TRIAL PROTOCOL

CaPE

Calcium Supplementation for Prevention of Pre-eclampsia in High Risk Women: CaPE Trial

This protocol has regard for the HRA guidance

Version Number:	1.0
Version Date:	08/Oct/2021

Protocol development

Protocol Amendments				
The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version.				
Amendment number	**Date of amendment**	**Protocol version number**	**Type of amendment**	**Summary of amendment**

Funding and Support in Kind	
Funder (s)	**Financial and non-financial support given:**
NIHR Health Technology Assessment Programme	Financial
Funding Scheme (if applicable)	18/23 Calcium supplementation for women at high-risk of pre-eclampsia
Funder's reference number	NIHR 127325
This study is funded by the National Institute for Health Research (NIHR) Health Technology Assessment Programme (award number 127325) The views expressed are those of the author(s) and not necessarily those of the NHS, NIHR or the Department of Health and Social Care"	

Protocol Sign Off

CI Signature Page

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol.

I agree to ensure that the information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies from the trial as planned in this and any subsequent approved protocol will be explained.

This protocol has been approved by:

Trial Name:	Calcium Supplementation for Prevention of Pre-eclampsia in High Risk Women: CaPE Trial
Protocol Version Number:	1.0
Protocol Version Date:	08 October 2021
CI Name:	Dr. Shireen MEHER
Trial Role:	Chief Investigator
Signature and date:	 08 / Oct /2021

Sponsor statement:

By signing the IRAS form for this trial, the University of Birmingham, acting as the sponsor of this trial confirms approval of this protocol.

Compliance statement:

This protocol describes the CaPE trial only. The protocol should not be used as a guide for the treatment of women not taking part in the CaPE trial.

The trial will be conducted in compliance with the approved protocol, UK Policy Framework for Health and Social Care Research, Medicines for Human Use (Clinical Trials) Regulations 2004, the Data Protection Act 2018 and the principals of Good Clinical Practice (GCP) as set out in the UK Statutory Instrument (2004/1031) and subsequent amendments thereof. Every care has been taken in the drafting of this protocol, but future amendments may be necessary, which will receive the required approvals prior to implementation.

Reference Numbers

Funder (NIHR HTA) Reference number	NIHR127325
EudraCT number	2020-004435-25
Sponsor number	RG_20-128
ISRCTN reference number	ISRCTN12033893
IRAS reference number	262719

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The undersigned confirm that the following protocol has been agreed and accepted and that the Principal Investigator (PI) agrees to conduct the trial in compliance with the approved protocol.

I agree to ensure that the information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

This protocol has been approved by:

Trial Name:	Calcium Supplementation for Prevention of Pre-eclampsia in High-Risk Women: CaPE Trial
Protocol Version Number:	Version: 1.0
Protocol Version Date:	08 October 2021
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ABBREVIATIONS

