

# Calcium supplementation for prevention of pre-eclampsia

|  |   |   |
|--|---|---|
| <b>Submission date</b><br>19/05/2021   | <b>Recruitment status</b><br>No longer recruiting     | <input checked="" type="checkbox"/> Prospectively registered<br><input checked="" type="checkbox"/> Protocol            |
| <b>Registration date</b><br>25/05/2021 | <b>Overall study status</b><br>Ongoing                | <input type="checkbox"/> Statistical analysis plan<br><input type="checkbox"/> Results                                  |
| <b>Last Edited</b><br>24/07/2025       | <b>Condition category</b><br>Pregnancy and Childbirth | <input type="checkbox"/> Individual participant data<br><input checked="" type="checkbox"/> Record updated in last year |

## Plain English summary of protocol

### Background and study aims

Pre-eclampsia affects around one in 30 pregnancies in the UK. It usually presents with high blood pressure and protein in the urine but may also affect other organs in the body. While most women have a good outcome, the complications of pre-eclampsia can make women very unwell, and include fits and bleeding. The baby may also be affected by reduced growth and being born too early. In severe cases, the mother or baby may even die. The impact of the disease on women and their families is often considerable, related to the effect on their wellbeing as well as needing additional tests, admission to hospital and early delivery. This is also costly for the NHS.

At present doctors use aspirin to prevent pre-eclampsia in women who are more likely to develop it, but it only reduces the chance of getting pre-eclampsia by 10-20%. Delivery is the only cure.

Previous studies suggest calcium may be beneficial for preventing pre-eclampsia. However, most studies have been conducted in populations with low dietary calcium intake, so findings have not been viewed as applicable to a population with adequate calcium intake, such as in the UK. Moreover, little research has focused on the impact of calcium on women at high risk of pre-eclampsia.

This study will assess whether calcium supplementation during pregnancy along with usual antenatal care (including aspirin) is more effective than usual antenatal care alone in reducing the risk of pre-eclampsia in women who are at high risk.

### Who can participate?

Pregnant women over the age of 16 years who are at high risk of developing pre-eclampsia based on various risk factors.

### What does the study involve?

Once the women agree to participate in the trial, they will sign a consent form and be asked to provide information about their dietary calcium intake as well as general health (some information will also be taken from their medical notes). Half of the women will receive calcium tablets and the other half will receive placebo (dummy) tablets. The groups will be decided by chance, and neither the maternity team at the hospital, the research team, nor the participant will know which treatment they have received during the trial. The tablets will be started from

between 12 to 22 weeks' gestation, and taken until delivery, along with usual antenatal care (including aspirin). Participants will be asked to respond to text messages sent over their phone once a month to ask them how many of their tablets they have taken over the past week. Once the study is completed, information about pregnancy outcomes for the woman and her baby will be collected from medical notes.

What are the possible benefits and risks of taking part in the study?

By taking part in the study participants may reduce their risk of developing pre-eclampsia and its complications. It is also possible that participation may not lower their risk. The knowledge gained from their participation in this study will help inform future treatments and possibly lead to improved care for women at risk of pre-eclampsia.

Calcium supplementation given at the prescribed dose in this trial is unlikely to put the woman or her developing baby at risk of any side effects. However, as with taking any medication there is always a risk no matter how small. The rare side-effects reported for calcium are: feeling sick, stomach ache, constipation, diarrhoea, wind, or heartburn. Excessive calcium in the blood or urine can lead to very rare effects (less than 1 in 10,000 women) of skin rashes and itching and kidney stones or other kidney problems.

Where is the study run from?

University of Birmingham (UK)

When is the study starting and how long is it expected to run for?

November 2020 to July 2026

Who is funding the study?

National Institute for Health Research (NIHR) (UK)

Who is the main contact?

