Academic and Clinical Central Office for Research and Development

Study Protocol

A Feasibility Study Investigating **P**ravastat**i**n for the Prevention of **P**reterm B**i**rth in Wome**n**

PIPIN

Co-sponsors	The University of Edinburgh & Lothian Health Board ACCORD The Queen's Medical Research Institute 47 Little France Crescent Edinburgh EH16 4TJ
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PROTOCOL APPROVAL SIGNATURE PAGE

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PIPIN

EudraCT

The undersigned accept the content of this protocol in accordance with the appropriate regulations and agree to adhere to it throughout the execution of the study.

Name			24/05/2019
Chief Investigator	**Signature**		**Date**
Name			
Trial Statistician	**Signature**		**Date**
Name			
Lead Co-Sponsor Representative	**Signature**		**Date**

For multi-site trials, the Principal Investigator must sign below to document that the protocol has been read and understood.

Name				
Principal Investigator	**Signature**		**Site**	**Date**

Following any amendments to the protocol, this page must be re-signed.

A signed copy of the protocol is required for R&D submission

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LIST OF ABBREVIATIONS

This is not an exhaustive list.
Any additional abbreviations used within the protocol must also be added here.

ACCORD	Academic and Clinical Central Office for Research & Development - Joint office for The University of Edinburgh and Lothian Health Board
AE	Adverse Event
AR	Adverse Reaction
CI	Chief Investigator
CK	Creatinine Kinase
CRF	Case Report Form
CSU	Catheter Specimen Urine
CSR	Clinical Study Report
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
CTG	Cardiotocography
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
ECTU	Edinburgh Clinical Trials Unit
EDD	Estimated Date of Delivery
EudraCT	European Clinical Trials Database
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HELLP	Haemolysis, elevated liver enzymes and low platelets
IB	Investigator Brochure
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
ISF	Investigator Site File
ISG	Investigational Supplies Group
ISRCTN	International Standard Randomised Controlled Trials Number
LFTs	Liver Function Tests

LLETZ	Large Loop Excision of the Transformation Zone
LPS	Lipopolysaccharide
LVS	Low Vaginal Swab
MHRA	Medicines and Healthcare products Regulatory Agency
MSU	Mid-Stream Urine
NICE	National Institute for Health and Care Excellence
PI	Principal Investigator
PIL (PIS)	Patient Information Leaflet (Sheet)
NIMP	Non-Investigational Medicinal Product
QA	Quality Assurance
QMRI	Queen's Medical Research Institute (Edinburgh)
QP	Qualified Person
RCOG	Royal College of Obstetricians and Gynaecologists
REC	Research Ethics Committee
ROM	Rupture of Membranes
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee

TRIAL SUMMARY

Trial Title	A Feasibility Study Investigating **P**ravastat**i**n for the Prevention of **P**reterm B**i**rth in Wome**n**
Study Acronym	PIPIN
Clinical Phase	Phase II
Trial Design	Randomised Control Trial
Trial Participants	Pregnant patients presenting in preterm labour between 24+0-35+6 weeks gestation
Planned Number of Participants	40
Planned Number of Sites	Initially single site, but may be extended to multi-site should this be required for recruitment
Countries Anticipated to be Involved in Trial	Scotland
Treatment Duration	7 days
Follow up Duration	28 days post estimated date of delivery
Total Planned Trial Duration	2 years
Primary Objective	To evaluate the feasibility of recruitment of patients in preterm labour to a randomised controlled trial
Secondary Objectives	Evaluate pravastatin for use in preterm labour to prolong pregnancy, reduce contraction frequency and lower maternal and fetal markers of inflammation. Identify any adverse effects associated with use of Pravastatin in preterm labour. Observation of average time from presentation of the participant to first dose of treatment received, acceptability of the trial and compliance with 7 days of blinded treatment. To perform pharmacokinetic studies of pravastatin in pregnancy
Primary Endpoint	Recruitment, retention and outcome collection of 40 Participants in established preterm labour

Secondary Endpoints	1) Retention, adherence and ability to collect clinical outcomes from participants 2) Time to delivery from presentation and gestation at delivery 3) Contraction frequency from presentation to delivery or cessation of regular uterine activity. 4) Maternal markers of inflammation including, but not limited to: IL-6, IL-10, IL-13, IL-17, TNFa, IL-1RA, sTNF-RI, sTNF-R2, and HO-1, as well as levels of the soluble IL-6R and the inhibitor spg130 (abbreviated hereafter to 'Inflammatory Profile') 5) Fetal measures of inflammation (cord IL-1, IL-6, IL-8) as well as levels of sIL-6R and sgp130. 6) Adverse events (maternal and fetal) 7) Time from 'time first seen' to delivery of first dose of trial medication 8) Compliance with 7 days of blinded treatment 9) Acceptability of the trial to those who have participated 10) Pharmacokinetic parameters as compared with current published data 11) Maternal outcomes: a. Proven maternal infection b. Safety of intervention to mother (self-reported AEs and biochemical monitoring of liver function tests and creatinine kinase). c. Pre-labour ROM d. Duration, location and level of care of hospital stay following presentation with suspected preterm labour AND following delivery. 12) Neonatal outcomes: a. Details of in utero transfers including mode of transport required b. Gestational age at delivery, morbidity and mortality, birthweight, duration and location of hospital stay post-delivery and up to 28 days post EDD. c. Safety of intervention
IMP(s)	Pravastatin 40mg Tablets, Teva UK LTD (encapsulated) Placebo 40mg capsules
IMP Route of Administration	Orally
NIMP(s)	Nil

Lay Summary of Trial	Preterm birth contributes to around 11% of all births worldwide and is the major cause of infant morbidity and mortality. Whilst in the UK survival of babies born preterm has improved, the proportion of survivors without long term developmental problems has not, and current treatments are ineffective at preventing this. This study aims to see whether women in preterm labour would be willing to be randomised to take a tablet (pravastatin) or placebo. Preterm labour is known to be due to both inflammation within the womb and contractions. Pravastatin in an anti-inflammatory agent which has been used safely in pregnancy, and which appears in in animal studies to reduce preterm labour associated events. We hope if women are willing to accept this trial and participate, this will help us develop a larger clinical study to find a new treatment for preterm labour.

1. INTRODUCTION

1.1 BACKGROUND

Spontaneous preterm labour is the biggest cause of preterm birth (Norman et al. 2009). Preterm birth is itself the major cause of infant mortality and morbidity, accounting for 11% of births worldwide (Blencowe et al. 2012). It is estimated that nearly one million children every year have neurodevelopmental disability as a direct consequence of preterm birth (Blencowe et al. 2013), with pulmonary, cardiac and gastrointestinal dysfunction all described in surviving infants (Rubens et al. 2014)

The aetiology of preterm birth remains an incompletely understood process, with roughly 75% occurring spontaneously in the UK (the remainder being iatrogenic for maternal or fetal reasons) (Rubens et al. 2014). Known aetiological factors contributing to preterm birth include infection and inflammation, uteroplacental haemorrhage or ischaemia, or uterine over distension such as in the multiple pregnancy(Goldenberg et al. 2008). There are also several well described clinical risk factors including previous preterm birth

Currently available treatments options include antibiotics, tocolysis and magnesium sulphate (for fetal neuroprotection as opposed to arrest of labour).(Preterm labour and birth | Guidance and guidelines | NICE n.d.) Unfortunately neither antibiotics nor tocolysis have been shown to provide short term benefit to both the mother and fetus (only in certain circumstances), and no long term benefit to children born at 37 weeks gestation or less (Flenady et al. 2013, Haas et al. 2012).

Magnesium sulphate, whilst recommended by NICE for fetal neuroprotection, does not prevent preterm labour. (Preterm labour and birth | Guidance and guidelines | NICE n.d.)

As considerable evidence implicates inflammatory mediators in both the underlying mechanisms of parturition (term and preterm), and initiation of brain damage which leads to neurodevelopmental disability associated with preterm delivery (Boyle et al. 2017), it follows that the ideal agent for the treatment of preterm labour would be one which both inhibits myometrial contractility and conveys anti-inflammatory benefit. . Our *in vitro* and pre-clinical *in vivo* studies suggest that statins have both actions. We hypothesise that statins may reduce preterm labour associated preterm birth AND reduce long term neurodevelopmental disability.

Of the statins in current clinical use, we have selected pravastatin for this feasibility study as it now has an established safety profile in pregnancy. (Bateman et al. 2015) (Lefkou et al. 2016)(Costantine, Cleary, Hebert, Ahmed, Brown, Ren, Easterling, Haas, Haneline, Caritis, Venkataramanan, West, D'Alton, Hankins, and Eunice Kennedy Shriver National Institute of Child Health and Human Development Obstetric-Fetal Pharmacology Research Units Network 2016). Furthermore, when pravastatin was being investigated for potential use in both refractory anti-phospholipid syndrome and pre-eclampsia, pregnancy was prolonged in the treatment group (STAMP - ISRCTN23410175) (Lefkou et al. 2016).

1.2 RATIONALE FOR STUDY

In this trial, we are aiming to demonstrate the feasibility of a randomised controlled trial of statins versus placebo for women presenting in preterm (24+0 to 35+6 weeks gestation) labour.

As aforementioned, the treatment of preterm labour remains an unmet clinical need and current therapeutic options provide little short term benefit to both the mother and fetus (and only in certain circumstances), and no long term benefit to children born at 37 weeks gestation or less.

Statins in pregnancy

Statins are widely used to treat hypercholesterolaemia and coronary heart disease. Statins act by inhibiting cholesterol synthesis but have pleotrophic anti-inflammatory properties (Sirtori 2014). Until relatively recently, statins were contraindicated in pregnancy due to concerns about teratogenic effects. This is based on a 1983 study, when fetal skeletal malformations were observed in rats given toxic doses (800 mg/kg/day) of lovastatin, a highly lipophilic statin. (Minsker et al. 1983). However, this effect was not seen when hydrophilic pravastatin was administered to pregnant rats in doses up to 1000mg/kg/day (around x120 the dose used in patients based on surface area) (StAmP, ISRCTN23410175) Importantly, in human studies, there is little evidence to support this concern: a recent comprehensive prospective study of over 1000 women found no increase in congenital malformations in women who had taken statins when increased background risk due to maternal illness was corrected for (Bateman et al. 2015). .