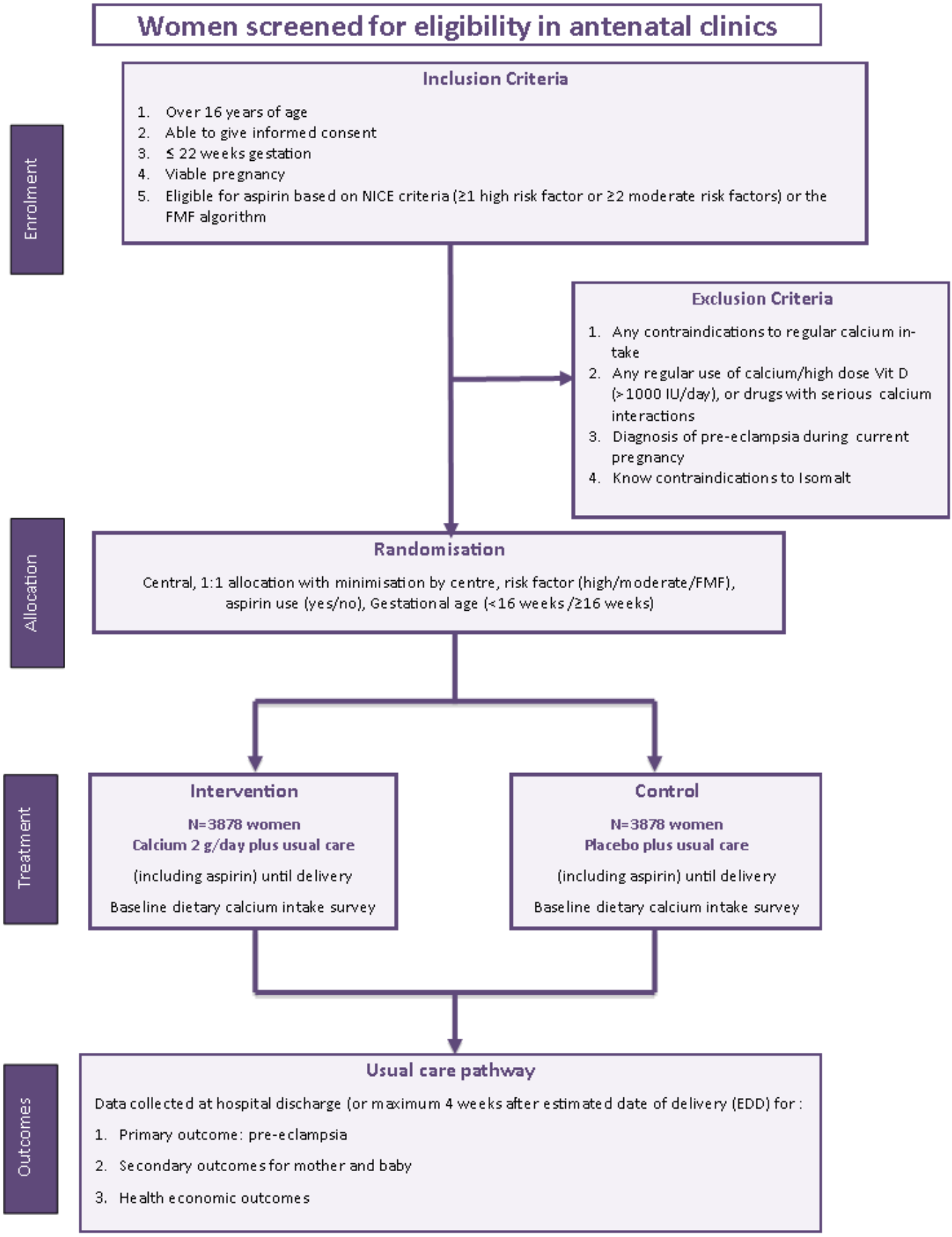
Abbreviation	Term
AKI	Acute Kidney Injury
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BCTU	Birmingham Clinical Trials Unit
BWCH	Birmingham Women's and Children's Hospital
CACE	Complier Average Causal Effects
CEAC	Cost-effectiveness Acceptability Curves
CI	Confidence interval
COS	Core Outcome Set
CRF	Case Report Form
CRN	Clinical Research Network
CTIMP	Clinical Trial of an Investigational Medicinal Product
DIC	Disseminated Intravascular Coagulation
DMEC	Data Monitoring and Ethics Committee
FMF	Fetal Medicine Foundation
GCP	Good Clinical Practice
GP	General Practitioner
HDU	High Dependency Unit
HELLP	Haemolysis Elevated Liver Enzymes Low Platelets
HTA	Health Technology Assessment
ICF	Informed Consent Form
IMP	Investigational Medicinal Product
IPD	Individual Participant Data
ISF	Investigator Site File
ISSHP	International Society for the Study of Hypertension in Pregnancy
ITU	Intensive Treatment Unit
IU	International Units
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	National Health Service
NICE	National Institute for Health and Care Excellence

NICU	Neonatal Intensive Care Unit
NIHR	National institute for Health Research
NNU	Neonatal Unit
PI	Principal Investigator
PIS	Participant Information Sheet
PPI	Patient & Public Involvement
PSA	Probabilistic Sensitivity Analysis
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RR	Relative Risk
SAP	Statistical Analysis Plan
SCBU	Special Care Baby Unit
SLE	Systemic Lupus Erythematosus
SMS	Short Message Service
TMG	Trial Management Group
TSC	Trial Steering Committee
UoB	University of Birmingham
WHO	World Health Organization

