Historically, pregnant people have been excluded from clinical trials, limiting data on drug safety and efficacy in pregnancy. Repurposing appropriate medications could improve management options[25 26]. PIONEER will evaluate whether the statin Pravastatin can be repurposed for PTB prevention[27 28]. Further, if PIONEER establishes that Pravastatin has efficacy for reducing PTB risk in singleton pregnancies, we intend to continue this research to investigate its efficacy in multiple pregnancies, as this is another historically underserved population.

Review of existing evidence and how this research will fill an evidence gap

Statins have previously been avoided in pregnancy as animal studies and retrospective case reports indicated possible fetal toxicity[29-32]. However, this has since been refuted[31 33], and in 2021 the USA Food and Drug Association removed the Pregnancy Category X label for statins[34]. A cohort study including 1,152 pregnant women who took a statin during the first trimester showed no teratogenic effect[35], a finding supported by subsequent systematic reviews and meta-analyses (n=1,673[36];2,361[37];1,579[38];618[31];469[39]). Importantly, Pravastatin is hydrophilic (hydrophilic compounds cross the placenta less easily than lipophilic compounds) and has no reported fetal malformations associated with its use[32]. Its safety profile in pregnancy is enhanced by its recent use in randomised controlled trials (RCT) for prevention and treatment of pre-eclampsia [40-43] and antiphospholipid syndrome [44], with no safety concerns (n=1303).

A systematic literature review was performed using search terms ("preterm labour" OR "preterm birth") AND ("Pravastatin" OR "statin") in MEDLINE, EMBASE, and on ClinicalTrials.gov. There are no published or ongoing registered clinical trials for the prevention of PTB with Pravastatin in humans. We conducted the Pravastatin for the treatment of PTB (PIPIN) study, to ascertain the feasibility of conducting a RCT comparing Pravastatin with placebo for treatment of PTB, in women in threatened preterm labour between 24^{+0} and 35^{+6} weeks' gestation. Women were willing to take Pravastatin for treatment of PTB, however many eligible women birthed before they were randomised. There were no safety concerns. It was concluded that a prevention trial is likely more feasible than a treatment trial [45]. Three RCTs compared Pravastatin with placebo for management of pre-eclampsia and included PTB as a secondary outcome. All found Pravastatin increased GA at birth (PTB rate 10% Pravastatin vs 50% control (p>0.05), n=20[40]; hazard ratio Pravastatin vs placebo 0.84 (95%CI 0.50-1.40; p=0.6), n=62[42]; PTB rate 16% Pravastatin vs 36% control (p=0.048), n=80[43])) with no safety concerns. A non-randomised study compared Pravastatin vs no Pravastatin in 21 women with antiphospholipid syndrome: all in the no-Pravastatin group birthed preterm, whereas all in the Pravastatin group birthed close to term (median birth GA difference 13 weeks (IQR 10-15)), with no safety concerns[44].

Mechanisms of action hypotheses

We hypothesise that Pravastatin will reduce PTB risk for those at intermediate or high risk via one or more of the following mechanisms:

1. Directly modifying maternal inflammatory pathways
2. Indirectly modifying maternal vaginal and gut microbiota
3. Directly modifying maternal lipid profiles and reducing dyslipidaemia
4. Directly affecting smooth muscle contraction (we will not be investigating mechanism 4 in this trial).

Simvastatin reduces PTB in animal models, with anti-inflammatory effects[27 28]. Early activation of inflammatory pathways associated with spontaneous PTB is related to ascending bacterial infection from the vagina. Specifically, depletion of vaginal *Lactobacillus* is associated with increased risk for spontaneous PTB and PPROM[46-50]. In a recent immunophenotyping study of 133 women at high-risk of spontaneous PTB, we showed cervicovaginal concentrations of inflammatory cytokines IL-8, IL-6, and IL-2 significantly increased between two time points (12^{+0}-16^{+6} and 20^{+0}-24^{+6} weeks' gestation) in women who went on to have PTB. These women also displayed complement cascade pathway activation, characterised by increased mannose binding lectin (MBL), C3b and C5a, and activation of the adaptive immune response characterized by increased cervicovaginal fluid IgG1 and IgG3. Further, increased IL-8, IL-6, IL-1β, MBL, IgG1, IgG3, C3 and C5a, and lower IL-10, were significantly associated with a *Lactobacillus* species depleted vaginal microbiota. This supports a mechanism for PTB whereby inflammatory pathways of labour are activated prematurely via host-microbial driven inflammation activating the innate and adaptive immune response[51]. Depletion of vaginal *Lactobacillus* species is associated with Bacterial Vaginosis[52]. Bacterial Vaginosis is also associated with PTB, and often characterised by *Gardnerella vaginalis* dominance, which produces vaginolysin, a cholesterol-dependent cytolysis protein. Vaginolysin associates with cholesterol in host cell plasma membranes, forming large oligomeric pores, lysis of erythrocytes, and activation of epithelial cell inflammatory pathways[53-55]. Statin therapy is associated with reduced levels of vaginal *G.*

vaginalis and increased relative abundance of *Lactobacillus crispatus*[53], alongside reduced gut microbiota dysbiosis and associated systemic inflammation[56].

Statins are widely used to lower risk for cardiovascular disease via inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A reductase, which reduces serum low-density-lipoprotein (LDL)-cholesterol and increases protective high-density-lipoprotein (HDL)-cholesterol concentrations[57-61]. Maternal dyslipidaemia, where there is increased LDL and decreased HDL, is associated with PTB[62-64]. For example, in the USA, maternal dyslipidaemia was associated with a 49% increased odds for PTB after adjustment for key confounders (95% CI 1.39-1.59)[62]; likewise, in a study of 7,440 pregnant participants of the Born-in-Bradford cohort by our group, maternal dyslipidaemia in the second trimester was associated with a shorter GA at birth[65]. Resolution of maternal dyslipidaemia could therefore reduce PTB.

Statins also improve endothelial function independently of the LDL-lowering properties[66 67], and Simvastatin reduces PTB in animal models, with anti-inflammatory effects[27 28]. In human myometrial cells, Simvastatin treatment reduces proinflammatory mediator mRNA and protein expression, increases anti-inflammatory cytokine mRNA expression, and reduces cell contraction via inhibition of the Rho/ROCK pathway[27].

2. RESEARCH QUESTIONS, OBJECTIVES AND OUTCOMES

2.1 Research questions

1. Is Pravastatin better than placebo at extending the gestational length of pregnancy?
2. If so, does Pravastatin have this effect through changes to the maternal cervico-vaginal and blood inflammatory profiles, vaginal and gut microbiota, and/or serum lipids?

2.2 Primary objective

To evaluate the efficacy of Pravastatin versus placebo, administered from the second trimester of pregnancy until 37^{+0} weeks' gestation (or until birth, or if Erythromycin is commenced for PPROM, or if maternal ALT/AST is over 3 times the upper limit of normal (measured at 28^{+0} weeks' gestation), whichever occurs sooner), in reducing PTB in pregnant people identified as being at intermediate or high risk of PTB.

2.3 Secondary objectives

A) To estimate the difference between groups with respect to a range of secondary outcomes, as defined in the core outcome set developed for evaluation of interventions to prevent PTB[3]. Onset of labour and mode of birth will also be collected.

B) For mechanistic sub-study participants only, to investigate the mechanisms via which Pravastatin may prevent PTB by assessing the effect of Pravastatin vs placebo on the maternal:

- Cervicovaginal and blood inflammatory profile
- Vaginal and gut microbiota
- Stool metabolomics profile
- Serum lipid profile

C) For the offspring of pregnancies for those participants recruited during the first 18 months of the trial only, to investigate any differences between groups in cognitive and language development of offspring at 2 years corrected age (late neurodevelopmental morbidity assessment).

2.4 Primary outcome

GA in days at birth, obtained from clinical databases.

2.5 Secondary outcomes

A) Secondary maternal and neonatal outcomes will be collected from participant's maternity health records and will include:

- Maternal secondary outcomes: maternal mortality; antenatal infection requiring antibiotics; intrapartum infection requiring antibiotics; development of pre-eclampsia; PPROM; harm to mother from intervention; cervical cerclage; progesterone use; shortest cervical length measured. Onset of labour and mode of birth will also be collected.
- Neonatal secondary outcomes: premature birth (categorising <37 weeks' gestation, and <34 weeks' gestation); Apgar scores at 1, 5, and 10 minutes of age; admission to Neonatal Intensive Care Unit (NICU); birthweight; early neurodevelopmental morbidity; gastrointestinal and respiratory morbidity; neonatal mortality; infection requiring antibiotics; need for respiratory support; harm to offspring from intervention.

B) For mechanistic sub-study participants only, further mechanistic studies will be performed to assess maternal:

1. Cervicovaginal fluid concentrations of inflammatory markers of interest, including IL-8, IL-6, IL-2, MBL, IgG1, IgG3, C3b and C5a
2. Vaginal microbiota profile
3. Serum lipid profile: very-low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), low-density lipoprotein (LDL) and high-density lipoprotein (HDL) assessed via NMR metabolomics
4. Maternal blood inflammatory profile
5. Stool microbiota profile and metabolomics profile

Samples for 1-4 will be obtained at baseline, 24^{+0}- and 28^{+0}-weeks' gestation. Samples for 5 will be obtained at baseline and 28^{+0} weeks' gestation.

C) *For the offspring of pregnancies for those participants recruited during the first 18 months of the trial only,* assessment of cognitive and language development at 2 years of corrected age using the Parent Report of Children's Abilities-Revised (PARCA-R) questionnaire (late neurodevelopmental morbidity assessment)[4].

3. TRIAL DESIGN AND SETTING

3.1 Clinical Trial of an Investigational Medicinal Product

PIONEER is a Type B Clinical Trial of an Investigational Medicinal Product (CTIMP). As this trial involves a licensed medicinal product being used for a new indication, the risk to participants is *somewhat higher* than that of standard medical care.

3.2 Internal pilot

The first 12 months of participant recruitment will constitute an internal pilot, with the criteria and thresholds for progression shown in Table 1.

Table 1: Internal pilot assessment criteria

Progression Criteria	Green	Amber	Red
Number of sites open	12	6-11	≤5
Participants recruited	84	31-83	<30

If we achieve Green for the progression criteria, the trial will continue to the main recruitment phase with minimal modifications. If any of the criteria are in the Amber or Red zones, the Trial Management Group (TMG) will consider remediable issues and, if supported by the Trial Steering Committee (TSC) and funder, the trial will proceed with regular monitoring. In the event of an intractable issue arising that cannot be remedied, the trial will be terminated.

We will also monitor IMP adherence and blinding during the internal pilot.

3.3 Trial setting

Preterm Birth Prevention (PTBP) clinics across the UK, as described in the SBLCBV3[1] as the clinic to which those who are identified as being at intermediate or high risk for PTB should be referred to by 12 weeks' gestation (may also be termed PTB clinic)[1].

4. ELIGIBILITY CRITERIA

4.1 Trial population

Pregnant people referred to PTBP clinics across the UK, having been identified as being at intermediate or high risk for PTB.

4.2 Inclusion criteria

1. Pregnant people with a singleton pregnancy identified as being at high or intermediate risk for PTB according to criteria detailed in the SBLCBV3[1] (see Appendix 1), defined for trial purposes as:
   - High risk - at least of one of the following:
     - previous mid-trimester loss >16^{+0} weeks' gestation;
     - previous PTB <34^{+0} weeks' gestation;
     - previous PPROM <34^{+0} weeks' gestation;
     - previous use of cervical cerclage;
     - known uterine structural variant;
     - intrauterine adhesions;
     - history of trachelectomy (for cervical cancer).

OR

   - Intermediate risk - at least of one of the following:
     - previous birth by caesarean section at full dilatation;
     - history of significant excision of cervical cells (e.g., LLETZ where >15mm depth removed, or >1 LLETZ procedure carried out or cone biopsy)[1].
2. Between 16^{+0} and 20^{+0} weeks' gestation at randomisation.

4.3 Exclusion criteria

1. Multiple pregnancy.
2. <16 years of age.
3. Hypersensitivity to Pravastatin (active substance or any of the excipients).
4. Personal or first-degree relative with heritable muscle disorder.
5. Participating in the active phase of another CTIMP.
6. Lactose intolerance.
7. >14 units alcohol/week.
8. Past/current liver disease.
9. ALT or AST above upper limit of normal (as set by local laboratories), to be taken at the time of screening.*
10. Bilirubin above upper limit of normal (as set by local laboratories), to be taken at the time of screening.*
11. Creatine Kinase (CK) concentration >5 times upper limit of normal (as set by local laboratories), to be taken at the time of screening.
12. Currently breastfeeding.
13. Unable to provide informed consent.
14. Previously participated in PIONEER.
15. Currently taking medicines or groups of medicines that are contraindicated for concomitant use with pravastatin[2] (see sections 5.16)[§]

* It is acknowledged that the Liver Function Test may include different assessments at different sites, therefore for the purpose of the screening blood test, the term "Liver Function Test" at screening should include measurement of Bilirubin and at least one of ALT or AST. If any of these are above the upper limit of the normal, the person would not be eligible for inclusion in PIONEER, and should have ongoing follow-up according to local policy.

§ Those taking macrolides should be excluded from PIONEER, however, if a limited course of macrolides are prescribed with the course due to complete prior to 20^{+0} weeks' gestation, then it may be possible to recruit to PIONEER following completion of the course of antibiotics (if completion of the course of antibiotics is prior to 20^{+0}).

4.4 Co-enrolment in other research studies

If potential participants are enrolled in other studies or clinical trials, due care will be paid as to the burdens of co-enrolment in this trial. Co-enrolment (including interventional studies) will be considered on a case-by-case basis, taking into consideration other factors such as mechanism of action of intervention, comorbidities, social support and distances necessary to travel.

Participants taking part in the interventional (active) phase of another CTIMP cannot be co-enrolled in this trial.

5. TRIAL PROCEDURES

5.1 Recruitment of participating sites

There are over 70 specialist PTBP clinics across the UK and we intend to recruit from at least 25 of these sites. The initial focus will be on sites linked to trial collaborators. Additional PTBP clinics will be recruited via links with the UK PTB Clinical Network and NIHR Clinical Research Networks.

5.2 Trial advertising

Participating PTBP clinics will display posters in waiting rooms and may put information about the trial on their local Trust websites. Other hospital sites within participating Trusts may also display posters in relevant areas. The trial may also be advertised via local media.

The trial website will contain the participant information documentation for the trial and contact details. A short video, based on the participant information documents, will also be produced. A trial X (formerly Twitter) account, and potentially other social media accounts, will raise awareness and will be for information purposes only.

We may also engage with relevant national and local charities and maternity groups to raise awareness of the trial.