Whilst there have been some data suggesting an increased risk of the condition VACTERL (three or more of the following findings: vertebral, anal, cardiac, tracheal, oesophageal, renal, and limb defects), all of these cases (2 out of 52), the offending statin was lovastatin (lipophilic), and indeed all reports of congenital malformation following maternal statin exposure pertained to lipophilic statins (Edison and Muenke 2004). Furthermore, as the critical time period for organogenesis is first trimester, this is less relevant to our CTIMP where the intervention will specifically only be used above 24+0 weeks gestation.

Other trials using statins
Several trials have recently used Pravastatin in this pregnant population.

In the context of refractory antiphosphlipid syndrome, Pravastatin showed a pregnancy prolonging effect of pravastatin with no congenital abnormalities or late fetal deaths, and no evidence of maternal morbidity because of the use of pravastatin.(Lefkou et al. 2016). This is in keeping with a UK based biomarker efficacy study investigating the use of pravastatin for the severe form of pre-eclampsia. This will shortly report (6)(STAMP - ISRCTN23410175, manuscript in preparation). Whilst the STAMP trial showed that pravastatin did not affect levels of the primary outcome biomarker, it again prolonged pregnancy with no major safety issues (Williams, personal communication).

Statins as therapies for preterm labour

Anti-inflammatory effects

Pre-clinical studies have suggested that the statins pravastatin and simvastatin, administered to pregnant mice, exert anti-inflammatory effects within the feto-placental unit (Basraon et al. 2012). These feto-placental anti-inflammatory effects have been confirmed in human tissues by ourselves and others. For example, Basraon et al have shown that statins attenuate the production of pro-inflammatory cytokines induced by lipopolysaccharide (LPS) in a human fetal membrane explant model (Basraon et al. 2015). Additionally, in a myometrial cell line obtained from a pregnant woman, we show that 50μM simvastatin inhibits pro-inflammatory cytokine expression induced by LPS, AND that it inhibits LPS induced contractions.

Treatment of preterm labour in a pre-clinical model

Having shown that simvastatin exerts anti-inflammatory effects *in vitro*, we showed that simvastatin also reduces LPS induced IL-6 synthesis i*n vivo* in a mouse model of preterm labour. Importantly, we also showed that simvastatin attenuates LPS induced preterm birth and pup death. These data demonstrate the significant potential of statins as effective treatments for preterm birth.

Pharmacokinetics and potency of statin formulations

There are a variety of formulations of statins each of which have different potencies, chemical structures, bioavailablility, lipo/hydrophilicity, dependence on cytochrome P450 metabolism, cellular transport and pharmacokinetics (Sirtori 2014)(Bateman et al. 2015)(Egom and Hafeez 2016; Oliveira et al. 2016). Pravastatin was the statin chosen for the STAMP trial because its hydrophilicity means that placental transport (and hence fetal exposure to the drug) is likely to be minimal (Bedi et al. 2016). This assumption has largely been borne out in pharmacokinetic studies(Costantine, Cleary, Hebert, Ahmed, Brown, Ren, Easterling, Haas, Haneline, Caritis, Venkataramanan, West, D'Alton, Hankins, Eunice Kennedy Shriver National Institute of Child Health and Human Development Obstetric-Fetal Pharmacology Research Units Network, et al. 2016).

Furthermore, the pharmacokinetics of pravastatin compared with alternative statins (notably metabolism via chemical degradation in the stomach as opposed to via the cytochrome P450 enzyme chain, and dual elimination via both renal and hepatic routes) mean that there is a lower chance of drug interaction with required medications for the study group.

Benefits to participants

As this is a feasibility study, there is no direct proven benefit to participants. All Participants will receive the gold standard care for preterm labour as per local NHS guidelines. Importantly, where women will be recruited, we do not use any tocolysis, and erythromycin is only given to women with fetal membrane rupture (who would not be eligible for this study) so we do not anticipate any contradictions to usual practice due to involvement in this trial. Based on both our pre-clinical data, and data from the StAMP trail (STAMP - ISRCTN23410175), there may be some benefit from prolongation of pregnancy effect in the treatment arm of this trial.

2. STUDY OBJECTIVES

2.1 OBJECTIVES

2.1.1 Primary Objective

This CTIMP is a feasibility study of the acceptability of a randomised controlled trial of a statin or placebo for women in preterm labour.

2.1.2 Secondary Objectives

Overall, the goal of this study is to inform design of a multicentre randomised controlled trial, and the secondary objectives are based on aspects of this.

1) To evaluate whether administration of pravastatin when compared with placebo to women in preterm labour is associated with prolonged time to delivery , a reduction in contractions, and lower maternal and fetal markers of inflammation without adverse effects.
2) To evaluate whether administration of pravastatin when compared with placebo to women in preterm labour improves maternal and fetal outcomes
3) To monitor the average time from a participant's first contact with medical staff to delivery of the first dose study drug.
4) To ascertain the acceptability of the study design to participants after completion of the protocol.
5) Record participant compliance with treatment
6) To describe the pharmacokinetics of pravastatin in the study population as compared with published parameters.

2.2 ENDPOINTS

2.2.1 Primary Endpoint

For this trial, the primary endpoint the proportion of patients presenting in preterm labour between 24+0 and 35+6 weeks gestation who consent to enter the trial.

2.2.2 Secondary Endpoints

Secondary Endpoints:

1) Retention, adherence and ability to collect clinical outcomes from participants
2) Time to delivery from presentation and gestation at delivery
3) Contraction frequency as monitored at presentation and from randomisation to delivery or cessation of regular uterine activity.
4) Maternal markers of inflammation including, but not limited to: IL-6, IL-10, IL-13, IL-17, TNFa, IL-1RA, sTNF-RI, sTNF-R2, and HO-1, as well as levels of the soluble IL-6R and the inhibitor spg130 (abbreviated hereafter to 'Inflammatory Profile')
5) Fetal measures of inflammation including but not limited to: (cord IL-1, IL-6, IL-8, sIL-6R and sgp130.
6) Adverse events (maternal and fetal)
7) Time from time first seen in an acute obstetric care setting to administration of trial medication as documented in the participant medical records.
8) Compliance with 7 days of blinded treatment
9) Acceptability of the trial to those who have participated
10) Pharmacokinetic parameters as compared with current published data
11) Maternal outcomes:
    a. Proven maternal infection
    b. Safety of intervention to mother (self-reported AEs and biochemical monitoring of liver function tests and creatinine kinase).
    c. Pre-labour ROM
    d. Duration, location and level of care of hospital stay following presentation with suspected preterm labour AND following delivery.
12) Neonatal outcomes:
    a. Details of in utero transfers including mode of transport required
    b. Gestational age at delivery, morbidity and mortality, birthweight, duration and location of hospital stay post-delivery and up to 28 days post EDD.
    c. Safety of intervention

3. STUDY DESIGN

Type of Trial

This is a double blind randomised placebo controlled trial. We anticipate an 18 month period from first Participant recruitment, with a further 6 months for outcome ascertainment, analysis and reporting (see Figure 1, Appendix 3: study timeline for further details). Each participant will be asked to administer the intervention (pravastatin or placebo) for a total of 7 days or until delivery (whichever occurs soonest), and will be followed up until 28 days after the estimated date of delivery (EDD).

Potential participants for recruitment will be identified following presentation to acute obstetrics services with threatened preterm labour. Women at high risk of preterm labour and delivery will also be identified from Antenatal Clinics i.e. the Preterm Birth Clinic (if available locally) and provided with information regarding the trial. Should these women then develop signs and symptoms of preterm labour, it is hoped that pre-information about the trial will improve recruitment.

Duration of trial

The primary outcome (recruitment) will be measured from the first participant's first visit to 28 days post EDD of the last (40th) participant's (recorded as last participant's last visit). Monitoring of secondary outcomes will begin following consent of the first participant to EDD plus 28 days of the last participant recruited.

Treatment Phase

The total treatment phase will be 7 days for each participant, or until delivery (whichever occurs soonest). Follow up will continue until EDD + 28 days.

Outcome Measurement

On recruitment to the trial, all participants will receive a study diary. They will record adverse events, compliance with treatment and administration and exact timing of self-medication with the IMP. Contraction frequency will also be recorded, either as monitored by the clinical team caring for the participant, or the participant herself. These data will be collected daily by the participant for the duration of the intervention (7 days or until delivery, whichever occurs soonest). Diaries will be collected at the day 7 visit by the research team member conducting the visit, and transcribed to pCRF and/or eCRF. Other outcomes will be reviewed and collected from the participant's clinical medical notes.

Feedback Questionnaire

At, or close to, EDD + 28 days, feedback regarding the participants' experiences of PIPIN will be requested in the form of an itemised questionnaire with space for free-text comments. Participants will be contacted via their preferred method of contact (telephone, email or post). Should the conversation be via telephone, responses provided will be recorded by a member of the research team on the form.

Should participants express concern regarding their care, these concerns will be explored. Participants will be offered the opportunity of raising their concerns either formally, or informally, with a senior member of the research team. They can also be directed to the senior clinician responsible for their care, or to the formal NHS Lothian complaints team. Details of this are included in the PIL.

Location of trial visits

Should participants remain in hospital for the duration of the treatment phase, but not progress to delivery, all trial visits will occur in the inpatient setting.

For participants discharged to the community during the treatment phase by their obstetrician, a mutually convenient appointment will be made for the day 7 trial visit. This may occur in hospital or at the participants' home depending on their availability.

Blood Tests

All participants will have baseline LFTs and CK, a twice daily inflammatory profile (see 2.2.2 for details) on day 1, a single inflammatory profile on day 2, and a further inflammatory profile + LFTs/CK at the day 7 trial visit. Serum pravastatin level will also be checked at baseline, and concomitantly with all inflammatory profile measures for compliance assessment.

At the time of delivery, all participants will have serum and cord samples taken for an inflammatory profile as above, and, for those who deliver within the 7 day treatment phase, a serum and cord pravastatin level

A summary of these blood tests can be found in appendix 3, and exact methods for sampling, storage and processing will be detailed in a separate document.

Contraction Frequency

For participants who are contracting at a frequency ≥ 1 in 10 minutes post randomisation, uterine contraction frequency will be recorded every hour until delivery, or until contractions occur at a frequency of <1 in 10 for 4 consecutive hours. Participants will be shown how to monitor contraction frequency and will record this in their diary.

Compliance

Compliance (number of tablets taken) will be collected from the participants' medical records and at the day 7 trial visit (from the participant's diary) and the returned medication bottles. Serum pravastatin levels will also be taken to evaluate compliance.

