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# A feasibility study investigating pravastatin for the prevention of preterm birth in women

**Submission date**
22/10/2018

**Recruitment status**
No longer recruiting

**Registration date**
15/02/2019

**Overall study status**
Completed

**Last Edited**
19/01/2021

**Condition category**
Pregnancy and Childbirth

[_] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

## Plain English summary of protocol

Background and study aims
Preterm birth at less than 37 weeks of pregnancy is thought to leave one million children a year with a disability. Current treatments have only a small effect on timing of delivery with little protection against brain injury. While the survival of babies born prematurely in the UK has improved in the last 20 years, the proportion of survivors without disability has remained the same. It is thought that inflammation linked with preterm labour might cause brain injury. Statins have anti-inflammatory activity and can also reduce contraction frequency and time to delivery in animal studies. Pravastatin, one of these medications, has a known safety profile in pregnancy, and other trials have observed pregnancy-prolonging effects. The aim of this study is to find out whether women who come to hospital with signs of labour before 36 weeks' pregnancy would be willing to take pravastatin or a placebo (dummy) for 7 days. If the study shows that women are willing to take medication, this would support the initiation of a larger trial to investigate the effects of pravastatin in preterm labour..

Who can participate?
Women aged 16 or over who come to hospital with signs of early preterm labour before their waters have broken

What does the study involve?
Participants are randomly allocated take one tablet a day of either pravastatin or a placebo (dummy drug) for 7 days. During this time, researchers monitor their contractions, markers of inflammation in both the mother's and the baby's blood (from the umbilical cord), and how long after the mother comes to hospital they deliver their baby. After delivery, data is collected from both mothers and babies, and participants are asked about their experience of being involved in the study. Participants are involved from when they come to hospital until 28 days after their expected due date.

What are the possible benefits and risks of participating?
As this is a feasibility study, there is no direct proven benefit to participants. Statins have never been formally tested in pregnancy. However, information has been collected from women who

have accidentally taken statins whilst pregnant, and several studies investigating pravastatin for the prevention of conditions of pregnancy like pre-eclampsia have been performed. There have been no reports of harm to mothers or their babies from taking pravastatin during pregnancy.

Where is the study run from?
Royal Infirmary of Edinburgh (UK)

When is the study starting and how long is it expected to run for?
September 2017 to April 2020 (updated 16/01/2020, previously: August 2020)

Who is funding the study?
Chief Scientist Office and Tommy's Baby Charity (UK)

Who is the main contact?
Mrs Sonia Whyte
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### Study website
https://www.ed.ac.uk/usher/edinburgh-clinical-trials/our-studies/all-current-studies/pipin

# Contact information

### Type(s)
Public

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Scientific

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# Additional identifiers

### EudraCT/CTIS number
2017-005021-21

### IRAS number
234899

### ClinicalTrials.gov number

### Secondary identifying numbers
CPMS 39567, IRAS 234899

# Study information

### Scientific Title
A feasibility study investigating pravastatin for the prevention of preterm birth in women

### Acronym
PIPIN

### Study objectives
PIPIN is a randomised controlled trial to see whether women who come to hospital with signs and symptoms of labour before 36 weeks gestation would be willing to take a medication (Pravastatin) or placebo treatment.

### Ethics approval required
Old ethics approval format

### Ethics approval(s)
East of Scotland Ethics Board (EoSREC) (Tayside Medical Science Centre, Residency Block Level 3, George Pirie Way, Ninewells Hospital and Medical School, Dundee DD1 9SY), 26/03/2018, 18/ES/0007

### Study design
Randomised; Interventional; Design type: Treatment, Drug

### Primary study design
Interventional

### Secondary study design
Randomised controlled trial

## Study setting(s)
Hospital

## Study type(s)
Treatment

## Participant information sheet
See additional files

## Health condition(s) or problem(s) studied
Preterm labour

## Interventions
This is a double blind randomised placebo controlled trial. Participants will be randomised to active treatment, Pravastatin Sodium 40 mg tablets once daily for 7 days, or a matching placebo. Randomisation is a 1:1 ratio, and participants are randomised using a 'next sequential pack' methodology. 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.

## Intervention Type
Drug

## Phase
Not Applicable

## Drug/device/biological/vaccine name(s)
Pravastatin

## Primary outcome measure
The primary outcome is the proportion of patients presenting in preterm labour between 28+0 and 35+6 weeks gestation who consent to enter the trial. This 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).

## Secondary outcome measures
Secondary outcomes will begin following consent of the first participant to EDD plus 28 days of the last participant recruited:
1. Retention, adherence and ability to collect clinical outcomes from participants, assessed by direct participant questioning, participant study diary and electronic records
2.1. Time to delivery from presentation assessed by maternal electronic records
2.2. Gestation at delivery assessed using patient medical records
3. Contraction frequency as monitored at presentation and from randomisation to delivery or cessation of regular uterine activity, as assessed by CTG, participant self reporting and researcher palpation
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'). These are assessed using multiplex assays on maternal blood collected during the course of the trial
5. Fetal measures of inflammation including but not limited to: cord IL-1, IL-6, IL-8, sIL-6R and