5.3 Screening and identification of participants

Recruitment will be embedded in participating PTBP clinics. Pregnant people referred to PTBP clinics before 20^{+0} weeks' gestation, having been identified as being at high or intermediate risk for PTB, will be approached to take part in the trial. The initial approach will be provision of the Participant Information Sheet (PIS), sent ahead of the first PTBP clinic appointment. The direct clinical care team (at the participating site) will identify the person's preferred language from their booking information (if available) and will provide the PIS in this language if it is recorded in their booking information that their understanding of English is limited. The direct clinical care team may also call pregnant people who have been sent the invitation letter and PIS to confirm they have received this, to ask whether they have any questions and whether they would be happy to discuss the trial further at their first clinic visit. In some cases, if the participant has not received the PIS prior to the first clinic appointment, the PIS may be given during the first PTBP clinic appointment. This is possible as the full consent is not taken until the results of baseline blood tests are available (which would be over 24 hours from this first meeting); in such cases, consideration would be given as to whether potential participants had enough time to consider participation.

The initial discussion about the trial will take place when potentially eligible pregnant people attend their first PTBP clinic appointment. A member of the research team will ask whether they would like further information about the trial and whether they would be interested in taking part. For those for whom English is limited, a telephone interpreter will be offered. Any questions will then be answered.

5.4 Inclusivity

A key ambition of PIONEER is to make participation as inclusive as possible, ensuring equitable access to the UK pregnant population at intermediate or high risk of PTB, including those from under-served groups, those underrepresented in medical research, those whose first language is not English, and those from lower socioeconomic groups (Section 6.1b10.2)b). Strategies to achieve this include provision of translation services and participant materials in a range of languages for those who are less able to communicate using the English language. During the internal pilot, we will attempt to establish the need for translation of trial specific materials for use during the main phase of the trial. In this trial, being unable to speak or understand the English language is not an exclusion criteria. Further strategies to reduce barriers include provision of funding for travel and childcare costs and recruiting from sites across the whole of the UK,

including sites which may not have significant research infrastructure at present. Additional examples of inclusivity are outlined throughout this protocol (and other trial-related documents and delivery), and include consideration for key factors such as (but not limited to) social and economic factors.

In order to monitor for equality, diversity, and inclusivity of the PIONEER recruitment process, anonymised demographics will be collected on all participants screened, identified as eligible, approached, and recruited, including potential participants excluded at each stage with reasons why (see Section 6.1b10.2).

5.5 Consent

Potential participants who are interested in taking part will be asked to complete a two-stage consent process. Telephone interpretation services will be used throughout if preferred by the potential participant. Eligibility will be confirmed by, and consent received by, staff who are named on the trial delegation log with appropriately delegated tasks. Following consent, baseline data will be collected for all participants, both from direct questioning of the participant and via medical records. The participant will then be randomised and allocated their first batch of tablets (to last until 28^{+0} weeks gestation).

Stage 1 consent

ELIGIBILITY BLOOD TEST CONSENT: At the first PTBP clinic appointment (Visit 1), a partial eligibility assessment will be completed by a member of the research team. The potential participant will be asked to provide consent for screening blood samples to be taken (Liver Function Tests (LFTs) and CK concentration), to confirm full eligibility.

QRI CONSENT: Potential participants may also be invited to agree to an audio-recording of all discussions about the trial being made, for staff training and development (embedded QuinteT Recruitment Intervention - QRI, section 6.1), and invited to consent to being contacted to take part in a qualitative interview. Potential participants can give spoken or written consent to the QRI audio recording, and written consent to take part in an interview, using the specific QRI-Information Study Participant Consent form, which is independent of the consent provided for the PIONEER trial. If QRI consent has not been received at Stage 1, it should be sought at the start of Stage 2 discussions.

Stage 2 consent

CONSENT TO PIONEER: An appointment (Visit 2), either in-person or via telephone (eConsent), will be made to speak to the potential participant again once eligibility has been confirmed with the results of the screening blood tests and information obtained from the record review by a medically qualified doctor. Ideally this appointment will be within five working days of the first appointment to ensure participants are randomised within the window of 16^{+0} to 20^{+0} weeks. Potential participants will be informed that, should the screening blood tests be abnormal, a member of the research team will contact them to discuss this and cancel the research appointment, and that their clinical care team will be informed of the results and be asked to follow-up and/or make referrals via the relevant pre-existing local clinical pathways for abnormal LFTs and/or CK in pregnancy.

QRI consent may be obtained at the start of the Stage 2 consent appointment, as detailed above.

Stage 2 in-person consent (may be audio recorded if QRI consent to audio-recording is obtained at stage 1 or at the start of to Stage 2 discussion):

A member of the research team will meet the potential participant to:

a) confirm ongoing interest in taking part in the trial;
b) answer any questions;
c) confirm full eligibility (including review of screening blood tests) has been completed by a medically qualified doctor;
d) and receive the second part of consent to the full trial.

Stage 2 remote consent (eConsent) (may be audio recorded if QRI consent to audio-recording is obtained in Stage 1 or at the start of Stage 2 discussion):

Prior to the telephone appointment for eConsent, a medically qualified doctor will complete a full eligibility assessment of the potential participant, including review of screening blood tests and information obtained from the record review. The outcome of the eligibility assessment will be recorded; as above, if the potential participant is found to be ineligible, a member of the research team will contact them to cancel the scheduled telephone appointment.

Eligible participants will be contacted via telephone, as agreed, to complete eConsent. During this process, the participant will be emailed a hyperlink to an online survey on the REDCap database which contains the main PIONEER consent form which the participant completes (and, if not completed at Stage 1, the QRI written consent form). This information will be entered directly into the trial database. Once completed, a copy of the fully signed consent form(s) will be emailed to the participant via the database.

A member of the research team at the site will:

a) confirm ongoing interest in taking part in the trial;
b) answer any questions;
c) and receive the second part of consent to the full trial.

Participants who have provided eConsent will subsequently be required to attend the recruiting site to collect trial medication (Section 5.8) and, if these participants are also at a site which is part of the mechanistic sub-study (Section 5.9), have the relevant samples collected.

5.6 Randomisation

Participants will only be randomised after confirmation of eligibility and receipt of informed consent. Randomisation will take place using a secure web-based randomisation platform. Participants will be randomised in a 1:1 ratio to receive Pravastatin (intervention) or placebo.

Randomisation will be stratified by site and minimised by history of previous PTB (previous PTB $<34^{+0}$ weeks' gestation: yes vs no). Participants will be stratified by site to ensure that there are equal numbers of participants in each arm at the different sites throughout the country, as these will likely serve different populations, and to ensure that the results are as generalisable to the general population of the UK as possible. Randomisation will be minimised by history of previous PTB $<34^{+0}$ weeks' gestation, as this history is the greatest known risk factor for PTB. Imbalance of these characteristics between arms could otherwise introduce bias.

The randomisation procedure will involve a delegated member of the research team signing into the trial database and entering information regarding the relevant stratification and minimisation variables. Randomisation will take place using Sealed Envelope and the outcome returned to the trial database (access restricted to maintain blinding). The trial allocation (Pravastatin or placebo) will be shared with the local pharmacy.

In the rare event that the trial database and/or Sealed Envelope randomisation system is not available, investigators can contact the Bristol Trials Centre (BTC) central coordination team to perform a manual randomisation. Manual randomisations will be added to the randomisation system as soon as it becomes available.

The Sponsor trial pharmacy will be responsible for providing emergency unblinding (see 5.12). The BTC will be responsible for providing a non-emergency unblinding service during usual office hours (see 5.13).

The participant's GP will be informed that they are taking part in the PIONEER trial, and a request will be made for the participant's participation in PIONEER to be recorded as an alert on their maternity record, including that they may be taking Pravastatin during the intervention period.

The trial does not make any other changes to the clinical care of participants, who should receive the same individualised antenatal and postnatal care at their participating site as they would if they were not taking part in PIONEER.

5.7 Prescription of IMP

The delegated prescriber will be a doctor on the trial delegation log. After reviewing the eligibility criteria on the screening form to satisfy that they have been met, they will prescribe the first batch (two bottles) of trial medication using a trial-specific prescription to initiate the dispensing process.

Alternatively, if the prescriber believes that eligibility criteria has not been met and that prescriptions cannot commence, a member of the research team will notify the individual that it is not suitable for them to take part in the trial and update records, as required.

Prior to the 28^{+0} weeks' gestation visit, the delegated prescriber must review the participants medical records to confirm eligibility for the participants' ongoing participation in PIONEER. If confirmed, they will prescribe the second batch (one bottle) of trial medication using a trial-specific prescription to initiate the dispensing process. If the clinician believes that the participant should not continue to receive trial medication, they will indicate this on the database and the second batch of trial medication will not be prescribed.

If any serious concerns relating to side effects, or other serious safety concerns, are identified during the 28^{+0}-week trial visit, the researcher undertaking the visit should raise this immediately with the delegated clinician and ask for review, prior to provision of the trial medication.

5.8 Dispensing timepoints

At the time of randomisation, participants will be allocated their first batch (two bottles) of tablets to last until 28^{+0} weeks gestation.

At 28^{+0} weeks' gestation, all participants will return to collect their next batch of tablets (one bottle), to last until a maximum of 37^{+0} weeks' gestation. Participants will be asked to bring with them their remaining first batch of tablets so that the research team can perform a pill count to assess compliance. This pill count must be completed in front of the participant and the researcher must wear gloves for hygiene purposes. Leftover tablets from the first batch of tablets will be returned to the participant with the second batch, to ensure that the participants has enough tablets to last until 37^{+0} weeks. If participants forget to bring their remaining first batch of tablets to the 28 week visit, the pill count can be completed over the telephone after the visit. All participants will also complete a side effects questionnaire at this visit. If any concerns are raised from this questionnaire, participants should be referred for review by a medically qualified doctor to assess whether they can continue to take the trial medication.

5.9 Mechanistic sub-study

In a subset of 250 participants (125 in each arm) recruited from eight sites, further assessments will be performed to investigate the mechanism of action of Pravastatin.

Following receipt of Stage 2 consent, participants in the mechanistic sub-study will have three mid-vaginal swabs and three blood samples obtained by a member of the research team. Participants will also be provided with a box containing the necessary equipment and instructions to collect two stool samples (two samples from one defaecation) at home. This will include a stamped-addressed package in which to send the samples directly to Imperial College London for analysis.

Participants in the mechanistic sub-study will have an additional research visit at 24^{+0} weeks' gestation, during which a further three mid-vaginal swabs and three blood samples will be obtained by a member of the research team.

During the planned research visit at 28^{+0} weeks' gestation, participants in the mechanistic sub-study will have the final three mid-vaginal swabs and three blood samples obtained by a member of the research

team. Participants will also be provided with a box containing the necessary equipment for a further two stool samples (from one defaecation) to be collected at home and posted by the participants directly to Imperial College London for analysis.

At all timepoints, the three blood samples will be collected from one venepuncture: 1x lithium heparin plasma, 1x Ethylenediamine tetraacetic acid (EDTA) plasma and 1x red top serum; and the three vaginal swabs will be collected at the same time (held closely together) without need for a speculum.

5.10 Emergency contact procedure for participants

Details of what a participant should do if they experience any problems or side effects whilst taking part in the trial is detailed in a Participant Information Sheet (PIS).

If a participant experiences symptoms that are troublesome or serious, they are advised to seek medical help in the normal way, for example via 111, their GP, maternity hospital, or in an emergency via 999 or attendance at an Emergency Department. The trial team will only advise a participant on action to take with respect to the IMP and will not provide any other medical advice.

Participants will be provided with a card to carry on their person and instructed to show to any relevant medical professionals they encounter, informing them that they are taking part in the trial and potentially taking Pravastatin. Participants' handheld maternity notes and/or digital maternity notes held on local databases will have clear alerts to indicate that they are participating in a CTIMP and potentially taking Pravastatin. The alert will also indicate that participants should not take macrolides (including Erythromycin) and trial medication at the same time, and specifically that the trial medication should be stopped if Erythromycin is commenced for PPROM (the trial medication would not be restarted in such an event).

In the event of a medical emergency a UHBW (Sponsor) pharmacist will be available, 24 hour a day during the trial period to provide emergency unblinding (see 5.13).

5.11 Schedule of assessments

Table 2 provides a summary of trial assessments.

Participants recruited during the first 18 months of the recruitment period will be asked to complete the Parent Report of Children's Abilities-Revised (PARCA-R) questionnaire at 2 years' corrected age of their offspring. Prior to attempting this contact with these participants, the research team will use hospital records to check for infant or maternal mortality, and would not proceed with contact should either of these events have occurred. Questionnaires will be administered by the local research teams and can be completed via email, post, or telephone.

Table 2: Schedule of assessments

	Timepoint						
Assessment	First PTBP clinic attendance	Baseline (between 16^{+0} and 20^{+0} weeks gestation)	24^{+0} weeks' (+/- 1 week)	28^{+0} weeks' gestation (+/- 1 week)	Birth / loss of pregnancy	6-12 weeks' postnatal	2 years post-natal
Approach and partial eligibility assessment	●						
Consent for screening bloods: Liver Function Test (LFT) and Creatine Kinase (CK)	●						
Full eligibility assessment and trial consent		●					
Baseline characteristics		●					
Randomisation		●					
Dispensing of tablets		●		●			
Vaginal swabs		*	*	*			
Blood samples		*	*	*			
Stool samples (postal kit, collected at home)		*		*			
Side effects questionnaire				●			
IMP compliance assessment (pill count)				●			
Bang Blinding Index				●			
Liver transaminase (ALT or AST) test				●			
Assessment of vital signs	+	+	+	+		+	

Maternal physical examination	+	+	+	+		+	
Assessment of fetal wellbeing	+	+	+	+			
Gestational age of offspring at birth and secondary outcomes					●		
PARCA-R questionnaire							#
AE collection		●	●	●	●		
QRI interviews with participants		15-20 decliners				15-20 participants	
QRI interviews with TMG members and recruiters	Pre and during recruitment 4-8 TMG members 15-20 HCP recruiters						

Key: ● = all participants. * = mechanistic sub-study participants only. + = routine recommended antenatal care, as per standard care at participating site. # = participants recruited during first 18 months of recruitment only. QRI = Quintet Recruitment Intervention

In the event that a participant has a miscarriage or stillbirth, no information relating to the Birth timepoint will be collected directly from the participant. The trial team will liaise with the local research team and local bereavement/preterm birth teams to check whether the participant would like to speak with the PIONEER team again or not.

Alongside participation in PIONEER, participants will also be offered routine antenatal assessments and screening as part of the antenatal care provision by their local care providers. Table 3, below, summarises the routine antenatal care recommended by NICE to be offered to all pregnant people in England and Wales.