Timing from presentation to first dose administered

Timing of presentation to first treatment dose administered will be collected from the participants' medical records.

Delivery, post-natal and neonatal outcomes

At the time of delivery, secondary outcomes of gestational age at delivery, markers of fetal and maternal inflammation and pravastatin levels will be collected (via medical records and maternal and cord blood samples).

Maternal and neonatal outcomes will be monitored and information extracted from the participants medical records until EDD + 28 days.

Acceptability of the Trial

This will be collected at two points:

1) Percentage uptake of eligible participants to the trial
2) At or near 28 days post EDD, participants will be contacted using their preferred method of contact, thanked for their involvement and asked for feedback.

Stopping Rules

We have set the following safety rules for PIPIN based on maternal and neonatal deaths that are possibly or definitely related to IMP. We have based these rules on the expected frequency of maternal and neonatal deaths in the population.

We do not anticipate that there will be any maternal deaths (maternal death rate in the UK is 8.5 per 100,000). So in n=40 women we would not expect any deaths – we would need to recruit almost 12,000 women to expect 1 death.

We anticipate that the death rate of babies in the PIPIN population will be at least 6% (based on the Oracle study, which also recruited women in preterm labour (Kenyon et al. 2001). The Oracle study recruited women suspected clinically to be in preterm labour; in PIPIN we will recruit women in whom a "test" has additionally confirmed the onset of preterm labour, hence preterm birth (with associated neonatal death) is more likely to occur in PIPIN).

With an expected death rate of 6%, we consider that a doubling of this rate would be grounds for serious concern, if such deaths were thought to be related or possibly related to study IMP, that will prompt a halt in recruitment pending review by the independent DMC (iDMC), We will randomize around 20 to pravastatin, and assume there is no cross over from placebo to pravastatin (although of course as safety data these will be analysed according to treatment received). If there is 1 death thought to be related to IMP in any the first 10 randomised to pravastatin, or cumulatively 2 deaths in the first 20 randomised to pravastatin, this will trigger a review by the iDMC, and if the iDMC believes that it is plausible that the deaths are related to the IMP, the DMC will advise whether the trial should be stopped, or the circumstances under which the trial should continue.

The two most severe class side effects of statins, that is liver toxicity (defined by jaundice, hepatitis or fulminant hepatic necrosis) and muscular toxicity (rhabdomyolysis), both occur at a frequency of less than 1 < 10,000. Occurrence of these in any participant with reasonable suspicion of causation due to the IMP will prompt review of unblinded data by the DMC.

4. STUDY POPULATION

4.1 NUMBER OF PARTICIPANTS

We will to recruit 40 participants. Eligible participants are pregnant women presenting in preterm labour at 24+0 to 35+6 weeks gestation. Preterm labour is defined as regular uterine activity with either a positive fetal fibronectin (See Appendix 5) or evidence of cervical change as monitored through cervical length scanning or direct observation of dilation.

We estimate a duration of 2 years with an 18 month recruitment period. Follow up of participants to last Participant last visit will take up to another 6 months.

4.2 INCLUSION CRITERIA

To be eligible to take part in the PIPIN study, the below inclusion criteria must be met:

- Ability to Give Consent
- Gestation ≥24+0 and ≤ 35+6 weeks (based on dating scan obtained at ≤ 16 weeks gestation)
- Singleton pregnancy
- Aged 16 years or above
- Not previously recruited to this study in this pregnancy
- Intact membranes
- A positive fetal fibronectin test (See Appendix 5) OR a short cervical length (≤ 15mm) on ultrasound examination OR cervical dilation ≥ 3cm and less than fully dilated
- Uterine activity defined as ≥ 1 palpable contraction over 20 minutes of CTG monitoring.

- No major congenital anomalies evident on the 20 week anomaly scan, or any further anomaly scans performed subsequently. If an anomaly is present, this should be classified as per ICD-10 codes and minor anomalies discussed for inclusion on a case by case approach involving the clinical team, the PI and the participant.
- Not demonstrating any of the exclusion criteria as detailed below

4.3 EXCLUSION CRITERIA

- Immediate delivery deemed necessary for fetal or maternal reasons as determined by a senior clinician.
- Pre-labour, preterm rupture of membranes in the index pregnancy
- Obstetric Cholestasis as defined by RCOG (RCOG Green-Top Guideline, Number 43)
- Established severe pre-eclampsia or HELLP syndrome as defined by NICE guidance (Hypertension in pregnancy: diagnosis and management | Guidance and guidelines | NICE n.d.)
- Known History of hepatic or renal impairment
- Ingestion of drugs thought to alter the pharmacokinetics or efficacy of statins, including erythromycin and/or nifedipine.
- Taking any one of the prohibited drugs as listed the SmPC and in 6.7.3
- Lactose intolerance (due to excipient in Pravastatin and placebo)
- Current or previous alcohol misuse
- Personal or first degree relative with heritable muscle disorders
- Participating in another CTIMP trial

4.4 CO-ENROLMENT

Patients already recruited to a non-CTIMP trial will be permitted to co-enrol as per the ACCORD Co-enrolment Guidelines (GL001 Guidelines for Co-enrolment).

Patients already recruited to a CTIMP will not be eligible. This will be checked for by direct questioning of the patient and review of the patient's electronic health record.

5. PARTICIPANT SELECTION AND ENROLMENT

5.1 IDENTIFYING PARTICIPANTS

Two strategies of participant identification will be used. Those at high risk of preterm labour and delivery are routinely seen at a dedicated antenatal clinic, and during these visits will be offered an invitation letter by a member of their clinical care team. This letter will contain information about the trial. They will also be offered the opportunity to discuss the trial with their clinical team and the research team. This should improve participant understanding should they subsequently present acutely with preterm labour, and may improve recruitment.

Secondly, eligible participants will be identified by their clinical care team on presentation for acute assessment or care with signs and symptoms of preterm labour. Participants will be offered a PIL and the opportunity to discuss the trial, and should they wish to proceed, delegated clinical care providers will be able to assess for eligibility and consent participants.

Should participants require additional investigations to confirm eligibility e.g. a cervical length scan (in the case of contraindication to fetal fibronectin for example), this can be arranged through the scanning department or by contacting the trial team. Should participants be identified as appropriate by the clinical team and happy to discuss the trial, but no delegated personnel available for consent, the trial team can be contacted to attend.

5.2 CONSENTING PARTICIPANTS

Participants will be offered PIL by a member of their clinical care team at the time of presentation for acute assessment and care, and an appropriate amount of time allowed for consideration of participation. Whilst the nature of the intervention is time-critical, they will of course be offered as long as required to consider participation.

Both obstetric and midwifery staff who have completed the appropriate training will be delegated to consent participants.

Potential participants who may not adequately understand written or verbal information in English, an approved translator will be offered. Where this is not possible in a timely fashion, the NHS-approved telephone interpretation service will be offered. Signing interpreters will be offered where required and if available. For participants with a visual impairment, both the PIL and consent form can be verbally read to them, and completed in the presence of a witness.

5.3 SCREENING FOR ELIGIBILITY

Pre-randomisation assessments to confirm eligibility include one or more of the following:

- A positive fetal fibronectin (See Appendix 5), obtained in accordance with hospital guidelines.
- Clinically confirmed cervical dilation ≥ 3cm
- A cervical length < 15mm. (In the case of patients who have had multiple LLETZ procedures, and are known to have a shorter cervix from serial assessments, those with a > 50% reduction compared with a baseline length will also be eligible).

Eligibility will be confirmed by appropriately trained, delegated clinicians and confirmation of this recorded in the participants' medical records.

An anonymised screening log will be maintained of all patients considered for the trial, including those who decline to participate. This will include patient age and gestation at presentation, as well as the results of the above screening tests.

If a participant declines to participate, withdraws prior to randomisation, or is excluded following consent but prior to randomisation for any reason, the minimal anonymised information will remain on the screening log. If participants are willing to offer a reason for declining to participant, this will also be held on the screening log.

5.4 INELIGIBLE AND NON-RECRUITED PARTICIPANTS

Details will be maintained as above for ineligible participants including reason for ineligibility, and these patients will be treated as per local guidelines for preterm labour.

For participants who consent to participation but who are not randomised, reason for this will be recorded in the screening log e.g. Participant withdrew consent or delivered prior to administration of first dose of intervention. This is an intention to treat study therefore data will be collected from consented, non-randomised participants.

5.5 RANDOMISATION

5.5.1 Randomisation Procedures

Participants will be randomised to active or placebo in a 1:1 ratio. Randomisation block size will use permuted blocks of size 2, 4, and 6, randomly sorted, and spliced with occasional randomly inserted simple runs of random length to aid unpredictability. Randomisation codes will be provided to ISG by ECTU, and packs dispensed in a sequential fashion from these. Details of the study pack number allocated will be recorded in the Participant's notes, on the medication record as well as in the drug accountability log in the treatment room of labour ward.

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This trial will be double blinded. Randomisation codes will be held by both ECTU and the local Pharmacy department.

5.5.2 Treatment Allocation

Drug stocks will be held by the local pharmacy department with a small supply located in a locked cupboard in the clinical treatment area i.e. Labour Ward. Following randomisation, the next sequential pack as allocated will be detailed in the accountability log and removed from the clinical treatment area supply shelf, checked out with the consenting physician and an additional member of staff, and prescribed on the inpatient drug Kardex as 'study drug pravastatin/placebo code *** 1 tablet every 24 hours.' Following dispensing, the first dose will be administered to the participant in a timely fashion.

Whilst as an inpatient, the trial drug can be dispensed either by the midwife caring for the participant as with standard prescribed medication, or by the participant herself (marked as 'self' on the Kardex). The box containing the trial drug can be stored in the locked bedside cabinet to avoid loss / missed doses. Participants will receive instructions to take one tablet each day, at the same time each day.

Administration of the drug will be discontinued after 7 days (i.e. 7 doses) of treatment or following delivery if sooner.

Should the participant be discharged prior to completion of the 7 day course, the trial medication will be prescribed on the discharge letter under 'other drug' and using the same terminology as on the medication Kardex (including pack number). The participant will be advised to continue taking the medication once daily until there are no further tablets remaining.

There will be space in the participants' daily diary to record the time of dose administration.