CaPE TRIAL SUMMARY

Title	Calcium supplementation for prevention of Pre-Eclampsia in high-risk women: The CaPE Trial
Objective	To investigate the clinical and cost-effectiveness of calcium supplementation plus usual care compared with usual care alone for prevention of pre-eclampsia and its complications in women at high risk of pre-eclampsia.
Trial design	Randomised parallel arm triple-blinded placebo-controlled multi-centre trial with a 12-month internal pilot and a health economics evaluation. Central randomisation in 1:1 ratio, with minimisation.
Study centres	Approximately 40 NHS maternity units across the UK.
Patient population and Sample size	7756 women (approximately 3878 in each group). This will allow 90% power (p=0.05) to detect a 20% relative risk reduction in pre-eclampsia from 11.5% down to 9.2%, allowing for a 5% loss to follow up.
Eligibility criteria	Inclusion criteria: pregnant women over the age of 16 years with a viable intrauterine pregnancy at a gestation of 22 weeks or less, at high risk of pre-eclampsia, deemed eligible for aspirin based on either NICE guideline criteria (at least one high-risk factor or two or more moderate risk factors) or the Fetal Medicine Foundation (FMF) algorithm, and able to provide informed consent. Exclusion criteria: any contraindications to regular calcium intake, concurrent use of calcium supplements or regular high dose Vitamin D >1000 IU/day, or any medication with potential severe interactions with calcium, known contraindications to Isomalt or a diagnosis of pre-eclampsia in the current pregnancy prior to trial entry.
Interventions	**Intervention group**: calcium tablets 2 g/day starting between 12 to 22 weeks' gestation, taken until delivery, plus usual care (including aspirin). **Control group**: placebo tablets starting between 12 to 22 weeks' gestation, taken until delivery, plus usual care (including aspirin).
Outcome measures	Primary outcome: Clinician diagnosis of pre-eclampsia, as defined by the International Society for Study of Hypertension in Pregnancy (ISSHP): (blood pressure ≥140/90mmHg **AND** either significant proteinuria (protein/creatinine ratio (PCR) of 30 mg/mmol or more) **OR** maternal multiorgan dysfunction: acute kidney injury (AKI) (creatinine ≥90 µmol/L; 1 mg/dL), liver involvement (elevated transaminases e.g. ALT or AST>40IU/L) with or without right upper quadrant or epigastric abdominal pain), neurological complications (examples include eclampsia, altered mental status, blindness, stroke, clonus, severe headaches, persistent visual scotomata), haematological complications (thrombocytopenia – platelet count below 150,000/µL, DIC, haemolysis) **OR** uteroplacental insufficiency (fetal growth restriction, abnormal doppler, stillbirth) developing at or after 20 weeks gestation, assessed up to primary hospital discharge. Key secondary outcomes 1. Severe pre-eclampsia index: any one of severe pre-eclampsia, early onset pre-eclampsia <32 weeks, eclampsia, placental abruption, HELLP syndrome or severe gestational hypertension. 2. Preterm birth <37 weeks Secondary outcomes: 1. For the woman: Core outcome set (COS) outcomes: death, eclampsia, stroke, retinal detachment or cortical blindness, pulmonary edema, acute kidney injury, liver capsule haematoma or rupture, raised liver enzymes, low platelets, abruption, postpartum haemorrhage, ITU admission, and mechanical ventilation. In addition to these COS outcomes, we will record gestational hypertension, severe hypertension, severe pre-eclampsia, HELLP syndrome, early onset pre-eclampsia, preterm delivery at <37 weeks for pre-eclampsia, use of magnesium sulphate for pre-eclampsia, onset of birth, mode of birth, adverse effects: maternal hypercalcaemia, renal stones, and stopping of medication due to adverse effects. 2. For the baby: COS outcomes: death up to hospital discharge, gestational age at delivery, birthweight, small for gestational age, neonatal seizures, admission to neonatal unit, respiratory support, and neonatal brain injury (hypoxic ischaemic encephalopathy, stroke, intraventricular haemorrhage, periventricular leukomalacia). In addition to these COS outcomes, we will record chronic lung disease, necrotising enterocolitis requiring surgery, retinopathy of prematurity requiring treatment, a composite of death or serious morbidity, level of neonatal care and length of stay. 3. Health economics outcomes: We will combine the clinical data collected within the trial with cost data from previous studies and the NHS to calculate the cost per case of pre-eclampsia avoided.