Table 3. Summary of NICE recommended schedule of Routine Antenatal Care for England and Wales (ten routine appointments for nulliparous and seven for parous; precise timings may vary between sites); NG201[68]; https://www.nice.org.uk/guidance/ng201/resources/schedule-of-antenatal-appointments-pdf-9204300829 [$]routine antenatal care that participants will be offered and may undergo during their participation in the PIONEER Trial.		
Weeks gestation	Indication for assessment	Assessment
[$]At every antenatal appointment, carry out the following risk assessment:	ROUTINE CARE FOR ALL	1. Ask about general health and wellbeing. 2. As if any concerns they would like to discuss. 3. Provide a safe environment for such discussions. 4. Review and reassess plan of care for the pregnancy. 5. Identify those who need additional care. 6. Update maternity notes accordingly. 7. If any unexpected results at any stage, offer referral according to local pathways and ensure appropriate information provision and support. 8. If any change in venous thromboembolism risk factors, reassess risk. 9. Measure and record blood pressure at every routine face-to-face antenatal appointment using a validated device for use in pregnancy: a. If hypertension under 20 weeks' gestation, follow NICE recommendations for chronic hypertension (>140/90) in pregnancy; b. Refer those who have their first episode of hypertension (>140/90) to secondary care to be seen within 24 hours; c. Urgently refer women with severe hypertension (>160/110) to secondary care to be seen on the same day. 10. Offer urine dipstick test at every routine face-to-face antenatal appointment: a. Test for proteinuria; b. Test for glycosuria and consider further testing to exclude gestational diabetes if they have the following result: i. Glycosuria of 2+ or above on one occasion; ii. Glycosuria of 1+ or above on two or more occasions. 11. Offer symphysis fundal height (SFH) measurement at each antenatal appointment after 24^{+0} weeks' gestation (but not more frequently than every two weeks) for women with a singleton pregnancy unless they are having regular growth scans. Plot measurement onto a growth chart in line with saving babies lives care bundle version 3:

		a. If concerns regarding SFH measurement (large or small), refer for an ultrasound scan for fetal growth and wellbeing. 12. Discuss topic of babies' movements after 24^{+0} weeks': a. At every antenatal contact after 24^{+0} weeks' gestation, ask if any concerns regarding fetal movements; b. Advise to contact maternity services at any time of day or night if any concerns or if notices reduced movements after 24^{+0} weeks' gestation.
By 10^{+0}	ROUTINE CARE FOR ALL: Booking appointment	Ask regarding: 1. Medical/obstetric/family history. 2. Previous or current mental health concerns. 3. Current and recent medicines, including over-the-counter medicines, health supplements, and herbal remedies. 4. Allergies. 5. Occupation. 6. Family and home situation. 7. Other people who may be involved in care of the baby. 8. Contact details for partner and next of kin. 9. Smoking/tobacco use. 10. Alcohol consumption. 11. Recreational drug use. 12. Nutrition and diet. 13. Physical activity. Refer: 1. If woman or partner smokes or stopped within past two weeks, to offer referral to NHS Stop Smoking Services. 2. Clinical assessment by a doctor to detect cardiac conditions if concern based on history. 3. To obstetrician or other relevant doctor if there are medical concerns or if review of current long-term medicines is needed. Offer to measure: 1. Woman's height and weight and calculate body mass index (BMI). 2. Offer blood test to assess full blood count, blood group, and rhesus D status. Discuss and share information about, and then offer, the following screening programmes (inform can accept or decline any part of the screening programme):

		1. NHS infectious diseases in pregnancy screening programme (HIV, syphilis, and hepatitis B). 2. NHS sickle cell and thalassaemia screening programme. 3. NHS fetal anomaly screening programme. Assess for venous thromboembolism: 1. Assess for risk factors for venous thromboembolism (according to NICE guidance) at this first booking; if at risk, refer to an obstetrician for further management. Assess for risk for gestational diabetes: 1. At this first antenatal appointment, assess risk factors for gestational diabetes according to NICE guidance. 2. If found to be at risk, offer referral for an oral glucose tolerance test to take place between 24^{+0} and 28^{+0} weeks' gestation, according to NICE guidance[69]. Assess for pre-eclampsia and hypertension in pregnancy: 1. Assess woman's risk factors for pre-eclampsia (according to NICE guidance), and advise those at risk to take Aspirin. 2. Measure blood pressure using a device validated for use in pregnancy: a. If hypertension under 20 weeks' gestation, following NICE recommendations for chronic hypertension (>140/90) in pregnancy; b. Refer those who have their first episode of hypertension (>140/90) to secondary care to be seen within 24 hours; c. Urgently refer women with severe hypertension (>160/110) to secondary care to be seen on the same day. 3. Offer urine dipstick to assess for proteinuria and glycosuria (as above). Monitoring fetal growth and wellbeing: 1. Offer risk assessment for fetal growth restriction (using appropriate guidance, including SBLCBV3[1]). Discuss alcohol consumption: no amount of alcohol known to be safe; can lead to long-term harm; safest approach is to avoid alcohol altogether to minimise risk to the baby. Assess for risk of preterm birth and stratify to low, intermediate and high-risk pathways (according to SBLCBV3[1]): 1. Assess smoking status and aim to be smoking-free before 15 weeks' gestation.
At booking appointment	FOR THOSE AT INTERMEDIATE OR HIGH RISK	1. Assess whether any previous preterm birth may be related to placental disease, and discuss prescribing Aspirin if so. 2. Test for asymptomatic bacteriuria by sending off a midstream urine (MSU).

	OF PRETERM BIRTH	
Between 11^{+2} and 14^{+1}	ROUTINE CARE FOR ALL:	Offer ultrasound scan to: determine gestational age; detect multiple pregnancy; if opted, screen for Down's syndrome, Edwards' syndrome, and Patau's syndrome
$^{\$}$16 week (14 to 18 weeks' gestation) Community Midwife (CMW) appointment	ROUTINE CARE FOR ALL	1. Reassess risk for pre-eclampsia as above. 2. Start discussing birth preferences. 3. Measure blood pressure and perform urine dipstick test, as above.
$^{\$}$Between 18^{+0} and 20^{+6}	ROUTINE CARE FOR ALL	Offer ultrasound scan to: screen for fetal anomalies (per Fetal Anomaly Screening Programme); determine placental location.
$^{\$}$18-22 weeks' gestation	FOR THOSE AT INTERMEDIATE OR HIGH RISK FOR PRETERM BIRTH	At least one transvaginal scan to assess cervical length as a minimum, plus more frequent cervical length and assessments (frequency and specific timings will vary according to local pathways).
$^{\$}$25 week appointment (CMW)	NULLIPAROUS WOMEN ONLY	1. Measure SFH if not having regular growth scans, as above. 2. Discuss fetal movements. 3. Discuss birth preferences. 4. Measure blood pressure and perform urine dipstick test, as above.
$^{\$}$28 weeks' gestation (CMW)	ROUTINE CARE FOR ALL	Offer: 1. Anti-D prophylaxis to rhesus-negative women. 2. Blood test to assess full blood count, blood group and antibodies. 3. Measure SFH if not having regular growth scans, as above. 4. Discuss fetal movements. 5. Discuss birth preferences. 6. Measure blood pressure and perform urine dipstick test, as above.
$^{\$}$31 weeks' gestation (CMW)	NULLIPAROUS WOMEN ONLY	As per 25 week appointment.

[$]34 weeks' gestation (CMW)	ROUTINE CARE FOR ALL	1. Measure SFH if not having regular growth scans, as above. 2. Discuss fetal movements. 3. Discuss birth preferences. 4. Measure blood pressure and perform urine dipstick test, as above
[$]36 weeks' gestation (CMW)	ROUTINE CARE FOR ALL	As per 34 weeks' gestation appointment, PLUS, if suspect breech presentation, refer for ultrasound scan
[$]38 weeks' gestation (CMW)	ROUTINE CARE FOR ALL	As per 36 weeks' gestation appointment.
[$]40 weeks' gestation	ROUTINE CARE FOR NULLIPAROUS ONLY	As per 36 weeks' gestation appointment.
[$]41 weeks' gestation	ROUTINE CARE FOR ALL	As per 36 weeks' gestation appointment, PLUS, discuss prolonged pregnancy and options on how to manage this.

5.12 Blinding and unblinding

Site staff and participants will be blinded to the allocation of treatment group, except for the site pharmacy staff, Sponsor trial pharmacy and Sealed Envelope. The trial statistician will see data by masked allocation (e.g. A vs B), but will not know which group is which. Blinding of participants is maintained by the use of Pravastatin and a matched placebo tablet. Any instances of deliberate or inadvertent unblinding will be recorded in the trial case report forms (CRFs) and will follow a strict protocol to limit the number of people who are unblinded.

Treatment codes will only be released to the central trial team once written confirmation has been received that the trial database has been locked. These will be retrieved directly from either the Sealed Envelope randomisation service or by download from the trial database. Participants will be informed of their allocation following completion of all data collection and planned analyses; they will be offered the choice of an online meeting, telephone call, or written information.

5.13 Emergency unblinding

The safety profile of the IMP is established, therefore emergency unblinding is not expected unless clear clinical need or other emergency dictates this. In such an event, the participant's treating doctor will contact the Sponsor, University Hospitals Bristol and Weston NHS Foundation Trust (UHBW), who will provide a 24-hour unblinding service. During office hours Monday to Friday 08:30 – 17:00 the UHBW Clinical Trials Pharmacy should be contacted,. An Emergency Duty Pharmacist will be available out of office hours. Contact details for emergency unblinding will be on the PIS and contact card. Sites will follow the trial specific instructions for unblinding, including recording the reason for unblinding within trial CRFs; these reasons will be reviewed and monitored by the TMG.

5.14 Non-emergency unblinding

In the event of non-emergency unblinding being required during office hours, investigators will be advised to contact the Bristol Trials Centre on +44 1174560633. Sites will follow the trial specific instructions for unblinding requests, including recording the reason for unblinding within trial CRFs; these reasons will be reviewed and monitored by the TMG.

5.15 Discontinuation of trial treatment

Participants can choose to discontinue trial medication at any time, without having to give a reason. If they choose to discontinue, a member of the trial team will enquire as to whether they would agree to share their reason for discontinuation; if the participant prefers not to share, this will be recorded as an undisclosed reason. If a participant discontinues treatment but does not ask to be withdrawn from the trial, efforts will be made to continue to obtain outcome and follow up data according to intention to treat analysis, unless the participant explicitly requests that this is not done. Subsequent antenatal and postnatal care would continue as per their local maternity teams, according to usual local practice.

If a participant discontinues taking the medication, they will also be invited to speak with a member of the QRI team to explore their reasons for discontinuing the medication and their experience as a participant and to have this conversation recorded, as part of the embedded QRI investigation.

5.16 Prior and concomitant therapies

Taking any of the following medicines or groups of medicines is contraindicated when taking Pravastatin: fibrates (e.g. gemfibrozil, fenofibrate); colestyramine/colestipol; vitamin K antagonists (including warfarin); systemic treatment with Fusidic acid; colchicine; nicotinic acid; rifampicin; lenalidomide. Therefore, taking these medications are a contraindication to recruitment to PIONEER, and if these medicines are prescribed

while a person is participating in PIONEER then the participant should discontinue the study medication and not recommence. Outcome data would continue to be collected and analysed according to intention to treat analysis for these participants.

Taking a macrolide is contraindicated when taking Pravastatin as macrolides have the potential to increase statin exposure when used in combination. Macrolide antibiotics include erythromycin, clarithromycin, roxithromycin. Those taking macrolides should be excluded from PIONEER, however, if a limited course of macrolides are prescribed with the course completed prior to 20^{+0} weeks' gestation, then it may be possible to recruit to PIONEER following completion of the course of antibiotics (if completion of the course of antibiotics is prior to 20^{+0}).

If macrolides are required while a person is recruited to PIONEER and taking PIONEER medication, an alternative antibiotic should be considered in discussion with local microbiologist teams. However, if no alternative is possible and a macrolide is commenced, the PIONEER study medication should be discontinued and not recommenced. A specific case for this is for prescription of Erythromycin in the case of PPROM: NICE guidance recommends that women who experience PPROM are offered the antibiotic Erythromycin for 10 days, or until birth if sooner. Therefore, if a participant experiences PPROM during the trial and is commenced on Erythromycin, they will be asked to stop taking trial medication at the point that Erythromycin is commenced. PPROM will be assessed for and diagnosed by the local clinical team, according to NICE guidance [NG25][5], evidence for PPROM includes pooling of amniotic fluid in the vagina and/or speculum at vaginal examination and/or positive insulin-like growth factor binding protein-1 test or placental alpha-microglobulin-1 test of vaginal fluid. Participants will be asked not to recommence trial medication once Erythromycin treatment is completed. Start of Erythromycin or other macrolide and cessation of trial medication must be recorded in trial CRFs. Outcome data would continue to be collected and analysed according to intention to treat analysis for these participants.

5.17 Elevated maternal liver transaminase

NICE guidance recommends that people who commence Statins should have their liver transaminase concentration (AST or ALT) assessed 2-3 months following commencement of the statin to assess response to treatment[70]. Statins should be stopped if the liver transaminase level is over three times the upper limit of normal (upper limit is set by local laboratories).

For PIONEER, maternal liver transaminase concentration will be measured at 28^{+0} weeks' gestation, which will be 2–3 months after participants commence the trial medication. The participants will continue to take trial medication while the liver transaminase test is being analysed. The following actions will be taken according to the following potential outcomes of the test:

A. If the liver transaminase level is below the locally-set upper limit of normal, no further action is required.
B. If the liver transaminase (either ALT or AST) level is over 3 times the locally-set upper limit of normal, the participant will be called as soon as possible by a member of their local research team and advised to stop taking trial medication. The participant will then be referred into the local pathway for follow-up of abnormal LFTs in pregnancy. Safety information will be collected for these participants following the Adverse Event of Special Interest reporting process detailed in Section 8.4. The participant's trial outcome data will continue to be recorded and analysed, according to Intention To Treat analysis.
C. If the liver transaminase level is less than 3 times the locally-set upper limit of normal but is higher than the locally-set normal upper limit, the participant should continue to take the trial medication and be referred by their local research team into the usual local pathway for elevated LFTs in pregnancy.

N.B. It is expected that most participating sites will measure either ALT or AST within the LFTs. Where both ALT and AST are measured at a site, the following will apply. A - If both ALT and AST are below the locally-set upper limit of normal, no further action. B - If one of ALT or AST are over 3 times the locally-set upper limit of normal, participant to stop trial medication and be referred for follow-up. C- If one of ALT or AST are less than 3 times the locally-set upper limit of normal but higher than the locally-set normal upper limit, participant to continue trial medication and be referred for follow-up.

5.18 Withdrawal from the trial

Participants will be able to fully withdraw from the trial at any time, without having to give a reason. The Chief or Principal Investigators can also decide to withdraw participants based on clinical opinion at any time during the trial. Although it is the participant's right to withdraw without giving a reason, it is a Good Clinical Practice requirement that a reason be sought and recorded if given. As an excessive number of withdrawals would affect the interpretation and power of the trial, it is desirable to avoid this, and the trial team will continuously review processes in case they affect the rate of withdrawal. In the event of any form of withdrawal, data obtained up to the point of withdrawal will be retained for analysis, as advised in the PIS. Data relating to the participant will continue to be collected, unless the participant asks for this to stop. The trial will be analysed according to intention to treat. Following withdrawal from the trial, ongoing care would continue as usual with their maternity team, according to usual local practice. As part of the embedded QRI, any participants who withdraw will be invited to discuss their reasons for this and their experience of trial participation with a member of the QRI team. Where possible, this process would seek to establish which elements of the trial, if any, caused a participant to withdraw (Section 6.3).