5.5.3 Emergency Unblinding Procedures

Breaking of the study blind should only be performed where knowledge of the treatment is absolutely necessary for further management of the participant

There will be no central unblinding facility but the on-site pharmacy will hold the unblinding information held in sealed envelopes. Thus unblinding (emergency or otherwise) can be carried out by a pharmacist 24 hours a day, 7 days a week, if requested by a senior clinician (normally a consultant). The name of the clinician requesting the unblinding and the reason for it will be sent to the Chief Investigator via e-mail. Reasons for unblinding will be collected via the e-CRF. Unless there is a clinical requirement, the blind will not be broken to the trial team until after data entry is complete and the database locked. Details of the unblinding will be kept in pharmacy.

In the event of SUSAR, the Co-Sponsor will be able to unblind by the same mechanism as above.

5.6 WITHDRAWAL OF STUDY PARTICIPANTS

Participants are free to withdraw from the study at any point or a participant can be withdrawn by the Investigator. Pre-specified investigator initiated indications for study withdrawal includes:

- Consent withdrawn
- SUSAR
- Fetal demise in utero
- If the participant develops severe pre-eclampsia or HELLP syndrome
- The clinical team judge that immediate delivery is advised, for example in the case of development of severe sepsis or evidence of fetal compromise.

Note that delivery is not a reason for withdrawal as this is an outcome.

If withdrawal occurs, the primary reason for withdrawal will be documented in the participant's medical records and CRF if possible. The participant will have the option of withdrawal from:

(i) Taking the study medication, with continued study procedures and collection of clinical and safety data

(ii) all aspects of the trial but continued use of data collected up to that point

If a participant wishes to withdraw from the trial, the trial team will be informed and withdrawal will be recorded in the medical notes, along with the aspects from which they wish to withdraw.

Participants that withdraw following administration of the first dose of intervention or any doses thereafter will not be replaced. Data will continue to be collected where possible to allow intention to treat analysis.

6. INVESTIGATIONAL MEDICINAL PRODUCT AND PLACEBO

6.1 STUDY DRUG

6.1.1 Study Drug Identification

Pravastatin Sodium 40mg tablets

6.1.2 Study Drug Manufacturer

The IMP (Pravastatin 40mg) will be manufactured by:

Teva UK Limited
Ridings Point
Whistler Drive
Castleford
WF10 5HX
Tel: +44 (0) 1977 628500

It will be supplied to ISG (Investigational Supplies Group) who will perform overencapsulation of the pravastatin, and who will manufacture the placebo to be used.

6.1.3 Marketing Authorisation Holder

Teva UK Limited, Marketing Authorisation PL-00289/0409

6.1.4 Labelling and Packaging

Medication labels will be in the local language (English) and comply with the legal requirements of Annex 13 of the European Union's Good Manufacturing Practice (GMP).

Additional packaging for the trial will be provided by the GMP compliant company ISG and released to site by a QP. This involves overencapsulation of the IMP in 'Swedish Orange' 00 capsules, with a back filling of lactose. Placebo will be created using the excipient of pravastatin (lactose), again overencapsulated in Swedish Orange 00 capsules. 60 bottles of IMP / Placebo,each containing 7 doses will be provided. The bottles will blind labelled according to randomisation with 'Study Drug Pravastatin/Placebo, 7 capsules, Code ***' The label will have a space on which to write the participant's name..

6.1.5 Storage

The majority stock of trial drugs (including both pravastatin and placebo-containing bottles) will be stored in the local hospital pharmacy. A subset of this stock, ready for dispensing to participants, will be kept on in a locked cupboard in the clinical treatment area i.e.labour ward, from where it can be dispensed in as previously described. When stock in clinical area reaches critical levels as determined by the randomisation block size, further stock will be ordered from the local pharmacy to replenish.

Daily temperature monitoring during the working week (Monday – Friday) will occur both in pharmacy and on labour ward, and a log retained for accountability. Over the weekend maximum temperature inside the storage cupboard will be recorded.

Should the temperature rise above 30C, the IMP subjected to this will be quarantined and a risk assessment performed to assess suitability for ongoing use.

Drugs will be transported from ISG via courier.

6.1.6 Regulatory Release to Site

This will be performed by the QP from ISG, in two batches of 30 bottles. Batch one will be released prior to randomisation of the first participant, and batch 2 approximately 12 months after this. However, batch 2 may be released sooner if recruitment warrants this.

6.1.7 Destruction of Trial Drug

Destruction of trial drug will be via the local pharmacy. At the end of the 7 day intervention period, the bottles will be collected by the trial team (at the day 7 visit). Compliance will be checked by the trial team through a count of any tablets remaining. This will be recorded in the pCRF / eCRF, and the bottles then returned to pharmacy for a further accountability check. All counts should be recorded in the accountability log.

From there, pharmacy will dispose of any remaining drug after receiving confirmation to do so from the sponsor or the sponsor's delegate. Destruction will occur as per local protocol and where possible the Certificate of Destruction retained within the pharmacy file.

6.1.8 Summary of Product Characteristics (SPC) or Investigators Brochure

The Pravastatin Sodium 40mg Summary of Product Characteristics (SPC) (06/07/2016) is provided in a separate document with a cover sheet and signature page (signed and verified by the CI and Sponsor) and is filed in the TMF.

Please refer to Pravastatin Sodium SPC and simplified IMP dossier.

6.2 PLACEBO

As the principal excipient in pravastatin sodium is Lactose monohydrate 286.62mg, this will be used for the placebo. It will be formulated into a Swedish Orange hard gelatin capsule, size 00.

6.2.1 Labelling and Packaging

Medication labels will be in the local language (English) and comply with the legal requirements of Annex 13 of the European Union's Good Manufacturing Practice (GMP). They will include storage conditions for the drug, but no information about the participant.

The Investigational Supplies Group will be packaging the placebo and labelling.

ISG

2nd floor, 1 George Square

Edinburgh

EH8 9LD

The placebo will be packaged into bottles each containing 7 tablets, and the bottles will be blindlabelled led as per the active treatment described in paragraph 6.1.4 .

6.2.2 Storage

See paragraph 6.1.5 for a description of storage arrangements for the placebo, which are the same as the active treatment.

6.3 DOSING REGIME

Participants will receive 1 dose orally per 24 hour period +/- 6 hours for a total of 7 days. The drug will be dispensed immediately following randomisation from the stock in labour ward and administered at 24 hour intervals or as close to this as is practicable thereafter. The maximum dose will be one tablet in 24 hours with provision for two tablets within a 24 hour period should this enable a more practical regime (i.e. if first dose is taken at 0100, we will allow second dose at either 2200 the same day, or 0700 the following). Participants will self-dispense following the first dose, and record the time taken in their individual diaries. They will be encouraged but not enforced to take the dose at the same time each day.

6.4 DOSE CHANGES

No dose changes are anticipated, other than withdrawal of study medication for the reasons noted above.

6.5 PARTICIPANT COMPLIANCE

Compliance will be monitored in hospital via the participants' medication Kardex where a signature from the member of staff either dispensing the drug, or observing the participant dispensing and self-administering the medication is required. Non-compliance will be defined as two or more missed doses in a 48 hour period, or a total of 3 missed doses during the treatment period.

Any reasons for non-compliance or missed doses will be documented where possible and used to identify any common themes.

Should a participant be discharged home whilst enrolled in the trial and with further IMP to be taken, the remaining tablets will be prescribed on the discharge letter as documented above in section 5.5.2. Each page of the 'participant diary' will have a specific location for recording the time the participant has taken each dose.

In the day 7 trial visit, compliance will be assessed as reported by the participant and corroborated with her diary as well as a count of the remaining tablets (if any) remaining in the dispensing bottle. Serum pravastatin levels will also be assessed during the treatment phase.

6.6 OVERDOSE

Women will be advised to take one tablet only per day.

In the participant's diary, there will explicit information including contact details in the case of overdose. Should any participant take more than the prescribed dose, she will be asked to contact the obstetric triage area. She will be assessed by a member of the clinical care team

with a member of the trial team informed as soon as possible. Bloods will be obtained for LFTs, renal function and CK, and the participant will be monitored for as long as is clinically necessary as judged by her attending obstetrician. There is no specific treatment in the event of overdose, and participants should be treated symptomatically and supportive measures instituted as required.

Following overdose, continuation of the trial drug will be a discussed between the participant, her obstetric team and the research team. Details of discontinuation of treatment will be reported in the medical notes.

6.7 OTHER MEDICATIONS

6.7.1 Non-Investigational Medicinal Products

There are no NIMPs used in this CTIMP

6.7.2 Permitted Medications

All medications other than those detailed in the SPC and 6.7.3 prohibited medications are permitted.

Medications that participants have been prescribed pre-pregnancy and which have been continued during the pregnancy as per the supervising clinician responsible for participant care may be taken during the trial.

6.7.3 Prohibited Medications

Should any of the below prohibited medications be inadvertently co-administered with the IMP, the participant should contact their obstetric team and attend for assessment as required.

Erythromycin and clarithromycin
Macrolide antibiotics have been shown to cause a small but significant increase in the Cmax and actual body exposure of patients to pravastatin when the two are co-administered.
As erythromycin is only administered to patients with ruptured membranes (who are excluded from this trial) this is unlikely to occur. Clarithromycin will occasionally be given to patients when there is a suspicion of atypical bacteria lower respiratory tract infection

Fibrates
There is an increased rate of muscle related adverse events with concomitant use and therefore fibrates will be prohibited.

Colestyramine
40 to 50% reduction in bioavailability of pravastatin if administered concomitantly; no change if pravastatin administered one hour before OR four hours following cholestryramine. Not prohibited, but to be dosed as above.

Ciclosporin
Prohibited due to a 4 fold increase in the systemic exposure of pravastatin. As ciclosporin use is associated with preterm birth and low birth weight infants, these patients will be excluded from the trial.

7. STUDY ASSESSMENTS

7.1 SAFETY ASSESSMENTS

Safety assessments

We will collect data on side effects from all participants using a self-reported daily questionnaire to report any potential adverse events. Baseline and day 7 LFTs and CK will be used to monitor for hepatotoxicity or muscular toxicity.

7.2 STUDY ASSESSMENTS

Details of all sampling, processing and reporting of all blood tests can be found in the 'Working Practice Document'.

A. Screening

Demographics including gestational age and EDD, blood pressure, CTG and fetal fibronectin and/or cervical dilation will be collected as per local protocol for patients presenting with threatened preterm labour.

Following verbal consent, but prior to formal written consent, a cervical length scan may be required to assess eligibility and thus may be considered a screening condition.

B. Randomisation

Following written consent and randomisation, bloods for haemoglobin, renal function, LFTs, CK and an inflammatory profile with pravastatin levels will be taken.