Trial Schema



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1. BACKGROUND AND RATIONALE

1.1 Background

Pre-eclampsia is a multisystem disorder that complicates around 2.8% of pregnancies in the UK (1). It usually presents with new-onset high blood pressure after 20 weeks' gestation, accompanied by proteinuria and/or evidence of maternal acute kidney injury, liver dysfunction, neurological features, haemolysis or thrombocytopenia, or fetal growth restriction (2). Serious complications include eclampsia (seizures), stroke, Haemolysis Elevated Liver enzymes Low Platelets (HELLP) syndrome, disseminated intravascular coagulation (DIC), and pulmonary oedema. Pre-eclampsia is also associated with 2.8% of stillbirths (3) and is a common cause of iatrogenic prematurity (4). Women with pre-eclampsia utilise substantial NHS resources as they may need closer surveillance with day unit visits, investigations, hospital admission, medication, and higher level care for the woman and/or baby (5).

The underlying cause of pre-eclampsia remains unclear. It is thought to occur secondary to poor placentation and endothelial cell damage, resulting in widespread vasoconstriction, abnormal coagulation and poor organ perfusion (6). Once diagnosed, delivery is the only cure. Antenatal care focuses on increased surveillance to allow early detection of complications and optimisation of timing of delivery. Clinical trials have evaluated numerous preventative interventions but results have been disappointing, including those of the recently published FACT trial assessing folic acid supplementation (7). Best available evidence suggests that antiplatelet agents (usually low dose aspirin) and calcium may be effective in reducing the risk of pre-eclampsia (5), as described below.

Aspirin: a Cochrane review including 77 randomised trials (40,249 women, and their babies) showed that aspirin is associated with a modest, but clinically and statistically significant risk reduction of 18% for pre-eclampsia, 14% for death in the baby, 9% for preterm birth <37 weeks, 16% for having a small for gestational age baby, and 10% for having a pregnancy with serious adverse outcome (a composite outcome including maternal death, baby death, pre-eclampsia, small for gestational age, and preterm birth) (8). Benefits are more marked in high-risk women (those with previous severe pre-eclampsia, chronic hypertension, renal disease, diabetes, and autoimmune disease). NICE guideline for management of hypertension in pregnancy now recommend low-dose aspirin for pregnant women at increased risk of pre-eclampsia (Table 1) (9). Risk factors have been identified from comprehensive systematic reviews (10-11). Women may be offered aspirin if they have a one or more high risk factors, or two or more moderate risk factors, but there are few data on the risk of pre-eclampsia in women with multiple risk factors.

Aspirin probably slightly increases the risk of postpartum haemorrhage of more than 500 mls (Relative Risk (RR) 1.06, 95% Confidence Interval (CI) 1.00 to 1.12); however, the quality of evidence for this outcome was not high, due to concerns of clinical

heterogeneity in measurements of blood loss. Antiplatelet agents probably slightly increase placental abruption (RR 1.21, 95% CI 0.95 to 1.54), but the quality of the evidence was not high due to low event numbers and wide 95% CI.

Data from two large trials which assessed children aged 18 months (including results from over 5000 children), did not identify clear differences in development between the two groups (8).

Advise women at high risk of pre-eclampsia to take 75 -150 mg aspirin daily from 12 weeks until the birth of the baby. Women at high risk are those with any of the following:
1. hypertensive disease during a previous pregnancy 2. chronic renal disease 3. autoimmune disease such as SLE or antiphospholipid syndrome 4. type 1 or 2 diabetes 5. chronic hypertension
Offer women with more than one moderate risk factor for pre-eclampsia 75 to 150 mgs aspirin daily from 12 weeks. until birth of the baby. Factors indicating moderate risk are:
1. first pregnancy 2. age more than 40 years 3. BMI more than 35 at first visit 4. family history of pre-eclampsia 5. multiple pregnancy 6. pregnancy interval >10 years