5.19 Participant payments and communication

Participants will be able to claim for reasonable expenses related to attendance at trial-specific research visits, including for travel and childcare provision. Payment may be provided in advance if required, dependant on individual recruiting site policies. All expenses will initially be reimbursed by the participating site, who will then invoice the Sponsor for these costs.

Participants will be sent regular newsletters (approximately four throughout the timeline of the trial) to update them on trial progress. The trial will also maintain a website and social media profile.

5.20 End of Trial

Participants end their involvement with the trial when either:

a) Those recruited during the first 18 months have had the relevant maternal and neonatal outcomes collected, and the PARCA-R questionnaire has been completed or reasonable attempts have been made to complete this.
b) Those recruited after the first 18 months of recruitment have completed their pregnancy, and relevant maternal and neonatal outcomes have been collected by the research team.

The end of trial will be when the last participant has completed their involvement with the trial, data collection is complete and any data queries have been resolved, the database has been locked, and subsequent planned data analyses have been completed.

5.21 Trial stopping rules

The trial may be prematurely discontinued by the Sponsor, Chief Investigator (CI), Regulatory Authority, or Funder, based on new safety information or for other reasons provided by the Data Monitoring and Safety Committee (DMSC) or TSC, regulatory authority, or ethics committee.

The trial may also be prematurely discontinued due to lack of recruitment or upon advice from the TSC, who will advise on whether to continue or discontinue the trial and make a recommendation to the Funder. If the trial is prematurely discontinued, no new participants will be recruited and a decision on data collection for active participants will be made in discussion with the TSC, DMSC and Sponsor.

6. EMBEDDED QUINTET RECRUITMENT INTERVENTION (QRI) AND QUALITATIVE INTERVIEWS DURING TRIAL FOLLOW-UP

A Quintet Recruitment Intervention (QRI) is embedded within the PIONEER trial.

This aims to explore any challenges or obstacles for recruitment and to optimise unbiased trial information delivery to ensure full informed consent is standardised at all sites. The QRI is referred to as the 'Information Study' in participant facing information.

6.1 QRI Phase 1

The QRI work will begin during the trial set-up phase, investigating what may influence recruitment and training recruiters before recruitment begins. Recruitment processes will be investigated in-depth at trial sites as they open. The QRI researchers will use a mixed methods approach, combining quantitative screening log data with qualitative data collection and triangulation of data during analysis[71], to investigate site-specific or more general recruitment obstacles.

a) Pre-trial workshops: professionals' views will be explored in workshops involving relevant clinical co-applicants and trial recruiters at participating sites to facilitate discussions about the participant screening/identification pathway, eligibility criteria and equipoise. The QRI researcher will observe all Trial Management Group meetings during which the more detailed trial protocol is developed, with a focus on discussions and presentation of trial information, and application of the eligibility criteria. Patient and Public Involvement (PPI) views on taking medication in general, and statins in particular, during pregnancy and participation in PIONEER will be investigated in parallel during regular trial PPI meetings (Section 11.5).

b) Mapping of eligibility and recruitment pathways: site investigators will collect details of potential participants at each recruiting site who are screened (S), eligible (E), approached to take part (A), and randomised (R) for analysis using the SEAR framework[72]. A key ambition of PIONEER is to make participation as inclusive as possible, ensuring equitable access to the UK pregnant population at intermediate or high risk of PTB, including those from under-served groups and those that are underrepresented in medical research, in particular those whose first language is not English and those from lower socioeconomic groups. In order to assess whether PIONEER fulfils this aim, screening data will be collected for all pregnant people referred to PTBPCs before 20^{+0} weeks' gestation, having been identified as being at high or intermediate risk for PTB. Sex (all screened will be biologically female), pregnant (all screened will be pregnant), English as a first language (yes/no) to assess whether language is a barrier to participation, year of birth (used to characterise population), and ethnicity, to allow monitoring of trial inclusivity, will be collected for all screened pregnant people irrespective of whether they decide to participate. Postcodes of those screened will also be entered into the trial database and immediately (so that full postcode is not stored) converted into an Index of Multiple Deprivation (IMD) to assess if there is a difference between socioeconomic groups in those that decide to take part in the trial. This information will be collected to assess any difference in the people that do not take part compared to those that do, to establish whether any of these factors are barriers to participation. Analyses will identify points in the recruitment pathway at which potential participants continue with recruitment to the trial or drop out, with data monitored for any evidence of systematic exclusion of particular groups. 10.2

c) Recruitment discussions, where the trial is presented by recruiters to potential participants, will be audio-recorded with consent (Section 5.5 for consent process). These recruitment discussion recordings provide insight into actual presentation of trial information to potential participants, help identify recruitment difficulties and provide the basis for rapid feedback to sites and/or training as required. Recordings will be sought from a range of recruiting sites to ensure maximum variation and analysed by the QRI researcher (target minimum 50 recordings across at least 8 sites).

d) In-depth interviews will be conducted and audio-recorded by the QRI researcher with (i) members of the Trial Management Group (n=4-8), (ii) healthcare professionals (HCPs) (Principal Investigators, research midwives etc.) involved in trial recruitment (n=15-20), and (iii) a sample of eligible potential participants who have been approached but declined to take part in the trial (n=15-20) and consented to take part in a QRI interview. Interviews will investigate acceptability of the trial, views about applying the eligibility criteria in practice and variation in application of the protocol in clinical sites with the aim of identifying recruitment barriers.

e) Trial documentation, including the Participant Information Sheets and Informed Consent Forms, will be scrutinised to optimise presentation of the trial and its arms, applying experience from previous QRIs and the trial-specific insights gained when mapping recruitment pathways, interviewing potential participants/participants and clinicians, and recording recruitment conversations (1-4 above). Trial team meetings (TMG/TSC) will be observed and issues relevant to recruitment noted.

6.2 QRI Phase 2

Findings from Phase 1 will be fed back iteratively to the Chief Investigator and the Trial Management Group to determine a joint plan of actions to optimise recruitment. Actions may include: feedback to individual recruiters or groups as appropriate, template participant pathways, individualised or generic 'tips' sheets for recruiters and delivery of recruiter training. Insights from workshops with professionals and PPI members will inform the content of participant facing information for the trial. Training of recruiters will raise awareness of key 'hidden' challenges when recruiting people to trials involving medications taken during pregnancy and how these can be addressed[73 74], as well as including insights into particular issues identified as relevant to the PIONEER trial in how to deal with peoples' preferences and convey reassurance about taking medication during pregnancy. [72]The QRI in the main trial will be informed by the pilot phase findings. QRI actions to optimise recruitment will be evaluated throughout, using screening log and qualitative data from interviews and audio-recordings.

6.3 Qualitative interviews during PIONEER trial follow-up

In-depth interviews to investigate participants' experience of PIONEER trial participation and follow-up will be undertaken and audio-recorded by the QRI researcher with 15-20 participants at 6-12 weeks post-partum. Participants will be purposively sampled to include those who have consented to a follow-up interview and i) show good and less good adherence according to the pill count at 28^{+0} weeks' gestation and ii) those who choose to withdraw from the PIONEER trial. Local research midwives will check obstetrics records for all participants who have consented to a follow-up interview. If a participant has had a miscarriage or stillbirth they will not be contacted. The QRI researcher will contact consenting participants to arrange the interview.

Interviews will explore what factors motivated participants to accept participation, reservations about participation, experiences regarding trial process in general, including reasons for withdrawal if applicable, side effects and birthing experience.

For participants who have withdrawn from the PIONEER trial, qualitative contact will be determined by their decisions as to which parts of the trial they are withdrawing from:

- Participants who withdraw from the PIONEER trial may wish to not be contacted further. Even if these participants had initially agreed to a follow-up interview, they will not be contacted about the qualitative interview.
- Participants who withdraw from the PIONEER trial can agree to be contacted. If these participants have consented to a follow-up interview, they will be approached by the QRI researcher about the follow-up interview.

6.4 Consent process for QRI and qualitative interviews

Audio-recording recruitment discussions

Healthcare professionals in site teams involved in recruitment discussions will be invited to participate in the embedded QRI, prior to their site opening to recruitment. These site team members will be provided with a QRI Healthcare Professional Participant Information Sheet and Consent Form, inviting participation in the QRI and consent for their recruitment discussions to be recorded (provided the potential trial participants also consent). As the trial progresses, newly appointed research site team members will also be approached for consent to participate in the embedded QRI process.

Potential PIONEER participants will be first approached for consent to audio-record recruitment discussions at the time of the Stage 1 consent discussion (Section 5.5); information regarding audio-recording of recruitment discussions and reasons for doing so will be provided within the PIONEER Participant Information Sheet. At the time of Stage 1 of the consent process, potential participants will be invited to give verbal or written consent to the QRI. Consent to take part will be documented on the specific QRI-Information Study verbal and/or written Consent Forms. Those who consent to audio-recording will sign the specific QRI written consent form to confirm consent for audio-recording of all trial recruitment discussions with the research team in the lead-up to the potential participant making their decision about participation in the trial. Potential participants have the option of consenting to participate in the embedded QRI/qualitative study and decline participation in the PIONEER trial, and vice versa.

QRI Interviews for eligible potential participants who have declined to take part in the trial

Potential participants who decide not to take part in the PIONEER trial, will be invited to take part in an interview to explore experiences of being invited to join the trial. This will be confirmed by the potential participant signing the QRI-Information Study Participant Consent Form, if they have not already done so. If consent is provided, the QRI team will contact the potential participant to arrange an appropriate time for a QRI interview via telephone or Sponsor-approved video conferencing software, in line with potential participant preference. Local research midwives will check obstetrics records for all participants who have consented to an interview, before contact is made. If a participant has had a miscarriage or stillbirth they will not be contacted.

Interviews with members of the Trial Management Group and HCPs involved in trial recruitment

Interviews with TMG members and HCPs will take place throughout the trial duration using purposeful sampling. Most interviews will take place via telephone or using Sponsor-approved video conferencing software, although some may be face-to-face. Taking part will be optional. Written informed consent will be obtained for all TMG member and HCP interviews using the QRI-Information study HCP Consent Form. The consent form will be completed over the telephone for those staff not participating in face-to-face interviews and a note made on the consent form that consent was received over the telephone.

Interviews for eligible potential participants who have agreed to participation in the trial (including those who later withdraw)

If a potential participant agrees to participation in the PIONEER trial, the local research team will ask if they would be happy to take part in an interview to explore their experience of taking part in the trial and follow-up processes, at 6-12 weeks post-partum. This will be confirmed by the potential participant signing the QRI-Information Study Participant Consent Form if they have not already done so. Verbal consent will also be confirmed during the interview owing to the time period between initial consent and the interview taking place.

If a participant withdraws from the PIONEER trial but has consented to a follow-up interview, as part of the withdrawal conversation the participant will be asked if they agree to being contacted about the follow-up interview 6-12 week post-partum. Consent will be captured using the PIONEER – Information Study Participant Consent Form. Only participants who have provided consent will be contacted (see Section 6.3 for details of approach for follow-up interviews).

6.5 Data protection and participant confidentiality in relation to the qualitative data

All PIONEER participant audio-recordings (trial recruitment discussions and interviews) will be made using an encrypted audio-recorder. Audio-recorded recruitment discussions captured by recruiting healthcare professionals on the encrypted audio-recorder will be transferred to University of Bristol researchers as soon as possible after each appointment, either via secure NHS.net email or secure data transfer of encrypted memory cards/audio-recorders. Audio-recordings of PIONEER participant interviews will be captured by the University of Bristol researcher directly and transferred to a secure server in line with the University's data storage policies.

Interviews with healthcare professionals may be recorded using the encrypted audio-recorder and following procedures outlined above or conducted through a video conferencing platform. If the latter, only the audio-recording file will be transferred securely to the University of Bristol and both the audio and video files will be deleted from the video-conferencing platform. All data will be stored on password protected computers maintained by the University of Bristol.

Audio-recordings (trial recruitment discussions and interviews) will be transcribed by University of Bristol employees or University approved transcription services. Transcripts will be labelled with a trial-assigned participant number, edited to ensure anonymity of respondents and stored securely adhering to the University's data storage policies. Audio-recordings and transcripts will be retained by the University of Bristol where anonymised quotations and parts of voice modified recordings may be used by the University for training, teaching, research and publication purposes for this and future trials. Anonymised transcripts may be made available to other researchers (including those outside of the University) by controlled access if they secure the necessary approvals for purposes not related to this trial, subject to individual written informed consent from participants.

7. INTERVENTION/IMP

7.1 General information

Within the trial, the following are classed are as IMPs:

- Pravastatin: one tablet containing 20mg of pravastatin
- Placebo: formulated and manufactured according to a standard placebo composition to match the appearance of the active tablet

Both will be taken once daily by participants, from between 16^{+0} and 20^{+0} weeks gestation until 37^{+0} weeks gestation, or until completion of pregnancy, or commencement of Erythromycin for PPROM, or if maternal transaminase (ALT or AST) are more than 3 times the upper limit of normal (assessed at 28^{+0} weeks' gestation), or if the participant decides to leave the trial or is excluded for another reason, whichever occurs sooner.

7.2 Pravastatin

Pravastatin is a statin, used to lower the level of LDL cholesterol in the blood. It acts by competitively inhibiting 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase, the enzyme catalysing the early rate-limiting step in cholesterol biosynthesis. Firstly, with the reversible and specific competitive inhibition of HMG-CoA reductase, it effects modest reduction in the synthesis of intracellular cholesterol. This results in an increase in the number of LDL-receptors on cell surfaces and enhanced receptor-mediated catabolism and clearance of circulating LDL-cholesterol. Secondly, pravastatin inhibits LDL production by inhibiting the hepatic synthesis of VLDL-cholesterol, the LDL-cholesterol precursor.

Pravastatin is indicated: as an adjunct to diet for primary hypercholesterolaemia or combined (mixed) hyperlipidaemias in patients who have not responded adequately to dietary control; for the prevention of cardiovascular events in patients with previous myocardial infarction or unstable angina; as an adjunct to diet to prevent cardiovascular events in patients with hypercholesterolaemia; and for reduction of hyperlipidaemia in patients receiving immunosuppressive therapy following solid-organ transplantation.

The biological rationale for the use of pravastatin in the prevention of PTB is through one or more of the following mechanisms:

i. Directly modifying maternal inflammatory pathways
ii. Indirectly modifying maternal vaginal and gut microbiota
iii. Directly modifying maternal lipid profiles and reducing dyslipidaemia
iv. Directly modifying myometrial smooth muscle contraction (not tested in PIONEER)[27 28 46-49 51-67].

7.3 Assessment and management of risk

The trial is categorised as 'Type B' according to the MHRA. Pravastatin is licensed as a medicine in the UK, however the use within this trial is for a new indication (off-label). As such, the potential risk associated with the IMP is somewhat higher than that of standard medical care.

NICE advise that the risk of muscle pain, tenderness or weakness associated with Statin use is small and the rate of severe muscle adverse effects (rhabdomyolysis) because of Statins is extremely low. NICE add that there is a large body of evidence that shows that, when using high-intensity Statins (Pravastatin 5mg to 40mg is considered low-intensity), approximately 16% report muscle pain, but of these only around 1 in 12 were likely due to the Statin[75]. Pravastatin tablets contain lactose monohydrate, hence the exclusion of potential participants with lactose intolerance.