sgp130. These are assessed using multiplex assays on cord blood collected at delivery
6.1. Adverse events (maternal) collected from electronic records and maternal self reporting
6.2. Fetal adverse events collected from electronic records
7. Time from time first seen in an acute obstetric care setting to administration of trial medication as documented in the participant medical records, as assessed by participants electronic health records
8. Compliance with 7 days of blinded treatment, as assessed by participant reporting and pill count
9. Acceptability of the trial to those who have participated, as assessed by feedback questionnaire
10. Pharmacokinetic parameters as compared with current published data as assessed by serial pravastatin levels by LCMS
11. Maternal outcomes:
11.1. Proven maternal infection, collected from electronic records
11.2. Safety of intervention to mother (self-reported AEs and biochemical monitoring of liver function tests and creatinine kinase)
11.3. Pre-labour ROM assessed by clinical examination or electronic records
11.4. Duration, location and level of care of hospital stay following presentation with suspected preterm labour AND following delivery as assessed by electronic records
12. Neonatal outcomes:
12.1. Details of in utero transfers including mode of transport required as assessed by electronic records
12.2. Gestational age at delivery as assessed by patient records
12.3. Neonatal morbidity assessed as a composite of apgars and cord gases at delivery, details of resuscitation at delivery, neonatal infection, GI, respiratory and early neurodevelopmental morbidity, assessed using patient records
12.4. Neonatal mortality assessed using patient records
12.5. Birthweight assessed using patient records
12.6. Duration and location of hospital stay post-delivery and up to 28 days post EDD, assessed using patient records
12.7. Safety of intervention assessed as above for neonatal morbidity and mortality

### Overall study start date
01/09/2017

### Completion date
29/11/2019

## Eligibility

### Key inclusion criteria
Current participant inclusion criteria as of 17/06/2019:
1. Aged 16 years or above
2. Singleton pregnancy
3. Gestation ≥24+0 and ≤35+6 weeks (based on dating scan obtained at ≤16 weeks gestation)
4. Not previously recruited to this study in this pregnancy
5. Intact membranes
6. A positive fetal fibronectin test OR a short cervical length (≤15 mm) on ultrasound examination OR cervical dilation ≥3 cm and less than fully dilated
7. Uterine activity defined as ≥1 palpable contraction over 20 minutes of CTG monitoring.
8. 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.

Previous participant inclusion criteria:
1. Aged 16 years or above
2. Singleton pregnancy
3. Gestation ≥28+0 and ≤35+6 weeks (based on dating scan obtained at ≤16 weeks gestation)
4. Not previously recruited to this study in this pregnancy
5. Intact membranes
6. A positive fetal fibronectin test OR a short cervical length (≤15 mm) on ultrasound examination OR cervical dilation ≥3 cm and less than fully dilated
7. Uterine activity defined as ≥1 palpable contraction over 20 minutes of CTG monitoring.
8. 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.

## Participant type(s)
Patient

## Age group
Adult

## Sex
Female

## Target number of participants
Planned Sample Size: 40; UK Sample Size: 40

## Total final enrolment
7

## Key exclusion criteria
1. Immediate delivery deemed necessary for fetal or maternal reasons as determined by a senior clinician
2. Pre-labour, preterm rupture of membranes in the index pregnancy
3. Obstetric cholestasis as defined by RCOG (RCOG Green-Top Guideline, Number 43)
4. Established severe pre-eclampsia or HELLP syndrome as defined by NICE guidance (Hypertension in pregnancy: diagnosis and management | Guidance and guidelines | NICE n.d.)
5. Known history of hepatic or renal impairment
6. Ingestion of drugs thought to alter the pharmacokinetics or efficacy of statins, including erythromycin and/or nifedipine
7. Taking any one of the prohibited drugs as listed the SmPC and in 5.7.3
8. Lactose intolerance (due to excipient in pravastatin and placebo tablets)
9. Current or previous alcohol misuse
10. Personal or first degree relative with heritable muscle disorders
11. Participating in another CTIMP trial

## Date of first enrolment
13/08/2018

**Date of final enrolment**
29/11/2019

# Locations

**Countries of recruitment**
Scotland

United Kingdom

**Study participating centre**
**Royal Infirmary of Edinburgh**
47 Little France Crescent
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# Sponsor information

**Organisation**
The University of Edinburgh and/or Lothian Health Board

**Sponsor details**
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The Queen's Medical Research Institute
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**Sponsor type**
University/education

**ROR**
https://ror.org/01nrxwf90

# Funder(s)

**Funder type**
Government

**Funder Name**
Chief Scientist Office; Grant Codes: TCS/18/30

**Alternative Name(s)**
CSO

**Funding Body Type**
Government organisation

**Funding Body Subtype**
Local government

**Location**
United Kingdom

**Funder Name**
Tommy's Baby Charity; Grant Codes: 2018/0192

**Alternative Name(s)**

**Funding Body Type**
Private sector organisation

**Funding Body Subtype**
Other non-profit organizations

**Location**
United Kingdom

# Results and Publications

**Publication and dissemination plan**
The datasets generated and/or analysed for this study will be included in publications and 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).

**Intention to publish date**
07/08/2021

**Individual participant data (IPD) sharing plan**
The datasets generated and/or analysed during the current study during this study will be included in the subsequent results publication.

## IPD sharing plan summary

Other

## Study outputs

| Output type | Details | Date created | Date added | Peer reviewed? | Patient-facing? |
|---|---|---|---|---|---|
| Participant information sheet | version V1.1 | 16/03/2018 | 15/02/2019 | No | Yes |
| Protocol file | version v2.0 | 29/06/2018 | 15/02/2019 | No | No |
| Participant information sheet | version v2.0 | 10/04/2019 | 16/01/2020 | No | Yes |
| Protocol file | version v5.0 | 17/05/2019 | 16/01/2020 | No | No |
| Basic results | | 19/01/2021 | 19/01/2021 | No | No |
| HRA research summary | | | 28/06/2023 | No | No |