ideline recommendations for aspirin

Although other screening strategies have been explored, very few have been externally validated in separate populations and none has been recommended for use in clinical practice by NICE or the UK National Screening Committee. An Individual Patient Data (IPD) meta-analysis exploring validation of these models found that their predictive performance was limited, and their use could not be recommended in routine clinical practice at present (46). Therefore, to date, NICE clinical risk factor screening as outlined in Table 1 above remains the standard of care nationally for identification of high-risk women eligible for aspirin therapy in early pregnancy. A limited number of hospitals in the UK use the Fetal Medicine Foundation (FMF) algorithm to screen for risk of pre-eclampsia for aspirin eligibility (49). In addition to the maternal risk factors included in NICE guidelines, the algorithm uses biophysical (mean arterial pressure, uterine artery doppler) and biochemical (placental growth factor, PAPP-A) markers; this algorithm has been found to have a better detection rate for pre-eclampsia and preterm pre-eclampsia compared to the NICE criteria for a 10% screen positive rate (50).

Calcium: evidence from epidemiological studies suggests that there is an inverse relationship between calcium intake and risk of pre-eclampsia and eclampsia (12-15). Low calcium may lead to high blood pressure by stimulating either parathyroid hormone or renin release (16). Both hormones can increase intracellular calcium in vascular smooth muscle and cause vasoconstriction. Calcium supplementation may reduce parathyroid release and intracellular calcium, and thereby reduce smooth

muscle contractility and vasoconstriction. This may also result in lower resistance in uterine and umbilical arteries, increasing placental perfusion (17).

A Cochrane Review of 14 good quality randomised trials including 15,730 women showed that calcium supplementation with 1.5 to 2 g daily of elemental calcium was associated with a relative risk reduction of 55% for pre-eclampsia, 24% for preterm birth, and 20% for composite serious maternal morbidity and mortality (18) (Table 2 below). In addition, there is a possibility that it may have a preventative effect on the risk of hypertension in offspring (19). Increased risk of adverse events has not been reported in the trials, and the theoretical concern of renal calculi has not been substantiated in this population. Although two trials reported an increase in the risk of HELLP syndrome (RR 2.67, 95% CI 1.05 to 6.82, n=12,901), the absolute number of events was low (2.5/1000 versus 0.9/1000) and is countered by the reduction in other maternal adverse outcomes.

The World Health Organization (WHO) guideline now recommends that in populations where dietary calcium intake is low, pregnant women receive 1.5 to 2 g calcium daily, particularly those at increased risk of pre-eclampsia (women with obesity, previous pre-eclampsia, diabetes, chronic hypertension, renal disease, autoimmune disease, nulliparity, advanced maternal age, adolescent pregnancy and multiple pregnancy) (20).

Outcome	Number of trials	Number of women	Relative Risk (95% CI)
Pre-eclampsia	13	15,730	0.45 (0.31 to 0.65)
Maternal death/ morbidity	4	9732	0.80 (0.65 to 0.97)
Fetal or neonatal death	11	15,665	0.90 (0.74 to 1.09)
Preterm birth	11	15,275	0.76 (0.60 to 0.97)
Childhood systolic BP >95th percentile (7 year follow up)	2	514	0.59 (0.39 to 0.91)

Table 2. Cochrane review of calcium versus placebo: outcomes

1.2. Trial Rationale

Calcium supplementation for prevention of pre-eclampsia is currently not recommended in the UK (52) for a number of reasons:

- Most of the women recruited to previous studies had a low dietary intake of calcium. Subgroup analyses suggested that the benefits of calcium supplementation were apparent in those with a low baseline intake of calcium (RR 0.36, CI 0.20 to 0.65; 8 trials, 10,678 women) but was not for women with an adequate intake of calcium (RR 0.62, CI 0.32 to 1.20; 4 trials, 5022 women). Therefore, as a preventative intervention, it has not been viewed as applicable and relevant to populations considered to have an adequate intake of calcium such as in the UK.

- Although most women recruited to previous trials were generally low risk, healthy nulliparous women (15,143 women), subgroup analysis suggests that benefits are most marked for women at high risk of pre-eclampsia (78% reduction in pre-eclampsia: RR 0.22, CI 0.12 to 0.42; 5 trials, n=587). However, the trials where high risk women have been studied are small, and three out of the five trials included women with low baseline intake of calcium. In addition, the criteria used to define high risk were variable and included tests that are not used in routine clinical practice (nulliparous and/or <17 years, a positive rollover test and/or angiotensin II infusion test). The incidence of pre-eclampsia in the placebo group for trials recruiting high risk women ranged between 3% to 47%, and therefore the clinical usefulness of pooled results in this group is unclear. There are no large trials in high-risk women based on risk factors used in current clinical practice to identify women at increased risk of pre-eclampsia.