As discussed above, Statins have previously been avoided in pregnancy as animal studies and retrospective case reports indicated possible fetal toxicity[29-32]. However, this has since been refuted[31 33], and in 2021 the USA Food and Drug Association removed the Pregnancy Category X label for statins[34]. A cohort study including 1152 pregnant women who took a statin during the first trimester showed no teratogenic effect[35],

a finding supported by subsequent systematic reviews and meta-analyses (n=1673[36];2361[37];1579[38];618[31];469[39]). Importantly, Pravastatin is hydrophilic (hydrophilic compounds cross the placenta less readily than lipophilic compounds), and has no reported fetal malformations associated with its use[32]. Its safety profile in pregnancy is enhanced by its recent use in RCTs for prevention and treatment of pre-eclampsia[40-43] and antiphospholipid syndrome (APS)[44], with no safety concerns (n=1303).

The trial data will capture documentary evidence of a full chain of custody of IMP, from supply to destruction, from which both the quantities and quality of the IMP used can be determined. These records will follow guidance from ICH Document E6: Good Clinical Practice section 4.6, and will include: the product's delivery to the trial site, the inventory at the site, the use by each subject, and the return to the Sponsor or alternative disposition of unused product. These records will include dates, quantities, batch/serial numbers, expiration dates, and the unique code numbers assigned to the trial subjects.

Additional documentation will be provided to demonstrate the quality of the placebo and that the requirements of Good Manufacturing Practice have been satisfied.

Although Pravastatin does not require any special temperature storage conditions, shipments from the IMP distributer to sites will be sent with temperature loggers and extreme deviations (above 30°C) will be recorded.

A risk assessment and monitoring plan will be developed prior to the start of recruitment (see Section 12.1).

7.4 Manufacture of IMP

Pravastatin 20mg tablets will be provided by Eramol UK Ltd (UK MIA(IMP) 49160), a Medicines and Healthcare Products Regulatory Agency (MHRA)-licensed manufacturer of investigational medicinal products. They will also supply a matched placebo tablet, of which composition will be approved by the MHRA. This will be formulated and manufactured according to standard placebo composition to match the appearance of the active Pravastatin tablets.

7.5 Packaging, labelling, storage and shipping of IMP

Eramol UK Ltd (Unit 9, North Downs Business Park, Lime Pit Lane, Sevenoaks, TN13 2TL, UK), will package, label, store and Qualified Person (QP) release the trial IMPs, providing identical treatment bottles for Pravastatin and placebo containing 56 identical tablets for oral administration. To maintain blinding, the tablets and bottles will be identical and labelled with the same trial-specific label. The label texts for all packaging will comply with the requirements of Annex 13 of the Rules Governing Products in the European Union. Eramol will perform QP release prior to IMP being dispatched to sites. IMP will be ordered on an individual basis for each site and sent via courier with a temperature logger to the contact address provided by the site. Each site will receive at least two separate orders throughout the duration of the trial. For each delivery, sites will be required to complete and file documentation (provided by Eramol) to confirm receipt.

Storage requirements at site will be detailed in a trial specific working instruction.

7.6 IMP allocation

Each bottle will be allocated a bottle number during manufacture. Once dispensed to a participant, the bottle number will be recorded on the trial CRFs. Each bottle label will also have a tear-off portion, showing the bottle number and allocation, which will be affixed to the accountability log.

7.7 Dispensing of IMP to participants

Participants will be prescribed IMP at two timepoints: at baseline (two bottles), which will cover the period from randomisation until 28^{+0} weeks gestation, and at the 28^{+0}-week visit (one bottle). A separate prescription will be completed for each timepoint, which will not reveal the participants' treatment allocation to the participant or research staff (other than the pharmacy staff), to maintain blinding.

If the trial medication is lost or damaged between randomisation and the end of the participant's treatment period, the trial database will be used to request a new prescription from the site pharmacy. The participant will be allocated new bottles(s) from the site supply of their allocation, and the new bottle number(s) recorded.

7.8 Dosage and duration of IMP

Tablets will be taken once daily by participants, from between 16^{+0} and 20^{+0} weeks' gestation until 37^{+0} weeks' gestation, or until birth, or commencement of Erythromycin for PPROM, or if the maternal liver transaminase (ALT or AST) level is over three times the upper limit of normal (assessed at 28^{+0} weeks' gestation), whichever occurs sooner.

7.9 Return and destruction of IMP

When returning for the follow up research appointment at 28^{+0} weeks' gestation, participants will be asked to bring with them any remaining medication for a pill count to assess compliance. Participants will then be required to take this remaining medication away again, alongside their second batch of tablets, to ensure sufficient tablets for the duration of the trial. When the participant stops their trial medication (37^{+0} weeks' gestation, or birth, or if they commence Erythromycin for PPROM, or if their liver transaminase (ALT or AST) level is over 3 times the upper limit of normal (assessed at 28^{+0} weeks' gestation)), they will be asked to dispose of any remaining medication with community pharmacies. Any unused IMP held by trial site pharmacies at the end of the trial will be destroyed (when authorised by the Sponsor), in line with local site or trial specific instructions on the disposal of IMP.

7.10 Reference Safety Information

Reference Safety Information (RSI) defines which reactions are expected for the IMP being administered to subjects participating in a clinical trial. The RSI will be one single definitive list or document that determines which Serious Adverse Reactions (SARs) require expedited reporting to the MHRA as Suspected Unexpected Serious Adverse Reactions (SUSARs). The term 'expectedness' from a regulatory perspective (in relation to safety reports and SUSARs) means whether or not the reaction is an expected side effect of the IMP, thus establishing whether it does or does not need reporting in an expedited fashion.

The RSI for this trial is Section 4.8 of the Summary of Product Characteristics (Pravastatin sodium 20mg tablet) for Marketing Authorisation Holder Teva UK Limited, dated 16/03/2023[2].

There are some events of special interest in the RSI for this clinical trial and these will be reported as Adverse Events of Special Interest, see Section 8.4:

- Effects on the skeletal muscle, for example musculoskeletal pain including arthralgia, muscle cramps, myalgia, muscle weakness and elevated CK levels have been reported in clinical trials. The rate of myalgia (1.4% Pravastatin vs 1.4% placebo) and muscle weakness (0.1% Pravastatin vs < 0.1% placebo) and the incidence of CK level> 3 x ULN and> 10 x ULN in CARE[76], WOSCOPS[77] and LIPID[78] was similar to placebo (1.6% Pravastatin vs 1.6% placebo and 1.0% Pravastatin vs 1.0% placebo, respectively);
- Elevations of serum liver transaminases have been reported. In the three long-term, placebo-controlled clinical trials CARE[76], WOSCOPS[77] and LIPID[78], marked abnormalities of ALT and AST (> 3 x ULN) occurred at similar frequency (≤ 1.2%) in both treatment groups.

7.11 Post-trial

Administration of IMP to trial participants will not continue beyond 37^{+0} weeks' gestation. Any future administration of Pravastatin would be at the discretion of the participants normal clinician and should not occur until after the end of their participation in this trial.

7.12 Drug accountability

Drug accountability records will be maintained throughout the course of the trial by site pharmacies. Designated trial site pharmacy staff will document the date and quantity of IMP as it is received from Eramol and dispensed to trial participants.

Individual participant drug compliance will be assessed via a pill count at 28^{+0} weeks' gestation.

7.13 Intervention and IMP COVID-19 considerations

At the time of writing, there are no COVID-19 measures in place across the UK and no implications from the pandemic have been identified for this trial. The trial team will be responsive to any changes in this position and may be required to make adaptations to trial design, through amendments to this trial protocol.

8. PHARMACOVIGILANCE

8.1 Operational definitions

Pharmacovigilance will be carried out in accordance with the guidance set out by the European Commission Detailed Guidance CT-3 2011, and the requirements of the Medicines for Human Use (Clinical Trials) Regulations, including the terminology of adverse events and reactions and the assessment of seriousness, causality, and expectedness of an event.

Table 4: Definitions of adverse events and reactions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse event of special interest (AESI)	An adverse event of special interest (serious or non-serious) is one of scientific and medical concern specific to the investigational medicinal product, for which ongoing monitoring and rapid communication by the investigator to the sponsor is required
Adverse Reaction (AR)	Any untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication will qualify as adverse reactions. It is important to note that this is entirely separate to the known side effects listed in the Reference Safety Information. It is specifically a temporal relationship between taking the medicinal product, the half-life, and the time of the event or any valid alternative aetiology that would explain the event.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening[a] • requires inpatient hospitalisation or prolongation of existing hospitalisation[b] • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. [a] *"Life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.*

	[B] *"Hospitalisation" is defined as an unplanned overnight stay. Note, however, that the participant must be formally admitted – waiting in outpatients or an Emergency Department would not count as hospitalisation (even though this can sometimes be overnight). Prolongation of an existing hospitalisation qualifies as a SAE. Planned hospital stays would not be counted as SAEs, nor would stays in hospital for "social reasons" (e.g. respite care, the fact that there is no-one at home to care for the participant). Also, if participants had a day-case operation, this would not qualify as hospitalisation. However, if a planned operation was brought forward because of worsening symptoms, this would be considered as an SAE. Hospitalisations for the purpose of the intervention are an exception to SAE reporting, unless complications occur.*
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out in the Reference Safety Information: • in the case of a product with a marketing authorisation, this could be in the Summary of Product Characteristics (SmPC) for that product, so long as it is being used within its licence. If it is being used off label, an assessment of the SmPCs suitability will need to be undertaken • in the case of any other investigational medicinal product, in the investigator's brochure (IB) or IMPD relating to the trial in question
Suspected serious adverse reaction (SSAR)	A suspected serious adverse reaction (SSAR), is any serious adverse reaction that is considered consistent with information available about an Investigational medicinal Product (IMP).

Table 5: Classification of Severity

Mild event	An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
Moderate event	An event that is sufficiently discomforting to interfere with normal everyday activities.
Severe event	An event that prevents normal everyday activities.

Table 6: Classification of Relatedness

Not related	Temporal relationship of the onset of the event, relative to administration of the intervention, is not reasonable or another cause can by itself explain the occurrence of the event.

Unlikely to be related	Temporal relationship of the onset of the event, relative to administration of the intervention, is unlikely and it is likely there is another cause which can by itself explain the occurrence of the event.
Possibly related	Temporal relationship of the onset of the event, relative to administration of the intervention, is reasonable but the event could have been due to another, equally likely cause.
Probably related	Temporal relationship of the onset of the event, relative to administration of the intervention, is reasonable and the event is more likely explained by the intervention than any other cause.
Definitely related	Temporal relationship of the onset of the event, relative to administration of the intervention, is reasonable and there is no other cause to explain the event, or a re-challenge (if feasible) is positive.

Table 7: Classification of Expectedness

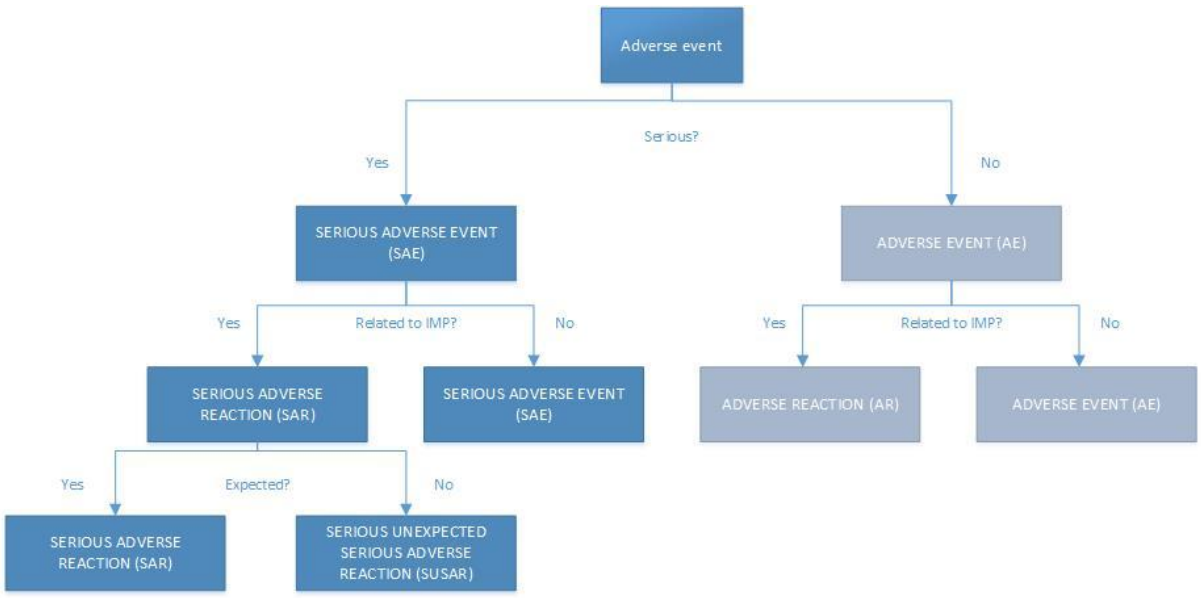
Expected	Reaction previously identified and described in the Reference Safety Information.
Unexpected	Reaction not previously described in the Reference Safety Information.

8.2 Adverse events classification flowchart

For each adverse event the seriousness, relatedness and expectedness will be determined (as per the definitions above) in order to appropriately classify the episode as per Figure 1.

The PI of each participating site (or appropriate delegate, e.g. doctor) is responsible for assessing and categorising AEs. For each AE the seriousness, relatedness to IMP and expectedness will be determined (as per the definitions in section 8.1) in order to appropriately classify, record and report (where applicable) the event.

Figure 1: Classification of adverse events flowchart



8.3 **Non-serious Adverse Events (AEs)**

Non-serious adverse events that are unrelated to the IMP should be recorded in the relevant CRF (Figure 2).