Dr Shireen Meher

[smeher@nhs.net](mailto:smeher@nhs.net)

### **Study website**

<https://www.birmingham.ac.uk/CaPE>

## **Contact information**

### **Type(s)**

Scientific

### **Contact name**

Dr Shireen Meher

### **ORCID ID**

<https://orcid.org/0000-0002-9866-7932>

### **Contact details**

3rd Floor, Birmingham Women's Hospital

Edgbaston

Birmingham

United Kingdom

B15 2TG

+44 (0)121 4721377  
smeher@nhs.net

### **Type(s)**

Public

### **Contact name**

Mr Max Hughes

### **Contact details**

Birmingham Clinical Trials Unit  
School of Health and Population Sciences  
Public Health Building  
University of Birmingham  
Birmingham  
United Kingdom  
B15 2TT  
+44 (0)121 414 7023  
cape@trials.bham.ac.uk

## **Additional identifiers**

### **EudraCT/CTIS number**

2020-004435-25

### **IRAS number**

262719

### **ClinicalTrials.gov number**

Nil known

### **Secondary identifying numbers**

IRAS 262719 RG 20-128, HTA - NIHR127325

## **Study information**

### **Scientific Title**

Calcium supplementation for Prevention of Pre-Eclampsia in high-risk women (CaPE)

### **Acronym**

CaPE

### **Study objectives**

In pregnant women at increased risk of pre-eclampsia, calcium supplementation given in a dose of 2 g/day during pregnancy plus usual care (including aspirin) is more effective than usual care alone at reducing the occurrence of pre-eclampsia.

### **Ethics approval required**

Old ethics approval format

**Ethics approval(s)**

Approved 29/12/2021, East Midlands - Leicester Central Research Ethics Committee (Equinox House, City Link, Nottingham, NG2 4LA, UK; +44 (0)2071048181; leicestercentral.rec@hra.nhs.uk), ref: 21/EM/0281

**Study design**

Randomized triple-masked placebo-controlled multi-centre trial with a 12-month internal pilot and a health economic evaluation

**Primary study design**

Interventional

**Secondary study design**

Randomised controlled trial

**Study setting(s)**

Hospital

**Study type(s)**

Prevention

**Participant information sheet**

<https://www.birmingham.ac.uk/research/bctu/trials/womens/cape/documentation.aspx>

**Health condition(s) or problem(s) studied**

Prevention of pre-eclampsia in women at increased risk

**Interventions**

Pregnant women who meet the eligibility criteria of the trial will be randomised using a minimisation algorithm to ensure balance in treatment allocation (central randomisation, 1:1 ratio, with minimisation). Participants will be allocated to receive either calcium carbonate tablets 2 g/day (1g tablet twice daily) commenced from 12 to 22 weeks' gestation, taken until delivery, plus usual care (including aspirin), or to placebo tablets plus usual care.

**Intervention Type**

Drug

**Phase**

Phase III

**Drug/device/biological/vaccine name(s)**

Calcium carbonate

**Primary outcome measure**

Pre-eclampsia, as defined by the International Society for the Study of Hypertension in Pregnancy (ISSHP), assessed up to primary hospital discharge after birth

**Secondary outcome measures**

All secondary outcomes will be measured using patient medical records up to hospital discharge or 4 weeks after estimated delivery, whichever is sooner.

For the woman: Pre-eclampsia Core Outcome Set (COS) outcomes, namely:

1. Death
2. Eclampsia
3. Stroke
4. Visual impairment: retinal detachment or cortical blindness
5. Pulmonary oedema
6. Acute kidney injury: creatinine  $\geq 90 \mu\text{mol/l}$ ; 1 mg/dl
7. Liver capsule haematoma (confirmed on ultrasound)
8. Raised liver enzymes: alanine aminotransferase (ALT) or aspartate aminotransferase (AST)  $> 40 \text{ IU/l}$
9. Low platelets  $< 150,000/\mu\text{l}$
10. Abruptio
11. Postpartum haemorrhage: estimated or measured blood loss  $\geq 500 \text{ ml}$  and  $\geq 1000$  after birth
12. Admission to Intensive Treatment Unit (ITU):
  - 12.1. Any admission
  - 12.2. Days of admission
13. Use of mechanical ventilation or intubation (for other than Caesarean section)

In addition to these core outcomes (woman), the researchers will record:

14. Gestational hypertension: new-onset hypertension  $\geq 140/90 \text{ mmHg}$  (at least two measurements several hours apart) after 20 weeks gestation in the absence of proteinuria or other features of pre-eclampsia
15. Severe hypertension: blood pressure  $\geq 160 \text{ mmHg}$  systolic and/or  $110 \text{ mmHg}$  diastolic
16. Severe pre-eclampsia, defined as pre-eclampsia with severe features (ACOG definition) including severe hypertension or low platelets  $< 100,000 \times 10^9/\text{l}$ , or abnormal liver function tests (LFTs) (liver enzymes at least twice the upper limit of normal) and right upper quadrant pain not accounted for by other diagnosis, or abnormal renal function (creatinine  $> 1.1 \text{ mg/dl}$ ), or pulmonary edema or visual impairment or severe headache unresponsive to medication and no other cause found.
17. HELLP syndrome based on a clinician diagnosis, supported by low platelets and raised liver enzymes as defined above with or without evidence of haemolysis (raised LDH enzyme or blood film)
18. Preterm pre-eclampsia:
  - 18.1. Diagnosed before 37 weeks
  - 18.2. Diagnosed before 32 weeks
19. Use of magnesium sulphate for pre-eclampsia
20. Onset of birth: spontaneous, induction of labour or elective Caesarean section
21. Mode of birth: vaginal birth, assisted vaginal birth, Caesarean section (emergency or elective)
22. Adverse effects: maternal hypercalcaemia, renal stones, neonatal hypocalcaemia, stopping of medication due to adverse effects

For the baby: COS outcomes namely:

1. Any death in the baby up to hospital discharge. The researchers will collect data separately for:
  - 1.1. Fetal loss  $< 22$  weeks gestation
  - 1.2. Fetal loss  $\geq 22$  weeks' gestation (stillbirth)
  - 1.3. Neonatal death (from birth up to 28 days)
    - 1.3.1. Early neonatal death (up to 7 days after birth)
    - 1.3.2. Late neonatal death (from 7 days up to 28 days)
  - 1.4. Perinatal death – stillbirth or neonatal death up to 7 days
2. Gestational age at delivery (median,  $< 28$  weeks,  $< 32$  weeks,  $< 37$  weeks)
3. Birthweight (mean,  $< 3^{\text{rd}}$  centile,  $< 10^{\text{th}}$  centile)
4. Admission to NNU

- 4.1. Any admission
- 4.2. Days of admission
- 5. Neonatal brain injury - hypoxic-ischaemic encephalopathy requiring therapeutic hypothermia of neonatal stroke, severe intraventricular haemorrhage (IVH) grade III/IV and/or cystic periventricular leukomalacia

In addition to these core outcomes (baby), the researchers will record:

- 6. Level of neonatal care (admission to neonatal intensive care unit (NICU)/special care baby unit (SCBU))
- 7. Respiratory support morbidity
  - 7.1. Surfactant use
  - 7.2. Use of mechanical ventilation
  - 7.3. Duration of respiratory support
- 8. Chronic lung disease (CLD) requiring oxygen therapy at 36 weeks post-menstrual age.
- 9. Necrotising enterocolitis (NEC) requiring surgery
- 10. Retinopathy of prematurity (ROP) requiring treatment with laser or anti-VEGF injection
- 11. Composite of death or serious morbidity: death or chronic liver disease (CLD), intraventricular hemorrhage (IVH) grade III/IV, necrotizing enterocolitis (NEC) requiring surgery or retinopathy of prematurity (ROP) requiring treatment

#### **Overall study start date**

01/11/2020

#### **Completion date**

31/07/2026

## **Eligibility**

#### **Key inclusion criteria**

- 1. Over 16 years of age
- 2. Able to provide informed consent to participate
- 3. After a dating scan has confirmed viability (usually between 10 and 14 weeks gestation)
- 4. 22 weeks' 0 days gestation or less
- 5. Women deemed eligible for aspirin therapy based on NICE guideline criteria below where a woman has either:
  - 5.1. One high-risk factor:
    - 5.1.1. Hypertensive disease during a previous pregnancy
    - 5.1.2. Chronic renal disease
    - 5.1.3. Autoimmune disease such as SLE or antiphospholipid syndrome
    - 5.1.4. Type 1 or 2 diabetes
    - 5.1.5. Chronic hypertension
  - 5.2. Or two or more moderate risk factors:
    - 5.2.1. First pregnancy
    - 5.2.2. Age more than 40 years
    - 5.2.3. BMI  $\geq 35$  at first visit
    - 5.2.4. Family history of pre-eclampsia
    - 5.2.5. Multiple pregnancy
    - 5.2.6. Pregnancy interval of 10 years or more
  - 5.3. Or the Fetal Medicine Foundation (FMF) algorithm for pre-eclampsia risk assessment, as

used locally

5.4. Or any other national pre-eclampsia screening criteria guidelines that may be used in the future

The study will also include women identified to be at high risk of pre-eclampsia based on any other national screening criteria guidelines that may be used in the future.