C. Daily Until Discharge / Delivery / Completion of Treatment phase (whichever occurs soonest)

For participants admitted for monitoring or treatment, an inflammatory profile will be obtained twice on day 1 (baseline and at or around 12 hours post dose), daily thereafter whilst an inpatient, and at day 7. Serum pravastatin levels will also be collected at this time.

D. Throughout Duration of Treatment Phase

Contraction frequency will be self-monitored and recorded in the participants study diary. This may either through inpatient CTG monitoring or participant self-monitoring.

AEs may be recorded at any point, either by recording in the participant diary, verbal report to the trial team or through assessment of participant electronic health records.

E. At the Day 7 Trial Visit

This will occur at a mutually agreed location, either in the trial hospital or the participant's home. Compliance will be assessed via the trial diary and the bottles of treatment, the trial diary collected with its included information about AEs and contraction frequency, and bloods for an inflammatory profile, serum pravastatin levels, and LFTs / CK taken.

F. At Delivery

Bloods will be obtained for an inflammatory profile from maternal serum and umbilical cord. If delivery occurs within the treatment phase (7 days), as well as serum and cord samples also will be obtained for pravastatin levels. Apgars at 1,5 and 10 minutes be recorded if obtained.

G. At or around EDD + 28 days

Information for maternal and neonatal outcomes (see section 2.2.2 for details) will be assessed. This will not require a direct participant visit as this information will be obtained from the participant and baby's electronic health records.

Participants will be contacted by their preferred method of contact and acceptability of the trial discussed with them.

The table below summarises this information.

Assessment or outcome	Screening	Randomisation	Day 1	Daily until discharge	Day 7	At Delivery	28 days post EDD
Clinical Measures							
Blood pressure	X						
Fetal Fibronectin / Cervical Length / cervical dilation (one only required)	X						
	X						
Contraction Frequency	X		X	X	X		
Biochemical Measures							
Urea		X	X				
Serum creatinine		X	X				
Albumin		X	X		X		
Liver transaminases		X	X		X		X
Inflammatory Profile		X	X	X	X	X	
Haematological Measures							
Haemoglobin		X					
Maternal							
Maternal mortality/ morbidity		X	X	X	X	X	X
Serious adverse events or reactions		X	X	X	X	X	X
Routine CTG		X	X	X	X		
Serum Pravastatin			X	X	X	X	
Fetal & Neonatal Measures							
Gestational age (from EDD by ≤ 16 week scan)	X					X	
Cord inflammatory profile						X	
Cord pravastatin levels						X	
Apgar score at 1,5,10 minutes						X	
Congenital anomalies	X					X	
Neonatal mortality/ morbidity						X	X
Length of maternal and perinatal hospital stay and location						X	X

7.3 COMPLIANCE ASSESSMENTS

Treatment Compliance will be recorded as described in paragraph 6.5.

7.4 LONG TERM FOLLOW UP ASSESSMENTS

All participants will be consented for long term (5 years) access to both maternal and baby notes. Following completion of the treatment phase (7 days / until delivery), participants will continue to be monitored for potential adverse effects via the electronic health record up until EDD +28 days. Participants will also be consented for preferred method of contact follow up for a period of up to 2 years. Should additional funding be secured, a 2 year follow up of maternal and child health in the form of medical notes review, questionnaire completion or developmental testing may be considered for which separate ethical approval will be sought.

There are no follow up visits planned after EDD + 28 days at this time.

7.5 STORAGE AND ANALYSIS OF SAMPLES

Fetal fibronectin samples will be obtained, analysed and disposed of within the assessing clinical area as per protocol.

Blood tests:

1) For baseline renal function as well as baseline and day 7 liver function and CK, these samples will be obtained in line with local protocol and processed via the NHS site central laboratory. They will then be disposed of after as per routine laboratory protocol.
2) All additional blood tests obtained for the purpose of this study will be obtained from the participant in line with local guidelines and transported to QMRI for processing, storage and analysis. For details of blood sampling techniques, sample processing and analysis, please see the Working Practice Documents.
    a. Pharmacokinetic / pravastatin monitoring samples will be analysed in the Mass Spec Core (QMRI) in such a way as to maintain study blinding. For samples for spectroscopy analysis, samples will be re-aliquoted, and study ID will be replaced by an anaylsis ID by an independent person. The Mass Spec Core will maintain the link between study ID and analysis ID and ensure this is not revealed to the study team Samples will be analysed as per their 'analysis ID' in batches of 6 or more at a time to further ensure blinding remains secure. Results will be recorded on an analysis ID-specific CRF, and the analysis ID and study ID only linked back together at the time of unblinding of the study.
    b. 'Inflammatory Profile' analysis will occur in the Tommy's Lab (W1.20, QMRI) by a trained individual following study specific procedure. For more detail of this, please see Working Practice Documents.
3) Consent will be sought for the long term storage of both maternal serum and cord blood, which will be done so in the Edinburgh Reproductive Tissue BioBank (ERTBB) in line with their protocols. The ERTBB is located in the QMRI, 47 Little France Crescent.

8. DATA COLLECTION

Data will be collected by the trial team from the participant verbally and confirmed where possible in the medical records (demographics (age, educational attainment, ethnicity, and Community Health Index (CHI) number for participant and their baby when born), details of

previous pregnancies, blood test results, time to delivery), by direct monitoring (contraction frequency) and Participant questioning (side effect reporting via questionnaires, compliance, acceptability, side effects). Results of blood tests processed outwith NHS laboratories will be collected directly from the analysing team by the research team. Contact details will include address, preferred method of contact and GP details.

Both pCRFs and eCRFs will be used, with all data to be held in a secure database as detailed below. For participants being discharged home who remain on the study drug, their trial diary will contain areas for recording contraction frequency, medication compliance and side effect reporting. These will be collected by the research team at the day 7 trial visit.

At or near 28 days post EDD, participants will be contacted using their preferred method of contact, thanked for their involvement and asked for feedback, in the form of a short questionnaire. End of trial participation will be recorded in the CRF and medical notes, if available locally.

8.1 SOURCE DATA DOCUMENTATION

Source data is defined as all information in original records and certified copies of original records or clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents.

Source documents are original documents, data and records where source data are recorded for the first time.

Data will be sourced from the participant's own and their babies Medical records, which may be paper or electronic. Data will also be sourced from medication charts, and either electronic or paper laboratory results. . The study diary is source data and will be transcribed on to pCRF, or following development and Sponsor approval, an identical eCRF.

8.2 CASE REPORT FORMS

All case report forms (paper and electronic) for this study will be approved the ACCORD Monitor prior to use (as per the sponsors SOP ACCORD SOP CR013 CRF Design and Implementation).

This trial will begin using a pCRF, with a direct replica eCRF used later following Sponsor Approval.

8.3 TRIAL DATABASE

Trial database will be developed and managed by the Edinburgh Clinical Trials Unit.
Data will be entered by the Chief Investigator, Clinical Research Fellow and Clinical trials manager, as well as by suitably trained and delegated individuals. This data will be anonymized and will be kept for 5 years in a secure fashion.

9. DATA MANAGEMENT

9.1.1 Personal Data

The following personal data will be collected as part of the research:
Participant's CHI Number, age, initials, ethinicity, estimated date of delivery, height and weight at booking.
Personal data will be stored by the research team in a secure, locked cabinet in a code-access controlled room in Royal Infirmary of Edinburgh (NHS Lothian). Only the

research team will have access to personal data. The code break can be provided by a member of the research team, as can location of the key for the cabinet.
Personal data will be stored for 25 years in line with MRC guidelines on clinical trials involving pregnant participants.

9.1.2 Transfer of Data

All data collected or generated by the study (including personal data) will not be transferred to any external individuals or organisations outside of the Sponsoring organisation(s).

9.1.3 Data Custodian

The data custodian is Professor Jane Norman

9.1.4 Data Controller

The data controller is ACCORD

10. STATISTICS AND DATA ANALYSIS

10.1 SAMPLE SIZE CALCULATION

A formal power calculation is not considered necessary or appropriate for a feasibility study: the primary outcome in this feasibility study is recruitment rate. Together with data on time to delivery, contraction frequency and participant acceptability, this will be used to determine whether a large randomised trial is warranted and feasible. The remaining outcomes will be used either as safety markers, or to inform the design of a large randomised trial.

10.2 PROPOSED ANALYSES

Measures to be reported:
Primary outcome data

1. Trial uptake: eligible participants as compared with recruitment.

Secondary Outcome Data

1. Routine participant demographics including past medical history and drug history
2. Any additional treatments received during inpatient stay (including magnesium sulphate, antibiotics, syntocinon / other methods of induction/augmentation and steroids)
3. Retention, adherence and ability to collect clinical outcomes from participants
4. Time from presentation with threatened preterm labour to delivery of first dose of IMP.
5. Time from presentation to acute care and assessment services with suspected preterm delivery to delivery itself, as well as gestation at delivery
6. Contraction frequency during treatment course, from presentation to delivery or cessation of regular uterine activity.
7. Bloods: Liver function tests, creatinine kinase levels (side effects), maternal and cord inflammatory profile (see 2.2.2 for details of measures within the inflammatory profile).
8. Compliance with treatment
9. Adverse events
10. Acceptability of the trial following completion of the protocol
11. Other clinical outcomes
    a. Maternal outcomes:
        i. Proven maternal infection (See Appendix 4: Glossary of Terms for definition)

ii. Safety of intervention to mother (self-reported AEs and biochemical monitoring of liver function tests and creatinine kinase).
iii. Pre-labour ROM
iv. Duration, location and level of care of hospital stay following presentation with suspected preterm labour AND following delivery.

b. Neonatal morbidity and mortality, safety of intervention, gestational age at delivery, birthweight, duration, location and level of care required following delivery. If in utero transfer occur, cause of method of transport used.

12. Pharmacokinetics of pravastatin

Participant uptake the study will involve a direct analysis of eligible participants presenting to acute care and assessment services compared with recruitment. Secondary outcomes 1 and 2 will be used to perform subgroup analysis and identify potential confounders between treatment and placebo arms. Outcomes 3 – 11 will be used to directly compare treatment and placebo arms of the trial, and inform design for a large scale trial in the future.

A formal statistical analysis plan will be completed and signed off before study unblinding.

Analysis will be performed on an intention to treat basis to minimise possible bias. Whilst every effort will be made to ensure completeness of data sets, sensitivity analyses will be performed to evaluate data robustness. Further detail can be reviewed in the Statistical Analysis Plan.