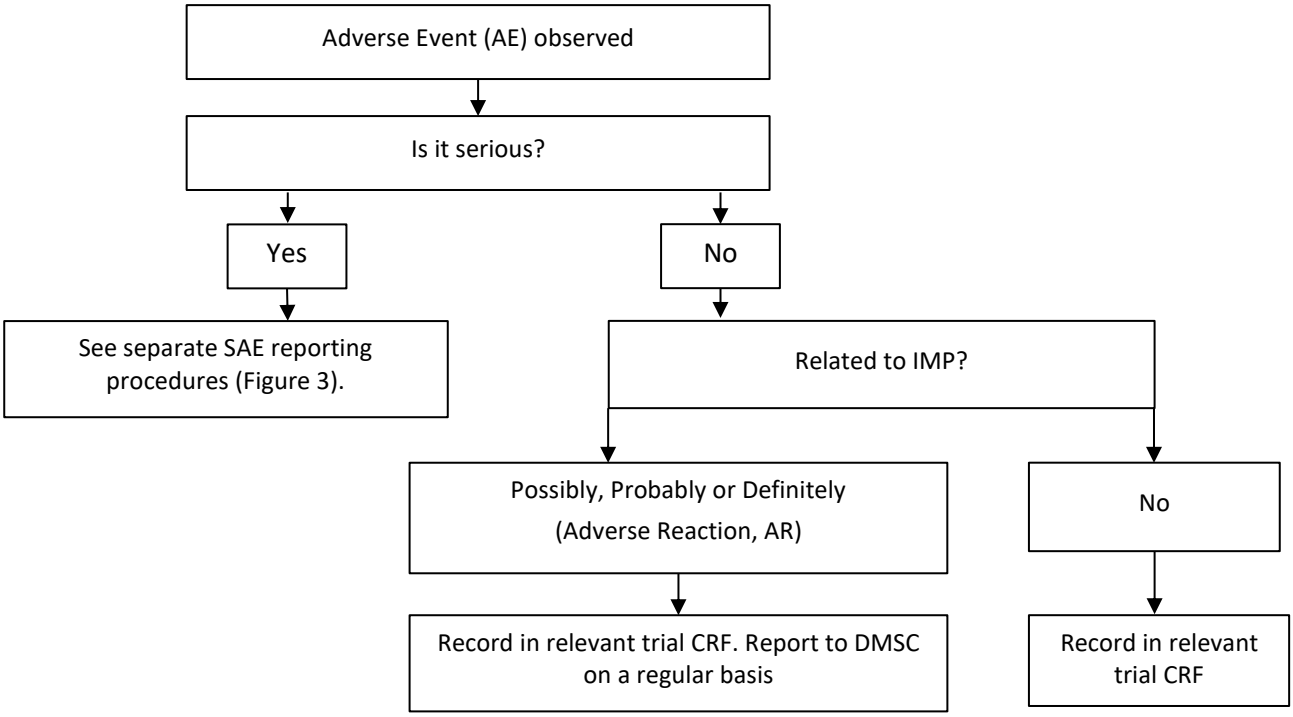
For non-serious adverse events that are assessed as being possibly, probably or definitely related to the IMP (adverse reaction, AR), details will be recorded in the relevant CRF (Figure 2). The central trial team will communicate with the local PI and site team if additional information is required e.g. to determine causality.

It is anticipated that the majority of AEs will be identified during trial visits. At the 24^{+0}-week visit, all mechanistic sub-study participants will be asked about any adverse events. At the 28^{+0}-week trial visit, all participants will be asked about any adverse events. Following birth, when collecting trial information from participants medical records, local research teams will also be asked to check for adverse events.

If a participant attends a routine (i.e. non-trial related) appointment and an AE is reported, the local research teams will assess and record this on the relevant CRF. Participants will also be instructed to carry a contact card with them, that encourages them to contact their local research team with any concerns, and is to be presented to any healthcare professional that is treating them.

AEs will be reviewed by the DMSC as a standing agenda item.

Figure 2: Recording framework for non-serious Adverse Events (AEs)



8.4 **Adverse events of special interest (AESI)**

The following events are considered AESIs for this participant population.

- Skeletal muscle side effects;
- Elevations of serum liver transaminase (ALT or AST) over three times the upper limit of normal (according to local laboratory values).

Non-serious AESIs should be reported to the BTC within 24 hours of the investigator becoming aware using the SAE form.

Serious AESIs (SAESIs) require expedited reporting to the Sponsor using the SAE form, see Figure 3.

8.5 Serious Adverse Events (SAEs)

The reporting framework for serious adverse events is presented in Figure 3.

Local research teams will record all SAEs (SAESI/SAE/SAR/SUSARs) using the relevant trial CRFs (SAE log and SAE form). The central trial team will review all reported SAEs for monitoring and reporting purposes, and will prepare regular summary reports of all SAEs for discussion at relevant oversight meetings, including the DMSC as per their written charter. The SAE CRFs will record, as a minimum, the following details for each event:

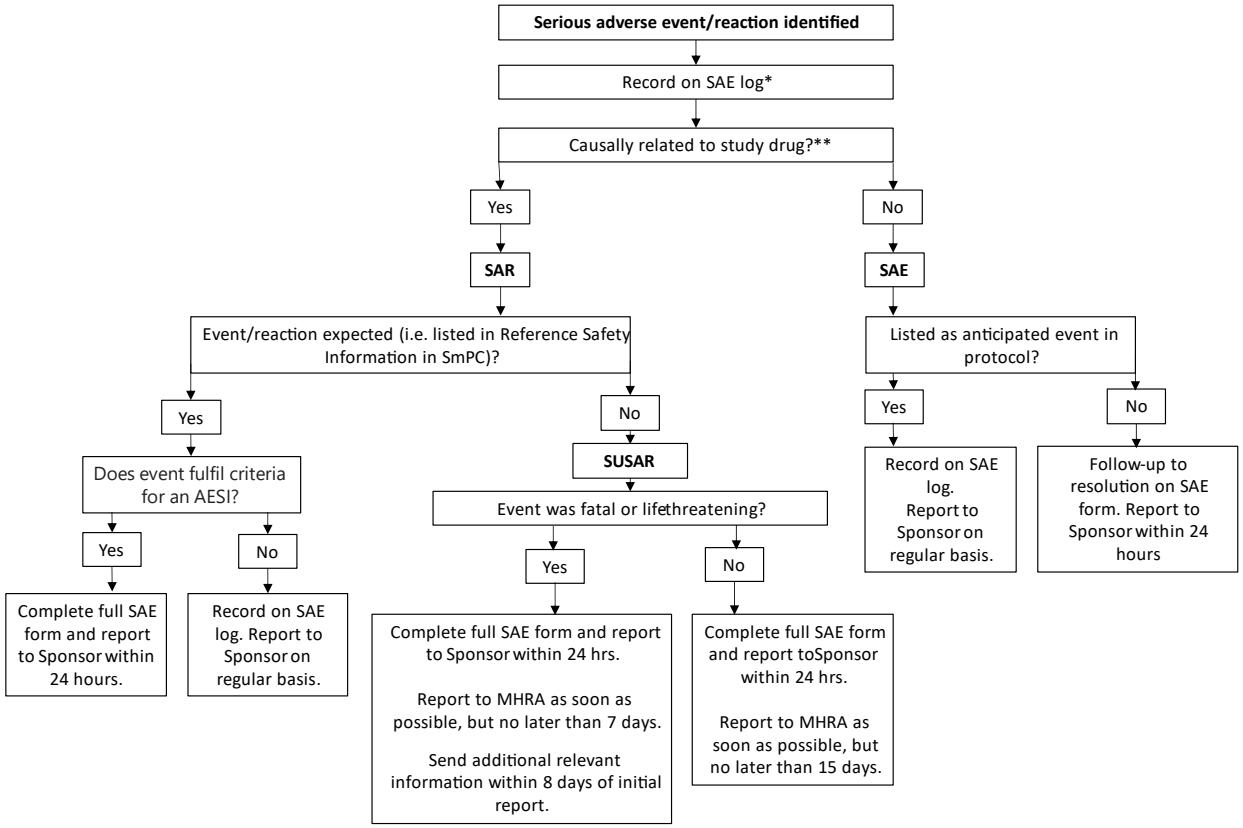
- Event number
- Brief description of the event
- Date (and time where known) that event started and stopped
- Reason event was an SAE
- Classification of severity
- PI/delegated doctors' assessment of whether the event was causally related to trial drug, within 24 hours of becoming aware of the event
- For events related to the trial drug, an assessment of whether the event was expected (as per Reference Safety Information for IMP)
- For events not related to the trial drug, an assessment of whether the event was anticipated (as per list of anticipated events in Section 8.8)
- Outcome of the event (including details about sequelae, where relevant)
- Whether the event resulted in death
- Details of any actions taken in response to the event

All participant deaths must be reported to Sponsor within 24 hours of the site becoming aware.

Hospitalisation for an elective procedure or for a pre-existing condition (prior to trial entry) which has not worsened, does not constitute a serious adverse event.

All unanticipated SAEs not resolved at the time of reporting will be followed up until the event has resolved, or a final outcome has been reached.

Figure 3: Reporting framework for all Serious Adverse Events (SAEs)



* All SAESI/SAE/SAR/SUSARs will be recorded using an SAE log or form and causality assessment undertaken within 24 hours of the site becoming aware of the event, as per the reporting framework. All participant deaths must be reported to Sponsor within 24 hours of the site becoming aware.
** Causality must have been assessed prior to reporting to Sponsor; however, as part of their assessment on behalf of the Sponsor, the central trial team will also review causality.

8.6 Expectedness of events

The expectedness of a Serious Adverse Reaction shall be determined according to the current approved Reference Safety Information (See Section 7.10).

8.7 Suspected Unexpected Serious Adverse Reactions (SUSARs)

For any SUSAR, a full written report will be made in writing to the Sponsor within 24 hours of the investigator(s) becoming aware of the event. Expedited reporting will be carried out within 7 days of the initial notification to the MHRA if the event is fatal or life-threatening, or within 15 days otherwise. The MHRA will liaise with the REC if deemed appropriate. This reporting approach will be adopted due to this trial being submitted for approval via Combined Review.

The local research team will provide any additional relevant information missing from the initial report within 8 days of the initial report to the necessary bodies. Any change of condition or other follow up information relating to a previously reported SUSAR will be reported on a separate trial Follow Up Report Form. All SUSARs will be followed up until the event has resolved, or a final outcome has been reached.

Occurrences meeting the definition of a SUSAR, which are spontaneously reported to the site trial team during the trial safety reporting period, will be evaluated by the Chief Investigator and central trial team. If appropriate, the usual SUSAR reporting procedure will be followed.

8.8 Anticipated Events

The following events are anticipated for this participant population. Events of this nature, that meet the definition of serious, will be recorded in the SAE log but not immediately reported to the Sponsor, unless deemed to be related to the trial drug:

- Hyperemesis;
- Reduced fetal movements;
- Gestational hypertension;
- Proteinuria;
- Gestational diabetes;
- Fetal growth restriction;
- Shortening cervix;
- Preterm pre-labour rupture of membranes (PPROM);
- Premature/preterm labour or threatened premature/preterm labour;
- Pre-eclampsia;
- Obstetric cholestasis.

8.9 Urgent Safety Measures (USMs)

In line with the University Hospitals Bristol and Weston NHS Foundation Trust (UHBW) Research Safety Reporting procedure, the Sponsor and Chief Investigator may take appropriate Urgent Safety Measures to protect a research participant from an immediate hazard to their health and safety. This measure can be taken before seeking approval from the competent authorities (i.e. the MHRA) and REC.

The first action is to protect participant safety/health. Following that, the Chief Investigator on behalf of the Sponsor should discuss the USM by telephone as soon as it has been put in place with an MHRA safety scientist in the first instance. A protocol amendment must be submitted within the following three days to the MHRA, and ethics committee. All communication between the MHRA, the REC, the CI/PI and the Sponsor should be documented and placed in the Investigator Site File (ISF) and Trial Master File (TMF).

The responsibility of reporting USMs is delegated to the CI and PI(s) – the CI is responsible for reporting USMs to regulatory bodies and to participating sites. The PIs are responsible for implementing USMs at sites.

8.10 Notification of deaths

All deaths occurring during the trial safety reporting period will be reported to Sponsor within 24 hours of research teams becoming aware.

8.11 Safety reporting period

The UHBW Research Safety Reporting procedure incorporates the requirements of the Medicine for Human Use (Clinical Trials) Regulations 2004. Bristol Trials Centre, on behalf of the Sponsor, assumes responsibility for appropriate reporting of adverse events to the regulatory authorities.

For each participant, the start of the safety reporting period for AEs and SAEs will be from consent and the end of the safety reporting period will be 30 days after birth or pregnancy loss.

Of note, a subset of participants will be followed up at 2-years corrected gestational age for their child, for completion of a questionnaire relating to neurodevelopment only. Safety events are not expected during this period (between 30 days after birth or pregnancy loss, and 2-years post-consent); as such, events will not be collected for these participants outside of the trial safety reporting period.

8.12 Development Safety Update Reports (DSURs)

The Bristol Trials Centre, on behalf of the Sponsor, will submit DSURs once a year throughout the trial (or as necessary) to the MHRA and, where relevant, the REC. As a Type B CTIMP, PIONEER will utilise the full report format DSUR. The report will be submitted within 60 days of the Developmental International Birth Date (DIBD) of the trial each year until the trial is declared ended.

9. STATISTICS AND DATA ANALYSIS

9.1 Sample size calculation

A difference of one week in GA has been considered the minimum for doctors to consider interventions such as Progesterone for the prevention of PTB[79] and was chosen as the minimum clinically important difference for PIONEER. The estimated standard deviation (SD) (4.2 weeks) was taken from the OPPTIMUM trial of vaginal Progesterone prophylaxis for PTB (n=1228)[80]. We propose a sample size of 750 participants (375 per group), which will allow an effect size of 0.24 (1/4.2) to be detected with 90% power at the 5% 2-tailed significance level, assuming complete data for the primary outcome and treatment compliance; 85% power for up to 4% missing data and 6% non-compliance; or 80% power, allowing for up to 4% missing data and 12% non-compliance.

Increasing the sample size beyond 750 participants would require a significant increase in trial duration and cost. There are over 70 specialist PTBP clinics across the UK and we intend to recruit from at least 25 of these sites, facilitated by the UK PTB clinical network (UKPTBCN). We believe 750 participants provides a balance between having sufficient power to answer the question and delivering an answer in a timely manner.

Sample size for mechanistic sub-study

For the mechanistic sub-study, a total of 250 participants (125 in each arm) will detect a 43% decrease in IL-6 for the Pravastatin arm at 24 weeks' gestation assuming a standard deviation of 1.6[51], moderate correlation between the measurements (0.5), 90% power and 5% 2-tailed significance level. This equates to an effect size of 0.356 on the log scale. This sub-group will be recruited from at least eight sites. The main trial randomisation process will be stratified according to site, which will ensure that there are equal numbers of intervention and control group participants within this sub-study.

9.2 Statistical analysis

Statistical analyses

Analysis and reporting will be in line with CONSORT guidelines with the primary analyses being conducted on an intention to treat (ITT) basis using complete cases. This differs slightly from a true ITT analysis which would use imputation or other methods of addressing missing data to ensure that all randomised participants are included in the final analysis. Analyses will be directed by a pre-specified Statistical Analysis Plan. Continuous data will be summarized as mean and SD or median and inter-quartile range (IQR) if distributions are skewed. Categorical data will be summarized as number and percentage. Where appropriate, missing items or errors on the PARCA-R questionnaires will be dealt with according to the scoring manual via imputation methods.

The primary outcome will be compared using linear mixed models. Randomised participants who fail to complete the full course of treatment will be included in the primary analysis. All models will compare the treatment groups and will be adjusted for site and previous PTB. Sensitivity analyses of the primary outcome, restricted to participants who take at least 80% of the trial medication (threshold for adequate compliance in OPPTIMUM[80]), will be conducted. The primary analysis will take place when follow-up is complete for all recruited participants. The value of including an interim analysis will be discussed with the Data Monitoring and Safety Committee.