- The reduction in risk of pre-eclampsia appears greatest in the smaller studies in the systematic review and has not been substantiated in the two largest trials (21-22), creating a disparity between the conclusions of the large, randomised trials and the systematic review. However, both large trials recruited low risk women. As small studies are more prone to random error, and publication bias, there is potential for an exaggerated effect size, and it is therefore difficult to determine the true effect of calcium on the prevention of pre-eclampsia.

Calcium supplementation is attractive as a potential intervention to reduce the risk of pre-eclampsia because it is relatively low cost, readily available, does not appear to increase risk of adverse effects, and would be easy to implement into clinical practice. Given the large effect size in studies recruiting high risk women, there is a need to conduct a large, randomised trial to assess the impact of calcium supplementation for prevention of pre-eclampsia in high-risk women in the UK, despite adequate calcium intake in the population. It has the potential to improve maternal and perinatal health, and result in substantial cost savings for the NHS. The need for this research has also been highlighted by NICE (9).

Low dose aspirin is now part of routine care of pregnant women at high risk of pre-eclampsia. Calcium and aspirin appear to reduce the risk of pre-eclampsia by different mechanisms – the former influences vascular tone and hypertension while the latter impacts the thromboxane pathway. The use of calcium and aspirin together may, in theory, address the two major pathological processes underlying pre-eclampsia, and therefore potential benefits may be greater with their combined use. One small, published trial assessing the combined impact of aspirin and calcium (versus placebo) in women with chronic hypertension did not demonstrate any differences in the risk of pre-eclampsia, but the trial was underpowered to detect such a difference (n=49) (23).

2. AIMS AND OBJECTIVES

Aim: To investigate the clinical and cost-effectiveness of calcium supplementation plus usual care compared with usual care alone for prevention of pre-eclampsia and its complications in women at high risk of pre-eclampsia

Primary objective: To test the hypothesis that 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 in reducing the relative risk for the occurrence of pre-eclampsia by at least 20%.

Secondary objectives

1. To assess the impact of calcium supplements on other important outcomes for the woman and baby

2. To assess the cost-effectiveness of calcium plus usual care compared to usual care alone.

3. To assess the degree to which pregnant women are able to adhere to a calcium supplementation regimen.

4. To assess whether calcium has a differential effect in pre-specified subgroups of women.

3. TRIAL DESIGN AND SETTING

3.1. Trial Design

A parallel-two-arm, randomised, triple-blinded, placebo-controlled multi-centre trial, with a 12-month internal pilot and health economics evaluation.

3.2. Trial Setting

Approximately 40 consultant-led maternity units in hospitals across the UK.

3.3. Identification of participants

All pregnant women are routinely screened for aspirin eligibility for prevention of pre-eclampsia, generally at their booking appointment, either in the hospital or in the community. We will make trial information available in booking offices in the community and in antenatal clinics in the hospital. We will invite eligible women to participate in the CaPE trial.

Eligible women will be identified by a member of their clinical care team at antenatal appointments, at either.

1. the booking appointment, or
2. after the dating scan, if different from the booking appointment, or
3. after the anomaly scan, or
4. any other antenatal appointment up to 22^{+0} weeks' gestation

The CaPE trial will be introduced by a member of the clinical team. If the participant agrees, further information will be provided by the research team with full knowledge of the trial. The potential participant will be advised that participation in the trial is entirely voluntary with the option of withdrawing from the trial at any stage. It will be made clear that participation or non-participation will not affect their usual care.

Where antenatal appointments are undertaken in the community, or over the telephone (e.g. during COVID 19 restrictions), the clinical care team will be asked to seek permission from eligible woman to be contacted by the research team over the phone (this will be recorded in the participants medical notes), and this information will be shared with the research team via an appropriate method as managed locally at the participating centre, for example via email, telephone, post etc. (if the woman agrees).