No interim analysis is planned at this time.

11. PHARMACOVIGILANCE

The Investigator is responsible for the detection and documentation of events meeting the criteria and definitions detailed below.

Full details of contraindications and side effects that have been reported following administration of the IMP can be found in the relevant Summary of Product Characteristics (SPC).

Participants will be instructed to contact their Investigator at any time after consenting to join the trial if any symptoms develop. All adverse events (AE) that occur after informed consent until EDD + 28 days must be recorded in the Case Report Form (CRF) or AE log. In the case of an AE, the Investigator should initiate the appropriate treatment according to their medical judgment.

11.1 DEFINITIONS

An **adverse event** (AE) is any untoward medical occurrence in a clinical trial participant which does not necessarily have a causal relationship with an investigational medicinal product (IMP).

An **adverse reaction** (AR) is any untoward and unintended response to an IMP which is related to any dose administered to that participant.

A **serious adverse event** (SAE), **serious adverse reaction** (SAR). Any AE or AR that at any dose:

- results in death of the clinical trial participant;
- is life threatening*;
- requires in-patient hospitalisation^ or prolongation of existing hospitalisation;
- results in persistent or significant disability or incapacity;
- consists of a congenital anomaly or birth defect;
- results in any other significant medical event not meeting the criteria above.

*Life-threatening in the definition of an SAE or SAR refers to an event where 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.

^Any hospitalisation that was planned prior to enrolment will not meet SAE criteria. Any hospitalisation that is planned post enrolment will meet the SAE criteria.

A suspected unexpected serious adverse reaction (SUSAR) is any AR that is classified as serious and is suspected to be related to the IMP, that it is not consistent with the information about the IMP in the Summary of Product Characteristics (SPC) or Investigators Brochure.

11.2 IDENTIFYING AEs AND SAEs

Participants will be asked about the occurrence of AEs and SAEs at every visit during the study. Open-ended and non-leading verbal questioning of the participant will be used to enquire about AE/SAE occurrence. Participants will also be asked if they have been admitted to hospital, had any accidents, used any new medicines or changed concomitant medication regimens. If there is any doubt as to whether a clinical observation is an AE, the event will be recorded.

AEs and SAEs may also be identified via information from support departments e.g. laboratories.

11.3 RECORDING AEs AND SAEs

When an AE/SAE occurs, it is the responsibility of the Investigator, or another suitably qualified physician in the research team who is delegated to record and report AEs/SAEs, to review all documentation (e.g. hospital notes, laboratory and diagnostic reports) related to the event. The Investigator will then record all relevant information in the CRF/AE log and on the SAE form (if the AE meets the criteria of serious).

Information to be collected includes dose, type of event, onset date, Investigator assessment of severity and causality, date of resolution as well as treatment required, investigations needed and outcome.

11.3.1 Pre-existing Medical Conditions

Pre-existing medical conditions (i.e. existed prior to informed consent) should be recorded as medical history and only recorded as adverse events if medically judged to have worsened during the study.

11.3.2 Worsening of the Underlying Condition during the Trial

Medical occurrences or symptoms of deterioration that are expected due to the participant's underlying condition should be recorded in the Participant's medical notes and only be recorded as AEs on the AE log if medically judged to have unexpectedly worsened during the study. Events that are consistent with the expected progression of the underlying disease should not be recorded as AEs.

11.4 ASSESSMENT OF AEs AND SAEs

Each AE must be assessed for seriousness, causality, severity and ARs must be assessed for expectedness by the Principal Investigator or another suitably qualified physician in the research team who has been delegated this role.

For randomised double blind studies, AEs will be assessed as though the participant is taking active IMP. SUSARs will be unblinded by ACCORD before they are reported to REC and CA (by ACCORD).

The Chief Investigator (CI) may not downgrade an event that has been assessed by an Investigator as an SAE or SUSAR, but can upgrade an AE to an SAE, SAR or SUSAR if appropriate.

11.4.1 Assessment of Seriousness

The Investigator will make an assessment of seriousness as defined in Section 10.1.

11.4.2 Assessment of Causality

The Investigator will make an assessment of whether the AE/SAE is likely to be related to the IMP according to the definitions below.

- Unrelated: where an event is not considered to be related to the IMP.

- Possibly Related: The nature of the event, the underlying medical condition, concomitant medication or temporal relationship make it possible that the AE has a causal relationship to the study drug. The assessment of causality will be made against the reference safety information found in the reference safety information of the SPC (refer to the appropriate section).

Where non Investigational Medicinal Products (NIMPs) e.g. rescue/escape drugs are given: if the AE is considered to be related to an interaction between the IMP and the NIMP, or where the AE might be linked to either the IMP or the NIMP but cannot be clearly attributed to either one of these, the event will be considered as an AR. Alternative causes such as natural history of the underlying disease, other risk factors and the temporal relationship of the event to the treatment should be considered and investigated. The blind should not be broken for the purpose of making this assessment.

11.4.3 Assessment of Expectedness

If the event is an AE the evaluation of expectedness will be made based on knowledge of the reaction and the relevant product information documented in the SPC.

The event may be classed as either:

Expected: the AE is consistent with the toxicity of the IMP listed in the SPC.

Unexpected: the AE is not consistent with the toxicity in the SPC.

11.4.4 Assessment of Severity

The Investigator will make an assessment of severity for each AE/SAE/SAR/SUSAR and record this on the CRF/AE log or SAE form according to one of the following categories:

Mild: an event that is easily tolerated by the participant, causing minimal discomfort and not interfering with every day activities.

Moderate: an event that is sufficiently discomforting to interfere with normal everyday activities.

Severe: an event that prevents normal everyday activities.

Note: the term ‘severe’, used to describe the intensity, should not be confused with ‘serious’ which is a regulatory definition based on participant/event outcome or action criteria. For example, a headache may be severe but not serious, while a minor stroke is serious but may not be severe.

11.5 REPORTING OF SAEs/SARs/SUSARs

*Once the Investigator becomes aware that an SAE has occurred in a study participant, the information will be reported to the ACCORD Research Governance **within 24 hours**. If the Investigator does not have all information regarding an SAE, they should not wait for this additional information before notifying ACCORD. The SAE report form can be updated when the additional information is received.*

The SAE report will provide an assessment of causality and expectedness at the time of the initial report to ACCORD according to Sections 10.4.2, Assessment of Causality and 10.4.3, Assessment of Expectedness.

The SAE form will be transmitted via email to safety@accord.scot Only forms in a pdf format will be accepted by ACCORD via email. Forms may also be sent by fax to ACCORD on **+44 (0)131 242 9447** or may be submitted by hand to the office. Where missing information has not been sent to ACCORD after an initial report, ACCORD will contact the Investigator and request the missing information. The Investigator must respond to these requests in a timely manner.

All reports faxed to ACCORD and any follow up information will be retained by the Investigator in the Investigator Site File (ISF).

For this study the following events are **NOT** considered SAEs:

- Pregnancy is not considered an AE or SAE, as it is part of the inclusion criteria

- Hospitalisations for treatment planned prior to randomisation and hospitalisation for elective treatment of a pre-existing condition will not be considered as an SAE. This includes pregnancy. However, ***complications occurring during such hospitalisation will be AE/SAEs.***

- The following are also not considered SAEs
    - Preterm delivery
    - Hospitalisation for "maternal discomfort"
    - Hospitalisation for "observation" or "monitoring" for which the women is admitted for a period of less than 12 hours
    - Delivery complications such as caesarean section or post-partum haemorrhage
    - Admission of the baby to the neonatal unit for a period of up to 14 days.

11.6 REGULATORY REPORTING REQUIREMENTS

ACCORD is responsible for pharmacovigilance reporting on behalf of the co-sponsors (The University of Edinburgh and NHS Lothian).

ACCORD has a legal responsibility to notify the regulatory competent authority and relevant ethics committee (Research Ethics Committee (REC) that approved the trial). Fatal or life threatening SUSARs will be reported no later than 7 calendar days and all other SUSARs will be reported no later than 15 calendar days after ACCORD is first aware of the reaction.

ACCORD (or delegate) will inform Investigators at participating sites of all SUSARs and any other arising safety information.

ACCORD will be responsible for providing safety line listings and assistance; however, it is the responsibility of the Investigator to prepare the Development Safety Update Report. This annual report lists all SARs and SUSARs reported during that time period. The responsibility of submitting the Development Safety Update Report to the regulatory authority and RECs, lies with ACCORD.

11.7 FOLLOW UP PROCEDURES

After initially recording an AE or recording and reporting an SAE, the Investigator should make every effort to follow each event until a final outcome can be recorded or reported as necessary. Follow up information on an SAE will be reported to the ACCORD office.

If, after follow up, resolution of an event cannot be established, an explanation should be recorded on the CRF or AE log or additional information section of SAE form.

12. TRIAL MANAGEMENT AND OVERSIGHT ARRANGEMENTS

12.1 TRIAL MANAGEMENT GROUP

The trial will be coordinated by a Project Management Group, consisting of the grant holders (Chief Investigator and Principal Investigator in Edinburgh), a Clinical Research Fellow and Trial Manager.

The Trial Manager will oversee the study and will be accountable to the Chief Investigator. The Trial Manager will be responsible for checking the CRFs for completeness, plausibility and consistency. Any queries will be resolved by the Investigator or delegated member of the trial team.

A Delegation Log will be prepared for each site, detailing the responsibilities of each member of staff working on the trial.

12.2 TRIAL STEERING COMMITTEE

A Trial Steering Committee (TSC) will be established to oversee the conduct and progress of the trial. The terms of reference of the Trial Steering Committee, the draft template for reporting and the names and contact details are detailed in CR015 DMC & TSC Charters.

12.3 DATA MONITORING COMMITTEE

An independent Data Monitoring Committee (DMC) will be established to oversee the safety of participants in the trial. The terms of reference of the Data Monitoring Committee and the names and contact details are detailed in CR0015 DMC & TSC Charters.

The DMC Charter will be signed by the appropriate individuals prior to the trial commencing.

12.4 INSPECTION OF RECORDS

Investigators and institutions involved in the study will permit trial related monitoring and audits on behalf of the sponsor, REC review, and regulatory inspection(s). In the event of an audit or monitoring, the Investigator agrees to allow the representatives of the sponsor direct access to all study records and source documentation. In the event of regulatory inspection, the Investigator agrees to allow inspectors direct access to all study records and source documentation.