The mechanistic and secondary outcomes will be compared using generalised linear models (binary variables), Poisson (count variables), Cox proportional hazards (time to event variables), or linear mixed model (continuous variables measured at multiple time points) regression, with placebo as the reference group. Mixed models allow all participants with data to be included in the analysis, i.e., partial missing data (assumed missing at random) is permitted. Model validity will be checked using standard methods; if a model is a poor fit, alternative models or transformations will be explored. Analyses will be adjusted for baseline values, and stratification and minimisation variables (centre and history of previous PTB $<34^{+0}$ weeks' gestation). Findings will be reported as effect sizes with 95% Confidence Intervals (CI).

Analyses for the mechanistic sub-study will be directed by a Sample Analysis Plan, provided by Imperial College London. Some analyses will be pre-specified; others will be exploratory and based on findings.

Subgroup analyses

We will perform one subgroup analysis, considering whether participants have previously had a Large Loop Excision of Transformation Zone (LLETZ) for treatment of abnormal cervical cells. This is to investigate whether Pravastatin may be particularly beneficial for this group, which is possible as they may have a shorter cervix (mechanical), and potentially different microbiome[81]. An interaction term will be added to the model to investigate whether there is a subgroup effect.

Frequency of analyses

The primary analysis will take place when follow-up is complete for all recruited participants. Safety data will be reported to the DMSC at a frequency to be agreed, together with any additional analyses the committee requests. In these reports, the data will be presented by group however the allocation will remain blinded.

9.3 Analysis of safety endpoints

We will use descriptive statistics to describe adverse events for participants who take one or more dose(s) of the trial drug.

9.4 QuinteT recruitment intervention and qualitative data analysis

9.4.1 Screening and enrolment logs

The QuinteT researcher will analyse screening log data using the SEAR framework to observe differences between sites in recruitment patterns as new sites open[72]. Simple descriptive analyses will identify points in the recruitment pathway at which potential participants are lost to recruitment to the trial and the reasons why. Detailed eligibility and recruitment pathways will be compiled for sites, noting the point at which potential participants receive information about the trial, which members of the clinical team they meet, and the timing and frequency of appointments. Recruitment pathways will be compared with details specified in the trial protocol and pathways from other sites to identify practices that are potentially more/less efficient. Numbers of screened, eligible, approached and recruited potential participants will be compared across sites and considered in relation to estimates specified in the protocol. These data will be triangulated with qualitative findings (see below) to identify barriers, and potential solutions, to recruitment.

9.4.2 Recordings of recruitment conversations and qualitative interviews

The audio-recordings (trial recruitment discussions and interviews) will be used to explore information provision and decisions about participation, to identify recruitment difficulties and improve information provision. Audio-recorded recruitment discussions will be subjected to targeted transcription with relevant sections first identified then transcribed and identifying data removed before fuller analysis. Analysis will employ content, thematic, and novel analytical approaches, including targeted conversation analysis[82] and quanti-qual appointment timing (the 'Q-Qat method')[83], as described in the QuinteT recruitment intervention protocol[84]. Interview data will be analysed thematically using constant comparative approaches derived from Grounded Theory methodology[85].

10. DATA MANAGEMENT

10.1 Source Data

The primary source data will be the participants' maternity healthcare records, side effects questionnaire and PARCA-R questionnaire, alongside the trial Case Report Forms (CRFs). Where the trial CRF is the site of original recording, this will be considered source data. Data will be inputted to the online trial database.

10.2 Data collection

Each participant will be assigned a unique trial ID number at the point of eligibility screening. Any data relating to the participant collected on paper (e.g. consent form) should be placed in to the CRF folders, which will be stored securely at participating sites. Data collected on paper should be entered to the trial database in a timely manner.

Screening data will be collected for all pregnant people referred to PTBP clinics before 20^{+0} weeks' gestation, having been identified as being at high or intermediate risk for PTB. Sex (all screened will be biologically female), pregnant (all screened will be pregnant), English as a first language yes/no (to assess whether language is a barrier to participation), year of birth (used to characterise population) and ethnicity (to allow monitoring of trial inclusivity) will be collected for all screened pregnant people irrespective of whether they decide to participate. Postcodes of those screened will also be entered into the trial database and immediately converted into an Index of Multiple Deprivation (IMD), to assess if there is a difference between socioeconomic groups in those that decide to take part in the trial. This screening data will be collected to assess any difference in the people that do not take part compared to those that do, to establish whether any of these factors are barriers to participation. Reasons for non-inclusion will also be collected. Contact details will also be collected so that participants can be sent questionnaires and be contacted for qualitative interviews.

Partial eligibility assessment will take place, prior to receiving consent for screening blood samples (for LFTs and CK). A full eligibility assessment will take place once the results of screening blood tests are known. Full trial consent will then be received and participants will be randomised.

Baseline data will be collected after full consent has been received, prior to dispensing of trial drug. This will include, but not be limited to: demographics (including age, level of education and smoking history), pre-existing conditions, and concomitant medication use. A trial prescription will be produced for the first batch of tablets.

At 24^{+0} weeks' gestation, participants in the mechanistic sub-study will return to provide samples. These participants will also be asked about any potential adverse events they may have experienced, including SAEs.

At 28^{+0} weeks' gestation, all participants will return to collect their second batch of tablets and will be asked to complete a short side-effects questionnaire. Participants will also be asked about any adverse events they may have experienced, including SAEs. IMP compliance will be assessed at this timepoint using a pill count. Participants will also be asked to complete the Bang Blinding Index[86]. A trial prescription will be produced for the second batch of tablets.

Maternal liver transaminase concentration (ALT or AST) will be measured from a blood sample collected at 28^{+0} weeks' gestation. The participants will continue to take trial medication while the sample is being analysed. The result of the ALT or AST blood test will be recorded on the trial CRFs.

For participants in the mechanistic sub-study, additional data will be collected from trial-specific samples: vaginal swabs, blood samples, and stool samples. These data will be provided by trial researchers at Imperial College London and linked to trial participants using their unique trial ID number.

Information collected as part of routine recommended antenatal care (e.g. vital signs, physical examination, assessment of fetal wellbeing) can be collected from the participants' maternity records. Assessments performed will differ as per standard care at participating sites.

Gestational age at birth will be collected for all participants from maternity healthcare records. Maternal and neonatal secondary outcomes should be collected from hospital records within 3 months of birth.

Participants recruited during the first 18 months of the trial will be contacted via email, post, or telephone to complete the PARCA-R questionnaire at 2 years' of corrected age of their offspring. A mortality check (participant and infant) will be completed prior to this contact and contact will not be attempted if either the mother or infant has died.

Data will be collected relating to the assessment and reporting of any AEs, SAEs and SUSARs experienced by participants during the trial safety reporting period (Section 8.11).

Reasons for non-completion of any assessment will be recorded and coded, where possible. Adherence rates will be reported in results, including the numbers of participants who have withdrawn from the trial, have been lost to follow up or died.

10.3 Case Report Forms (CRFs)

Case Report Forms will be completed on paper and then entered on to the trial database in a timely manner. The exception to this is the screening information which can be entered directly into the trial database. Questionnaires completed by participants will be identifiable only by the pseudonymised trial ID number. The trial database will be set up to prompt participating site teams as to when questionnaires are due.

10.4 Data quality

The quality of the trial data will be monitored throughout the trial and data completeness will be reported to the TMG, DMSC and TSC. Any cause for concern over data quality will be highlighted and an action plan put in place.

10.5 Data handling

Data will be collected and retained in accordance with the Caldicott Principles, UK Data Protection Act 2018, and UK General Data Protection Regulation (GDPR).

Data will be submitted to the Bristol Trials Centre directly into a purpose designed, secure, password-protected, web-interface database which is maintained on a MySQL Server database system within the University of Bristol. Trial data will only be accessible to relevant members of the local research team. Information capable of identifying participants will be held in the database with access restricted to PIONEER trial staff in the central trial team and staff holding associate contracts with the University of Bristol who require access to identifying information for purposes of the trial only e.g. on-site pharmacists who will need to view the participant name on trial prescriptions. Data validation and cleaning will be carried out throughout the trial. BTC Standard Operating Procedures (SOPs) for database use, data validation and data cleaning will be followed.

10.6 Data storage

For this trial, research data will be kept for at least 25 years after the end of the trial. Data will be kept at the University of Bristol and/or participating sites for this time and, at the end of the archiving period, will be destroyed by confidential means with the exception of a final trial dataset which will be made available for data-sharing purposes.

Where trial related information is documented in the medical records, these records will be identified by a label bearing the name and duration of the trial and clearly stating the 'do not destroy before' date. Where electronic records are in use, local site policy will be followed.

An archiving plan will be developed for all trial materials storage, at the central trial team and participating sites, in accordance with the BTC archiving policy. All audio-recording files will be retained in a secure location during the conduct of the trial and for 25 years after the end of the trial, when these files will be deleted. The CI (or delegate) will provide oversight of all data destruction.

Data held at the University of Bristol will conform to the University of Bristol Data Security Policy and be held in compliance with the UK General Data Protection Regulation (GDPR), tailored by the Data Protection Act 2018.

10.7 Access to data

For monitoring purposes, the CI will allow monitors from the Sponsor (or delegate), persons responsible for audit, representatives of the Research Ethics Committee (REC) and other Regulatory Authorities to have direct access to source data/documents.

The Data Manager (in collaboration with the Chief Investigator) will manage access rights to the data set. Prospective new users must demonstrate compliance with legal, data protection and ethical guidelines before any data are released.

10.8 Data sharing

Data will not be made available for sharing until after publication of the main results of the trial. It is the trial team's intention to share underpinning research data in order to maximise reuse and evidence findings. The data will be deposited at the University of Bristol Research Data Repository (data.bris.ac.uk/data) where, once published, they will be assigned a doi. A metadata record will be published openly by the repository and this record will clearly state how data can be accessed by bona fide researchers.

Anonymised recruitment consultation and interview transcripts may also be used to support teaching of qualitative research methods. We will store audio recordings, transcripts, and written feedback for 25 years after the end of the trial, on secure University of Bristol servers. We will make transcripts "Controlled Access". The anonymised transcripts will be stored in an online database and only made available to other researchers who secure the necessary approvals. All data will be anonymised before they are made available.

Access to the final trial dataset

Anonymous research data will be stored securely and kept for future analysis. Members of the TMG will develop a data sharing policy consistent with University of Bristol policy. Requests for access will be directed to the Research Data team at Bristol, who will assess the motives of potential data re-users before granting access to the data.

11. TRIAL OVERSIGHT

11.1 Day-to-day management

The trial will be managed by the CI, with mentoring and support from senior members of the central trial team/Bristol Trials Centre who provide experience of implementing large scale clinical trials, and the Trial Manager, with full support from the wider BTC. The BTC has an established track record of designing, conducting, managing, and reporting multi-centre clinical trials. The BTC has experience in building database systems with integrated randomisation services.

The CI and BTC team will work with the co-applicants to prepare the final protocol and submissions for regulatory approvals; REC, Health Research Authority (HRA) and MHRA. The BTC will prepare trial training materials, and design and implement the data management systems.

The CI, BTC team and Sponsor (UHBW) will endeavour to ensure that the trial runs according to the agreed timetable, recruitment targets are met, the CRFs are completed accurately, the trial complies with relevant ethical and other regulatory standards, and that all aspects of the trial are performed to the highest quality. The CI and BTC team will also train investigators at participating sites, check that sites are ready to start ("green light") and monitor their progress during the trial. The Trial Manager will be the contact point to provide support and guidance to the participating sites throughout the trial.

11.2 Trial Management Group (TMG)

The trial will be managed by a TMG, which will meet approximately monthly for the duration of the trial. The TMG will be chaired by the Chief Investigator and will include trial co-applicants and representatives from the BTC.

The TMG will have responsibility for the day-to-day management of the trial and will report to the TSC.

11.3 Data Monitoring and Safety Committee (DMSC)

An independent DMSC will be established to review safety data during the course of the trial and will advise on interim analyses. The DMSC will develop a charter outlining their responsibilities and operational details. The DMSC will meet jointly with the TSC before recruitment in the trial begins and then approximately every six months during the course of the trial. The DMSC will comprise a Chairperson, Statistician and Clinician as independent members. The Chief Investigator, Trial Manager and Lead Statistician (open session only) and Trial Statistician (attending both open and closed sessions) will also attend the DMSC. The DMSC will meet prior to the TSC and will provide their recommendations.

11.4 Trial Steering Committee (TSC)

A TSC will be established, in line with funder requirements, to oversee the conduct of the trial. It is anticipated that the TSC will comprise an independent Chairperson, Statistician, Neonatologist, Senior Obstetrician and Research Midwife as well as at least one participant representative. The Chief Investigator, Trial Manager, Qualitative Researcher and Lead Statistician will represent the TMG. The TSC will meet before recruitment to the trial begins and then approximately every six months during the course of the trial.

Membership, responsibilities, and reporting mechanisms of the TSC will be formalised in a TSC charter. The TSC will make recommendations/key decisions during the trial and minutes will be sent to the funder.

11.5 Patient and Public Involvement (PPI)

Members of the public with lived experience of PTB will be involved in every phase of the trial. This will involve: group meetings; specific roles on the Trial Management Group and Trial Steering Committee; input to and review of the protocol, participant information documents and consent forms; and informing dissemination of the trial findings to participants and the wider community.

A PIONEER PPI group will be established and maintained through the life of the trial, meeting approximately monthly prior to the start of recruitment and then two to three times a year for the remainder of the trial. PPI contributions will be reimbursed in line with the NIHR payment guidance.

We will observe the principles set out in the NIHR UK Standards for Public Involvement:

- Use plain language for well-timed and relevant communications, including to a wider audience: For meetings involving PPI, we will try to avoid jargon and provide a glossary of definitions for commonly used terms. “PPI” will be a standing item in TMG meetings, and the meeting chair/PPI coordinator will specifically seek lay opinion on matters as they arise. Outside of meetings, we will aim to strike the right balance between keeping PPI contributors (co-applicant, TSC and group members) informed and involved, without over-burdening them. Our external communications will be targeted according to the intended audience, for example summary Plain English briefings via the trial website or brief updates on trial progress via social media.
- Value all contributions, building and sustaining relationships: The foundations for mutually respectful and productive working together has been laid in our work with PPI contributors pre-grant. Terms of reference will be agreed during trial set-up and activities that support this will be reviewed in an on-going manner. We will also offer training opportunities, so members can build their skills and confidence to contribute.
- Involvement in research governance, management and decision making, identifying and sharing the difference this makes to our research: Our previous experience is that good PPI often helps to identify problems and reassures the relevant regulatory authorities (including Sponsor and REC) about the design and acceptability of clinical trials. We will prospectively record how PPI influences decisions and actions, and report these at the end of the trial using the Guidance for Reporting Involvement of Patients and the Public-2 (GRIPP2) checklist.
- Communicate with a wider audience about public involvement and research, using a broad range of approaches that are accessible and appealing.

12. MONITORING, AUDIT & INSPECTION

12.1 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 and the Medicines for Human Use (Clinical Trials) Regulations 2004. All trial related documents will be made available on request for monitoring and audit by the Sponsor (or BTC if they have been delegated to monitor), the relevant REC and for inspection by MHRA and other licensing bodies.