Investigators on the delegation log can confirm eligibility and recruit women themselves or refer to the research midwife for recruitment.

3.4. Assessment of risk for the trial

Calcium supplementation in the recommended dose is not associated with any significant additional risk to the woman or her developing baby. The dose of 2 g/day administered in this trial is within the maximum daily intake unlikely to cause adverse health effects (Tolerable Upper Intake Level), which is around 2.5 g/day (19-50 years) to 3 g/day (14-18 years) during pregnancy (27). Previous randomised trials using a dose of 2g/day in over 4600 pregnant women with adequate baseline calcium intake (similar to the UK population) showed that it was safe to use and not associated with any increase in adverse effects (18, 22, 28-29, 30).

However, as with taking any pharmaceutical agent there is always a risk no matter how small. Women participating in the trial may experience some side effects including mild gastrointestinal symptoms such as constipation or diarrhoea, dyspepsia, flatulence, nausea and abdominal pain but these are rare (<1 in 1000 people). Serious side effects are very rare (<1 in 10,000 people) and only occur with toxicity from hypercalcaemia or hypercalciuria and can present as either itching or skin rashes, milk alkali syndrome (hypercalcaemia, alkalosis and renal impairment) or renal stones. Milk alkali syndrome has only been reported with excessive calcium of over 4 g/day or in those with underlying medical problems (31). To minimise these risks, we have excluded women with medical conditions or medications/supplements that make them susceptible to hypercalcaemia. Renal stones are highly unlikely to occur with a dose of 2g/day for the relatively short duration of therapy in pregnancy, and no increase has been found in previous trials in pregnant women.

Calcium is not associated with an increased risk of congenital anomalies. Case reports of neonatal hypocalcaemia and seizures have been reported in pregnant women with persistent hypercalcaemia who either had hyperparathyroidism (excluded in our trial), or where women were consuming excessive calcium-based supplements or antacids well above the recommended dose in this trial (28-29). To minimise risk, we have excluded women using additional calcium supplements and recommend that non-calcium-based antacids be used where needed.

Although pre-eclampsia prevention is not listed as an indication for use of calcium 1g chewable tablets, there is reasonably good quality evidence that suggests a possible reduction in pre-eclampsia and its complications with calcium in pregnant women where dietary calcium intake is low (18); therefore calcium is recommended for this purpose by the WHO guidelines. (20)

This trial is categorised as Type A = no higher than the risk of standard medical care based on effectiveness and safety data available from previous studies and current clinical practice.

4. ELIGIBILITY

4.1. Inclusion Criteria

- Over 16 years of age
- Able to provide informed consent.
- Confirmed viable pregnancy on a dating scan (usually done between 10 and 14 weeks) and any subsequent scans.
- Gestation 22^{+0} weeks' or less
- Women deemed eligible for aspirin therapy based on
  1) the NICE guideline criteria:
     either one or more high risk factor
     - hypertensive disease during a previous pregnancy
     - chronic renal disease
     - autoimmune disease such as SLE or antiphospholipid syndrome
     - type 1 or 2 diabetes
     - chronic hypertension

     Or two or more moderate risk factors
     - first pregnancy
     - age more than 40 years
     - BMI 35 or more at first visit
     - family history of pre-eclampsia
     - multiple pregnancy
     - pregnancy interval of 10 years or more

     OR
  2) the FMF algorithm for pre-eclampsia risk assessment (49)
     OR
  3) any other national pre-eclampsia screening criteria guidelines that may be used in the future.

4.2. Exclusion Criteria

- Any known contraindications to regular calcium intake (history of renal stones, known renal impairment with pre-pregnancy eGFR <30 mL/min/1.73^{m2} 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, patient may be re-assessed for inclusion in the trial, providing all other inclusion and exclusion criteria are met.

- 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) - the latter two are not usually used in pregnancy (36).

- Use of any additional calcium supplement either on its own or as part of other multivitamin or Vitamin D preparations, and unable or unwilling to stop them or change to other multivitamins without calcium, as this could lead to higher doses of calcium supplementation in the calcium group and contamination in the placebo group.

- 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., 20000 IU weekly for 6 weeks) to treat Vitamin D deficiency during pregnancy is NOT an exclusion criterion.