12.5 RISK ASSESSMENT

A study specific risk assessment will be performed by representatives of the co-sponsors, ACCORD monitors and the QA group, in accordance with ACCORD governance and sponsorship SOPs. Input will be sought from the Chief Investigator or designee. The outcomes of the risk assessment will form the basis of the monitoring plans and audit plans. The risk assessment outcomes will also indicate which risk adaptions could be incorporated into to trial design.

12.6 STUDY MONITORING AND AUDIT

ACCORD clinical trial monitors, or designees, will perform monitoring activities in accordance with the study monitoring plan. This will involve on-site visits and remote monitoring activities as necessary. ACCORD QA personnel, or designees, will perform study audits in accordance with the study audit plan. This will involve investigator site audits, study management audits and facility (including 3rd parties) audits as necessary.

13. GOOD CLINICAL PRACTICE

13.1 ETHICAL CONDUCT

The study will be conducted in accordance with the principles of the International Conference on Harmonisation Tripartite Guideline for Good Clinical Practice (ICH GCP).

Before the study can commence, all required approvals will be obtained and any conditions of approvals will be met.

13.2 REGULATORY COMPLIANCE

The study will not commence until a Clinical Trial Authorisation (CTA) is obtained from the appropriate Regulatory Authority. The protocol and study conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004, as amended.

13.3 INVESTIGATOR RESPONSIBILITIES

The Investigator is responsible for the overall conduct of the study at the site and compliance with the protocol and any protocol amendments. In accordance with the principles of ICH GCP, the following areas listed in this section are also the responsibility of the Investigator. Responsibilities may be delegated to an appropriate member of study site staff.

Delegated tasks must be documented on a Delegation Log and signed by all those named on the list prior to undertaking applicable study-related procedures.

13.3.1 Informed Consent

The Investigator is responsible for ensuring informed consent is obtained before any study specific procedures are carried out. The decision of a participant to participate in clinical research is voluntary and should be based on a clear understanding of what is involved.

Participants must receive adequate oral and written information – appropriate Participant Information and Informed Consent Forms will be provided. The oral explanation to the participant will be performed by the Investigator or qualified delegated person, and must cover all the elements specified in the Participant Information Sheet and Consent Form.

The participant must be given every opportunity to clarify any points they do not understand and, if necessary, ask for more information. The participant must be given sufficient time to consider the information provided. It should be emphasised that the participant may withdraw their consent to participate at any time without loss of benefits to which they otherwise would be entitled.

The participant will be informed and agree to their medical records being inspected by regulatory authorities and representatives of the sponsor(s).

The Investigator or delegated member of the trial team and the participant will sign and date the Informed Consent Form(s) to confirm that consent has been obtained. The original will be signed in the Investigator Site File (ISF). The participant will receive a copy of the signed consent form and a copy will be filed in the participant's medical notes.

13.3.2 Study Site Staff

The Investigator must be familiar with the IMP, protocol and the study requirements. It is the Investigator's responsibility to ensure that all staff assisting with the study are adequately informed about the IMP, protocol and their trial related duties.

13.3.3 Data Recording

The Principal Investigator is responsible for the quality of the data recorded in the CRF at each Investigator Site.

13.3.4 Investigator Documentation

Prior to beginning the study, each Investigator will be asked to provide particular essential documents to the ACCORD Research Governance & QA Office, including but not limited to:

- An original signed Investigator's Declaration (as part of the Clinical Trial Agreement documents);
- Curriculum vitae (CV) signed and dated by the Investigator indicating that it is accurate and current.
- ACCORD will ensure all other documents required by ICH GCP are retained in a Trial Master File (TMF) or Sponsor File, where required. The Principal Investigator will ensure that

the required documentation is available in local Investigator Site files ISFs. Under certain circumstances the TMF responsibilities may be delegated to the research team by ACCORD.

13.3.5 GCP Training

All study staff must hold evidence of appropriate GCP training.

13.3.6 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records must be identified in a manner designed to maintain participant confidentiality. All records must be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant. The Investigator and study site staff involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

13.3.7 Data Protection

All Investigators and study site staff involved with this study must comply with the requirements of the appropriate data protection legislation (including the General Data Protection Regulation and Data Protection Act) with regard to the collection, storage, processing and disclosure of personal information. Access to collated identifiable participant data will be restricted to individuals from the research team treating the participants, representatives of the sponsor(s) and representatives of regulatory authorities.

Computers used to collate the data will have limited access measures via user names and passwords.

Published results will not contain any personal data that could allow identification of individual participants.

14. STUDY CONDUCT RESPONSIBILITIES

14.1 PROTOCOL AMENDMENTS

Any changes in research activity, except those necessary to remove an apparent, immediate hazard to the participant in the case of an urgent safety measure, must be reviewed and approved by the Chief Investigator.

Proposed amendments will be submitted to the Sponsor for classification and authorisation.

Amendments to the protocol must be submitted in writing to the appropriate REC, Regulatory Authority and local R&D for approval prior to implementation.

14.2 PROTOCOL NON COMPLIANCE

14.2.1 Definitions

Deviation - Any change, divergence, or departure from the study design, procedures defined in the protocol or GCP that does not significantly affect a subjects rights, safety, or well-being, or study outcomes.

Violation - A deviation that may potentially significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being

14.2.2 Protocol Waivers

Prospective protocol deviations, i.e. protocol waivers, will not be approved by the sponsors and therefore will not be implemented, except where necessary to eliminate an immediate hazard to study participants. If this necessitates a subsequent protocol amendment, this should be

submitted to the REC, Regulatory Authority and local R&D for review and approval if appropriate.

14.2.3 Management of Deviations and Violations

Protocol deviations will be recorded in a protocol deviation log and logs will be submitted to the sponsors every 3 months. Each protocol violation will be reported to the sponsor within 3 days of becoming aware of the violation.Deviation logs / violation forms will be transmitted via email to QA@accord.scot Only forms in a pdf format will be accepted by ACCORD via email. Forms may also be sent by fax to ACCORD on **+44 (0)131 242 9447** or may be submitted by hand to the office. Where missing information has not been sent to ACCORD after an initial report, ACCORD will contact the Investigator and request the missing information. The Investigator must respond to these requests in a timely manner.

14.3 URGENT SAFETY MEASURES

The Investigator may implement a deviation from or change to the protocol to eliminate an **immediate hazard** to trial participants without prior approval from the REC and the MHRA. This is defined as an urgent safety measure and the investigator must contact the Clinical Trial Unit at the MHRA and discuss the issue with a medical assessor immediately (+44 (0) 20 3080 6456).

The Investigator will then notify the MHRA (clintrialhelpline@mhra.gsi.gov.uk), the REC and ACCORD, in writing of the measures taken and the reason for the measures within 3 days by submitting a substantial amendment.

14.4 SERIOUS BREACH REQUIREMENTS

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 participants of the trial; or

(b) the scientific value of the trial.

If a potential serious breach is identified by the Chief investigator, Principal Investigator or delegates, the co-sponsors (QA@accord.scot) must be notified within 24 hours. It is the responsibility of the co-sponsors to assess the impact of the breach on the scientific value of the trial, to determine whether the incident constitutes a serious breach and report to regulatory authorities and research ethics committees as necessary.

14.5 STUDY RECORD RETENTION

All study documentation will be kept for a minimum of 25 years from the protocol defined end of study point. When the minimum retention period has elapsed, study documentation will not be destroyed without permission from the sponsor.

14.6 END OF STUDY

The end of study is defined as the estimated date of delivery plus 28 days of the last participant recruited.

The Investigators and/or the trial steering committee and/or the co-sponsor(s) have the right at any time to terminate the study for clinical or administrative reasons.

The end of the study will be reported to the REC, Regulatory Authority, R&D Office(s) and co-sponsors within 90 days, or 15 days if the study is terminated prematurely. The Investigators will inform participants of the premature study closure and ensure that the appropriate follow up is arranged for all participants involved. End of study notification will be reported to the co-sponsors via email to resgov@ed.ac.uk.

In accordance with ACCORD SOP CR011, a Clinical Study Report (CSR) will be provided to the Sponsor (QA@accord.scot) and REC within 1 year of the end of the study.

Upon completion of the study, the Investigator will upload clinical trial results onto the EudraCT database on behalf of the Sponsor.

The Investigator will submit a short confirmatory e-mail to the MHRA (CT.Submission@mhra.gsi.gov.uk) once the result-related information has been uploaded to EudraCT, with 'End of trial: result-related information: EudraCT XXXX-XXXXXX-XX' as the subject line. The Sponsor(s) will be copied in this e-mail (QA@accord.scot). It should be noted that you will not get an acknowledgment e-mail or letter from the MHRA.

14.7 CONTINUATION OF DRUG FOLLOWING THE END OF STUDY

When the participant delivers her infant or completes 7 days of treatment (whichever occurs soonest), the drug will stop being administered.

14.8 INSURANCE AND INDEMNITY

The co-sponsors are responsible for ensuring proper provision has been made for insurance or indemnity to cover their liability and the liability of the Chief Investigator and staff.

The following arrangements are in place to fulfil the co-sponsors' responsibilities:

- The Protocol has been authored by the Chief Investigator and researchers employed by the University and collaborators. The University has insurance in place (which includes no-fault compensation) for negligent harm caused by poor protocol design by the Chief Investigator and researchers employed by the University.

- Sites participating in the study will be liable for clinical negligence and other negligent harm to individuals taking part in the study and covered by the duty of care owed to them by the sites concerned. The co-sponsors require individual sites participating in the study to arrange for their own insurance or indemnity in respect of these liabilities. Sites which are part of the United Kingdom's National Health Service have the benefit of NHS Indemnity.

- Sites out with the United Kingdom will be responsible for arranging their own indemnity or insurance for their participation in the study, as well as for compliance with local law applicable to their participation in the study.

- The manufacturer supplying IMP has accepted limited liability related to the manufacturing and original packaging of the study drug and to the losses, damages, claims or liabilities incurred by study participants based on known or unknown Adverse Events which arise out of the manufacturing and original packaging of the study drug, but not where there is any modification to the study drug (including without limitation re-packaging and blinding).

15. REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

15.1 AUTHORSHIP POLICY

Ownership of the data arising from this study resides with the study team. On completion of the study, the study data will be analysed and tabulated, and a clinical study report will be prepared in accordance with ICH guidelines.