### **Participant type(s)**

Patient

### **Age group**

Adult

### **Lower age limit**

16 Years

### **Sex**

Female

### **Target number of participants**

7756

### **Key exclusion criteria**

1. Any known contraindications to regular calcium intake (history of renal stones, known renal impairment with pre-pregnancy eGFR  $<30$  ml/min/1.73m<sup>2</sup> or serum creatinine  $>150$  (μmol/l), known history of hypercalcaemia or hypercalcaemia-causing diseases (e.g. parathyroid disease, sarcoidosis, malignancy), current severe persistent vomiting leading to dehydration or requiring hospitalisation (if persisting vomiting resolves, the patient may be re-assessed for inclusion in the trial, providing all other inclusion and exclusion criteria are met)
2. Use of drugs with potential for severe interactions with calcium: digoxin or other cardiac glycosides; antiretroviral drugs for HIV treatment, anti-neoplastic drugs, and diuretics (thiazide, thiazide-like or xipamide).
3. Use of any additional calcium supplement either on its own or as part of other multivitamin or Vitamin D preparations, and unwilling to stop them or change to other multivitamins, as this could lead to higher doses of calcium supplementation in the calcium group and contamination in the placebo group
4. Women who are taking vitamin D regularly in high doses  $>1000$  IU/day, as supplements or for conditions such as malabsorption syndromes. Note: a short course of high dose Vitamin D (e.g., 20,000 IU weekly for 6 weeks) to treat Vitamin D deficiency during pregnancy is NOT an exclusion criteria
5. Known contraindications to excipient Isomalt (e.g. hereditary fructose intolerance)

### **Date of first enrolment**

11/08/2022

### **Date of final enrolment**

11/06/2025

## **Locations**

**Countries of recruitment**

England

United Kingdom

**Study participating centre****Birmingham Women's Hospital**

Birmingham Women's and Children's NHS Foundation Trust

Mindelsohn Way

Birmingham

United Kingdom

B15 2TG

**Sponsor information****Organisation**

University of Birmingham

**Sponsor details**

Edgbaston

Birmingham

England

United Kingdom

B15 2TT

+44 (0)121 415 8011

Reserachgovernance@contacts.bham.ac.uk

**Sponsor type**

University/education

**Website**

<http://www.birmingham.ac.uk/index.aspx>

**ROR**

<https://ror.org/03angcq70>

**Funder(s)****Funder type**

Government

**Funder Name**

Health Technology Assessment Programme

**Alternative Name(s)**

NIHR Health Technology Assessment Programme, HTA

**Funding Body Type**

Government organisation

**Funding Body Subtype**

National government

**Location**

United Kingdom

## Results and Publications

**Publication and dissemination plan**

The results of this trial will be submitted for publication in a peer-reviewed journal. The manuscript will be prepared by the chief investigator and authorship will be determined by the trial publication policy.

**Intention to publish date**

29/02/2028

**Individual participant data (IPD) sharing plan**

The datasets generated during and/or analysed during the current study are/will be available upon request from the CaPE trial management group (cape@trials.bham.ac.uk).

**IPD sharing plan summary**

Available on request

**Study outputs**

| Output type                                   | Details | Date created | Date added | Peer reviewed? | Patient-facing? |
|---|---------|--------------|------------|----------------|-----------------|
| <a href="#">Participant information sheet</a> |         |              | 24/03/2023 | No             | Yes             |
| <a href="#">Protocol (other)</a>              |         |              | 24/03/2023 | No             | No              |
| <a href="#">HRA research summary</a>          |         |              | 28/06/2023 | No             | No              |