A Trial Monitoring Plan will be developed by the Sponsor based on the trial risk assessment, which may include on site monitoring. This will be dependent on a documented risk assessment of the trial.

The Sponsor usually delegates some monitoring activities to the central trial team. Checks of the following would be typical:

- Written informed consent has been properly documented
- Data collected are consistent with the trial protocol
- CRFs are only being completed by authorised persons
- SAE recording and reporting procedures are being followed correctly
- No key data are missing
- Data is valid
- Record is maintained of recruitment rates, withdrawals and losses to follow up

12.2 Training and monitoring of sites

Initiation training

Before the trial commences at each participating site, training sessions will be organised by Bristol Trials Centre. These sessions will ensure that personnel involved fully understand the protocol, CRFs and the practical procedures for the trial. These sessions may be provided virtually or on-site.

Site monitoring

The BTC will carry out regular central monitoring and audit of compliance of sites with Good Clinical Practice (GCP) and trial-specific data collection procedures described in the protocol. The trial database will have in-built validation and the TMG will review the completeness of the data throughout the trial. The BTC will not check CRFs or other source data against the data entered to the trial database, unless there are good reasons to visit a site to complete a monitoring visit (e.g. the central monitoring highlights a problem).

Investigators' responsibilities

Investigators will be required to ensure that local research approvals have been obtained and any contractual agreements required have been signed off by all parties before recruiting any participants. Investigators will be required to ensure compliance to the protocol and with completion of the CRFs. Investigators will be required to allow access to trial documentation or source data on request for monitoring visits and audits performed by the Sponsor, BTC or any regulatory authorities.

Investigators will be required to read, acknowledge and inform their team of any amendments to the trial documents approved by the HRA/REC/MHRA that they receive and ensure that the changes are complied with.

12.3 Protocol compliance

Prospective, planned deviations or waivers to the protocol are not allowed. Accidental protocol deviations will be documented and reported to the CI and Sponsor in line with the Sponsor's Management of Breaches in Research SOP. They will also be reported to the DMSC. In the event of systematic protocol deviations, investigation and remedial action will be taken in liaison with the CI, DMSC and the TMG.

Any potentially serious protocol breaches will be reported to the Sponsor as soon as possible and within 24 hours of becoming aware of the event. The Sponsor will determine whether it constitutes a serious breach, requiring onward reporting to the REC and MHRA.

12.4 Notification of Serious Breaches to GCP and/or the protocol

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

a. the safety or physical or mental integrity of the subjects of the trial; or
b. the scientific value of the trial.

In the event that a serious breach is suspected, the Sponsor will be notified as soon as possible and within 24 hours of becoming aware of the event. The serious breach will be reviewed by the Sponsor in collaboration with the CI and, if appropriate, the Sponsor will report it to the REC, MHRA and the relevant NHS host organisation within seven calendar days of become aware of the serious breach.

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1 Governance and legislation

This trial will be conducted in accordance with:

- The Medicine for Human Use (Clinical Trial) Regulations 2004 and subsequent amendments
- Good Clinical Practice guidelines
- UK Policy Framework for Health and Social Care Research
- UK General Data Protection Regulation

Before any site can enrol participants into the trial, BTC will obtain confirmation of capacity and capability from the local NHS Trust along with any other documentation required for the central trial team to provide a "green light" letter. Approved amendments will be submitted to participating NHS Trusts for information or approval, as required.

13.2 Research Ethics Committee review and reports

Ethics review of the protocol and other trial related participant facing documents will be carried out by a UK REC. Any amendments to these documents must be approved by the Sponsor, TSC (if required) and funder prior to submission to the HRA/REC/MHRA.

All correspondence with the REC will be retained in the Trial Master File (TMF). An annual progress report will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended. The CI will notify the REC of the end of the trial and if the trial is ended prematurely (including the reasons for the premature termination). Within one year of the end of the trial, the CI will submit a final report with the results to the REC.

GCP training and trial specific training for research staff members will be at a level commensurate with their involvement within the trial. Informed consent to participate in the trial will be sought and obtained according to GCP guidelines.

13.3 Risks and anticipated benefits

13.3.1 Potential risks

Side effects from Pravastatin

Information on side effects can be found in the Summary of Product Characteristics (Pravastatin sodium 20mg tablet) for Marketing Authorisation Holder Teva UK Limited, dated 16/03/2023[2]. As discussed above, NICE advise that the risk of muscle pain, tenderness or weakness associated with Statin use is small and the rate of severe muscle adverse effects (rhabdomyolysis) because of Statins is extremely low. NICE add that there is a large body of evidence that shows that, when using high-intensity Statins (Pravastatin 5mg to 40mg is considered low-intensity), approximately 16% report muscle pain, but of these only around 1 in 12 were likely due to the Statin [75]. Elevations of serum liver transaminases have been reported. In the three long-term, placebo-controlled clinical trials CARE[76], WOSCOPS[77] and LIPID[78], marked abnormalities of ALT and AST (> 3 x ULN) occurred at similar frequency (≤ 1.2%) in both treatment groups. NICE guidance recommends that people who commence Statins should have their liver transaminase levels (AST or ALT) assessed 2-3 months following commencement of the drug to assess response to treatment [70]. Statins should be stopped if the liver transaminase level is over three times the upper limit of normal (upper limit is set by local laboratories). Potential side-effects will be monitored via the Side Effects questionnaire at 28^{+0} weeks' gestation, and maternal serum transaminases will also be assessed at the 28^{+0}-week gestation visit (as detailed in section 5.11).

Allergic reactions

Allergic reactions from mild to severe may occur in response to any constituent of a medicinal product.

Pravastatin tablets contain lactose monohydrate, hence the exclusion of potential participants with lactose intolerance.

Phlebotomy

Localised bruising and discomfort can occur at the site of venepuncture. Infrequently fainting may occur. These will not be documented as adverse events if they occur. The total volume of blood drawn over a 12-week period will be approximately 68.5ml for participants who are in the mechanistic sub-study, and 13.5ml for those who are not. Blood volumes may vary slightly for participants at different participating sites due to use of different volume vacutainers for screening bloods, following local NHS Trust procedures. This should not compromise participants, as these volumes are within safe limits.

Vaginal swabs

Only applicable to participants taking part in the mechanistic sub-study. Taking a vaginal swab is an intimate procedure and will be conducted in such a manner as to maintain privacy and dignity, and by trained members of the research team. The procedure may cause mild discomfort but should not be painful. A speculum examination is not required for acquisition of these vaginal swabs.

Stool samples

To enhance privacy and comfort, participants will be provided with pre-packaged stool sampling kits to be posted to Imperial in the participants' own time. This may cause some inconvenience, but the kit is designed to reduce the potential embarrassment that may be associated with providing a stool sample.

Time

Attending research visits at the hospital and completing the follow up activities at home will take up participant's time. Trial activities are integrated into usual care visits where possible to reduce the burden of participation, and participant expenses will be reimbursed.

13.3.2 Potential benefits

People assigned to the intervention arm only: there is a possibility that participants who receive Pravastatin will have a lower chance of PTB; however, we cannot be certain. If Pravastatin does have this effect, benefits will be to future pregnant people assessed as being at risk of PTB.

Some people find taking part in research rewarding and benefit from the extra contact from being part of the trial.

Even if an individual does not directly benefit from taking part in this trial, their involvement will inform future treatment recommendations for people at intermediate or high risk for PTB.

13.4 Informing trial participants of possible benefits and known risks

Information about possible benefits and risks of participation will be described in the PIS.

13.5 MHRA review and reports

MHRA review of the protocol and other trial related documents relating to the IMP/placebo will be carried out by MHRA. Clinical Trial Authorisation (CTA) will be obtained.

After the initial CTA has been approved, any changes which effect: the safety (physical or mental integrity) of the participants; the scientific value of the trial; the conduct or management of the trial; or the quality or safety of any IMP, will constitute a substantial amendment. A request to the MHRA for approval will be submitted.

In addition to the expedited reporting required for SUSARs, a Development Safety Update Report (DSUR) will be submitted to the MHRA once a year throughout the trial and/or on request until the end of the trial

is declared. The DSUR should consider all new available safety information received during the reporting period and assess the safety of participants included in the trial.

The central trial team will submit an end of trial summary of results on the appropriate reporting platform within one year of the end of trial declaration being submitted.

13.6 Peer review

The proposal for this trial has been peer-reviewed through the NIHR Efficacy and Mechanism Evaluation (EME) process, which includes independent expert and lay reviewers.

13.7 Financial and other competing interests

The PIONEER trial team and all PIs must disclose any ownership interests that may be related to products, services or interventions considered for use in the trial or that may be significantly affected by the trial. Competing interests will be reported in all publications and in the final report.

13.8 Indemnity

The necessary trial insurance is provided by the Sponsor. The PIS provides a statement regarding indemnity.

This is an NHS-sponsored research trial. For NHS-sponsored research 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.

14. DISSEMINATION POLICY

A publication policy will be developed following the BTC template, with authorship models agreed in advance with the TMG.

Trial findings will be disseminated by usual academic channels, for example presentation at international meetings, peer-reviewed publications (including a report to the Funder), through public contributor organisations and sending newsletters to participants. Innovative methods of dissemination will be explored such as videos, YouTube clips and blogs that are accessible to the public, as well as providing a lay summary of the results.

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16. AMENDMENT HISTORY

Record of protocol version numbers and amendments:

Version		Notes
Number	**Date**	
1.0	09/02/2024	Original, approved protocol
2.0	04/04/2024	Amendments following MHRA review. The eligibility criteria in the Protocol were reviewed and an additional exclusion criteria added 'Currently taking medicines or groups of medicines that are contraindicated in the relevant Summary of Product Characteristics (Pravastatin sodium 20mg tablet)'. The trial database will contain a drop-down menu under this exclusion criteria which will list the contraindicated medications and capture information on any contraindicated medication that pregnant women may be taking which would exclude them from participating in the PIONEER Trial. Other areas of the protocol where this applies have also been amended (see section 5.16). An additional schedule of the antenatal assessments recommended by NICE to be offered as part of routine antenatal care was added to the protocol (Table 3). Table 2 of the protocol was also updated to include assessment of vital signs, maternal physical examination, and assessment of fetal wellbeing, and highlight where these align with trial visits. The current SmPC for Pravastatin 20mg was cross checked with the protocol and section 5.16 updated with the potential interactions of Pravastatin with other therapies and if these require changes to therapy.
3.0	17/06/2024	Non-substantial amendment 1. The onset of labour and mode of birth were added to the secondary outcomes to be collected. It was also added that the CHI number will be collected for participants and their baby/babies in Scotland. The NHS/CHI number of the baby/babies will be collected in order for sites to undertake a mortality check prior to sending out PARCA-R questionnaires to participants recruited in the first 18 months of the trial. Other minor changes to the protocol e.g. typos.
4.0	06/11/2024	Non-substantial amendment 3. Addition of a sentence to the protocol to clarify that potential participants who have been sent the invitation letter and PIS may receive a call from their direct clinical care team to confirm they have received this, to ask whether they have any questions and whether they would be happy to discuss the trial further at their first clinic visit. Protocol updated in include addition of an option to enter screening data directly into the trial database. Removal of sentence which says paper copies of source data is required for CTIMPs as this is incorrect. Minor changes to the Pharmacovigilance section of the protocol to help clarify this section for sites.
5.0	01/04/2025	Non substantial amendment 4. Changes made in response to request from funder. There was an error at the top of page 67 (under 13.5 MHRA review and reports) within the following sentence: "In addition to the expedited reporting required for SUSARs, a Development Safety Update Report (DSUR) will be submitted to the MHRA once a year

		throughout the trial and/or on request until the end of the trial is declared. *The DSUR should consider all new available safety information received during the reporting period and assess the safety of participants included in the trial*." The text in italic was replaced from V3 with a symbol. This error has been corrected. Changes listed in the version control table should provide the specific changes that have been made- this has been updated. The following funder acknowledgement statement has been added: This project (NIHR152798) is funded by the Efficacy and Mechanism Evaluation (EME) Programme, an MRC and NIHR partnership. The views expressed in this publication are those of the author(s) and not necessarily those of the MRC, NIHR or the Department of Health and Social Care. Update to section 6.5 to reflect that audio recordings cannot be uploaded to the trial database and that they will be transferred either via secure NHS.net email or secure data transfer of encrypted memory cards/audio-recorders. Clarification to the emergency unblinding process on pages 28 and 36, that in the event of a medical emergency and only if there is a clinical need contact UHBW pharmacy for emergency unblinding (24 hours/day). UHBW pharmacy (Sponsor) will be available during office hours Monday to Friday 08:30 – 17:00 and an Emergency Duty Pharmacist will be available out of office hours.

17. APPENDICES

17.1 Appendix 1: Risk assessment and management tool for pregnant women at risk of preterm birth, adapted from NHS England Saving Babies' Lives Version 3[1]

Risk factor	Pathway
High risk Previous preterm birth or mid-trimester loss (16 to 34 weeks gestation).Previous preterm prelabour rupture of membranes <34/40. Previous use of cervical cerclage. Known uterine variant (i.e., unicornuate, bicornuate uterus or uterine septum). Intrauterine adhesions (Ashermann's syndrome). History of trachelectomy (for cervical cancer).	Surveillance 1. Referral to local or tertiary Preterm Prevention (PP) clinic by 12 weeks. 2. Further risk assessment based on history +/- examination as appropriate in secondary care with identification of pregnant women needing referral to tertiary services. 3. All pregnant women to be offered transvaginal cervix scanning every 2-4 weeks between 16 and 24 weeks as a secondary test to more accurately quantify the risk of preterm birth. 4. Additional use of quantitative fetal fibronectin in asymptomatic pregnant women may be considered where centres have this expertise. Management 5. Interventions should be offered to pregnant women as appropriate, based on either history or additional risk assessment tests by clinicians able to discuss the relevant risks and benefits according to up to date evidence and relevant guidance, for example, [i]UK Preterm Clinical Network guidance[1 87] and NICE guidance. These interventions should include cervical cerclage, pessary and progesterone as appropriate.
Intermediate risk Previous birth by caesarean section at full dilatation. History of significant cervical excisional event i.e., LLETZ where >15mm depth removed, or	Surveillance 1) Refer to preterm birth prevention clinic by 12 weeks. 2) Further risk assessment based on history +/- examination as appropriate in secondary care

>1 LLETZ procedure carried out or cone biopsy (knife or laser, typically carried out under general anaesthetic).	with discussion of option of additional risk assessment tests, including: a) A single transvaginal cervix scan between 18-22 weeks as a minimum. b) Additional use of quantitative fetal fibronectin in asymptomatic pregnant women can be considered where centres have this expertise. Management 3) Interventions should be discussed with pregnant women as appropriate based on either history or additional risk assessment tests by clinicians able to discuss the relevant risks and benefits according to up-to-date evidence and relevant guidance. These interventions should include cervical cerclage, pessary and progesterone as appropriate. 4) Pregnant women at intermediate risk should be reassessed at 24 weeks for consideration of transfer back to a low-risk pathway.