15.2 PUBLICATION

The Clinical Study Report (CSR) will be submitted to the Sponsor and REC within 1 year of the end of the study. Where acceptable, a published journal article may be submitted as the CSR. The Chief Investigator will provide the CSR to ACCORD, for review, prior to finalization. The clinical study report may be used for publication and presentation at scientific meetings. Investigators have the right to publish orally or in writing the results of the study. The results of the study, together with other mandated information, will be uploaded to the European clinical trials database within 1 year of the end of the study.

Summaries of results will also be made available to Investigators for dissemination within their clinics (where appropriate and according to their discretion).

15.3 DATA SHARING

The clinical study report will be used for publication and presentation at scientific meetings. Investigators have the right to publish orally or in writing the results of the study.

Summaries of results will also be made available to Investigators for dissemination within their clinics (where appropriate and according to their discretion). A summary will be sent to participants.

15.4 PEER REVIEW

Peer review was received for this project as part of a submission to the charity Action Medical Research. Reviewers were generally supportive of the study: information is available on request.

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17. APPENDICES

17.1 APPENDIX 1: Trial Steering Committee and Data Monitoring Committee

Trial Steering Committee

Name of Member	Role in TSC	Responsibility	Independent
Professor Steve Thornton	Chair of TSC	*Oversight of TSC*	*Y*
Dr. Mairead Black	Member of TSC	Member of TSC	*Y*
Professor Jane Norman	Chief Investigator	*Oversight of Trial*	*N*
Mrs Sonia Whyte	Trial Manager	*Oversight of Trial Management*	*N*
Ms. Samantha MacFarlane	Member of TSC	*Lay member of TSC – assisting with PPI*	*Y*
Dr. Linda Williams	*Trial Statistician*	*Trial Statistician*	*N*
Mhairi Charlton	*TSC Sponsor Rep*	*Representative of ACCORD on TSC*	

Data Monitoring Committee

Name of Member	Role in DMC	Responsibility	Independent
Dr. Andrew Thomson	Chair of DMC	*Oversight of DMC*	*Y*
Professor Siladitya Bhattacharya	Member of DMC	Member of DMC	*Y*
Professor Jane Norman	Chief Investigator	*Oversight of Trial*	*N*
Mrs Sonia Whyte	Trial Manager	*Oversight of Trial Management*	*N*
Dr. Linda Williams	*Trial Statistician*	*Trial Statistician*	*N*

17.2 APPENDIX 2: Table of Blood/Urine Tests

	Time Point	Sample	Analysis
	Randomisation (Baseline)	Serum*	Renal Function
			Liver Function Tests (ALT, ALP)
			Creatinine Kinase
			Inflammatory Profile
			Pravastatin Levels
	Day 1 – 12 hours post dose	Serum	Inflammatory Profile
			Pravastatin Level
	Day 2 (24 hours post 1st dose)	Serum	Inflammatory Profile
			Pravastatin Level
	Daily thereafter whilst inpatients	Serum	Inflammatory Profile
			Pravastatin Level
	Day 7	Serum	Liver Function Tests (ALT, ALP)
			Creatinine Kinase
			Inflammatory Profile
			Pravastatin Level

	At Delivery	Serum	Inflammatory Profile
			Pravastatin level
		Cord Blood	Inflammatory Profile
			Pravastatin level

*serum refers to maternal serum unless otherwise stated

17.3 APPENDIX 3: Trial Schematics

Figure 1. Study Timeline

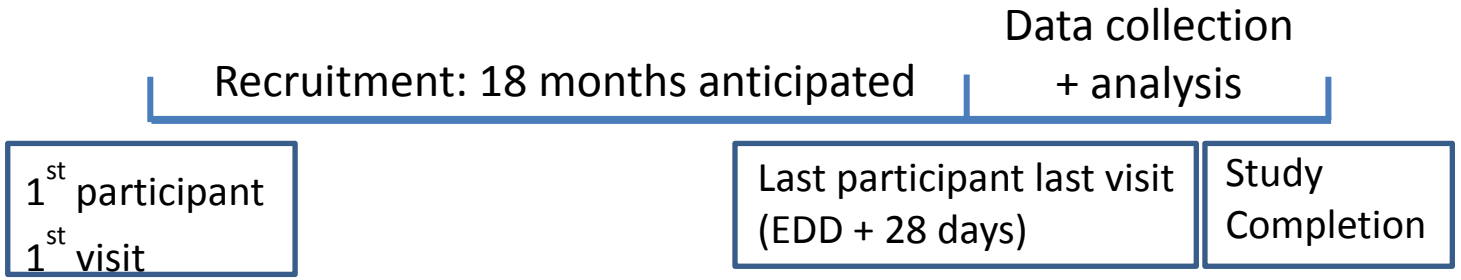
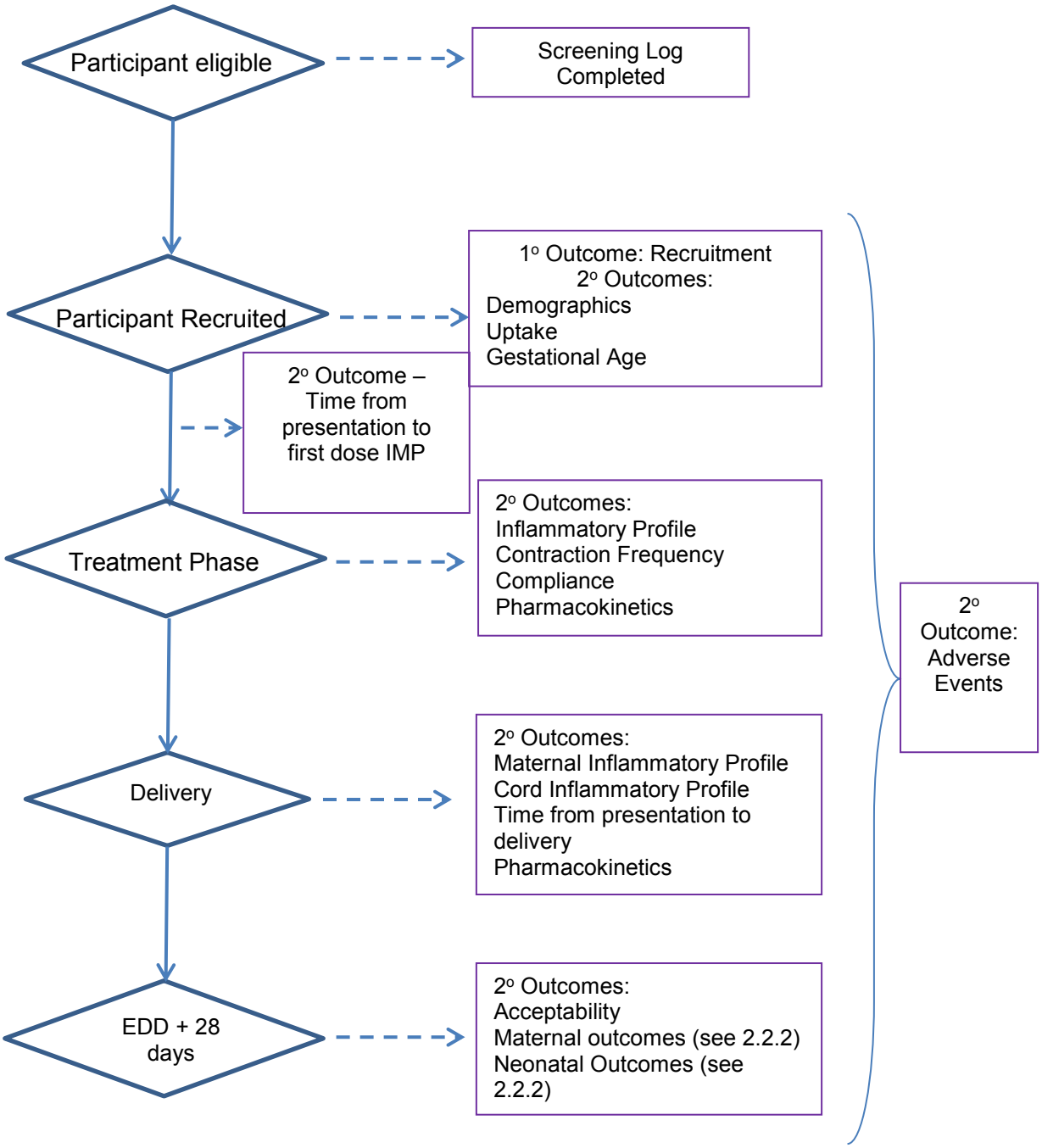


Figure 2: PIPIN OUTCOMES Flowchart



17.4 APPENDIX 4: Glossary of Terms

Proven Maternal Infection	Proven infection in the mother, defined as Either two of: Temperature> 38 oC on two or more occasions, raised CRP > 10, WCC > 12 or < 4 OR confirmed microbiological growth of an organism known to be pathogenic in blood cultures, MSU / CSU or LVS.
Threatened preterm labour	Patients between 24 and 37 weeks gestation, with painful uterine activity which may or may not progress to Preterm Labour and Delivery.
Gestational age at delivery	As calculated from a dating scan ≤ 16 weeks gestation
Neonatal Morbidity	Composite outcome calculated from multiple neonatal outcomes: • Requirement for admission to NNU or transfer between units, level and duration of care required • Respiratory morbidity: Surfactant requirement, ventilitation / CPAP / supplementary O2 use, early respiratory morbidity bronchopulmonary dysplasia • Feeding type, supplementary feeding requirement • Neurological: USS and MRI results, presence of bilateral periventricular leukomalacia or interventricular haemorrhage, additional neurological events e.g. seizures. • Gastrointestinal morbidity: necrotising enterocolitis and treatment, hyperbilirubinaemia • Cardiovascular morbidity: cardiac anomalies, patent ductus arteriosus • Sepsis (confirmed by culture) • Retinopathy of prematurity • Suspect long-term neurodevelopmental outcome at discharge

17.5 APPENDIX 5: Manufacturer's Guidance on Fetal Fibronectin: Qualitative (Positive / Negative) versus Quantitative (Numerical Result)

Where 'positive fetal fibronectin' is referred to as an inclusion criteria, a positive test is considered to be at levels > 50ng/ml, as defined by the NICE Guidance for Preterm Labour in the below statement:

'1.7.5 - If fetal fibronectin testing is negative (concentration 50 ng/ml or less), explain to the woman that it is unlikely that she is in preterm labour' (Preterm labour and birth | Guidance and guidelines | NICE n.d.)