- Known contraindications to excipient Isomalt (e.g. hereditary fructose intolerance).

- A diagnosis of pre-eclampsia in the current pregnancy, prior to trial entry.

4.3. Co-enrolment

Co-enrolment may be acceptable depending on the particular trial, but in all instances the recruiting centre should contact the Chief Investigator *via* the CaPE Trials Office prior to offering the other trial.

5. CONSENT

5.1. In hospital clinic

It is the responsibility of the PI (or delegate) to obtain informed consent for each trial participant, prior to performing any trial related procedures. A research nurse, research midwife or clinician is able to take consent providing that local practice allows this, and responsibility has been delegated by the PI as captured on the Site Signature and Delegation Log.

A Participant Information Sheet (PIS) will be provided to the participant to facilitate this process either at the time of initial consultation / hospital visit or sent through the post, via email, or by text (i.e. short message service – SMS) with a link to download the PIS from the trial website. The PI or their delegate(s) will ensure that they adequately explain the aim of the trial, trial treatment, and the anticipated benefits and potential hazards of taking part in the trial to the participant. The participant will be given sufficient time to read the PIS and have the opportunity to ask questions and discuss their participation with others outside of the site research team if they wish. If the participant decides to take part in the trial they will be asked to sign and date the latest version of the informed consent form (ICF). The PI or their delegate will then sign and date the ICF. A copy of the ICF will be given to the participant (electronic or hard copy), a copy will be filed in the medical notes, and the original placed in the Investigator Site File (ISF). Once the participant is entered into the trial, the participant's trial number will be entered on the ICF maintained in the ISF. In addition, the participant understands and acknowledges that, a copy of the signed ICF will be transferred to the trial team at BCTU for review.

5.2. Telephone Consent

Where the woman is unable to attend hospital appointments, she can provide consent to participate in the trial over the phone. If the woman agrees to be contacted at home after reading the PIS, she will receive a telephone call from the local Research Nurse, a member of the local clinical team or a clinical member of the central research team to discuss the trial and answer any queries. Women may make a decision at home to participate following this telephone call or during a subsequent visit to hospital.

Women who agree to participate following telephone discussion will be able to provide consent in the following ways:

1) Wet sign and date the latest version of the REC approved paper Informed Consent Form (ICF) in the presence of a member of the local trial team at their subsequent hospital visit.

2) Sign and date the latest version of an electronic Informed Consent Form (ICF) via a secure online web address provided by the Birmingham Clinical Trials Unit (BCTU).

3) Provide consent verbally to a member of the research team during their telephone call. Before taking consent the member of the local research team will ensure that they have a witness present who can verify that informed consent was taken. This witness does not have to be named on the CaPE Delegation Log. The member of the local research team who is taking remote consent will read each of the statements on the ICF to the potential participant and will insert their initials in each of the associated boxes to confirm that the participant agrees with the statement.

   After consent has been taken the witness will sign and date the ICF, and a copy of the completed form will be sent to the participant. A copy of the ICF will be placed in the participants notes.

4) Alternatively, the participant will be provided with a paper copy of the latest REC approved version of the ICF to complete, wet sign and date, and send through the post to the local team at their treating hospital for completion.

Details of the informed consent discussions will be recorded in the participant's medical notes.

Throughout the trial the participant will have the opportunity to ask questions about the trial. Any new information that may be relevant to the participant's continued participation will be provided. Where new information becomes available which may affect the participants' decision to continue, participants will be given time to consider and if happy to continue will be re-consented. Re-consent will be documented in the medical notes. The participant's right to withdraw from the trial at any time will remain.

Details of all patients approached about the trial will be recorded on the Participant Screening/Enrolment Log, and with the participant's prior consent, their General Practitioner (GP) will also be informed that they are taking part in the trial.

6. ENROLMENT AND RANDOMISATION

6.1. Enrolment

Women are eligible for recruitment to the CaPE trial providing they meet the inclusion and exclusion criteria detailed in Section 4 eligibility.

If the woman consents to participate in the trial, then, at enrolment, the woman will be asked to complete a short, validated survey to assess her baseline dietary calcium intake. The results of these surveys will not be made known to the women so as not to influence their future behaviour but will be used for subgroup analysis on whether baseline calcium intake impacts on trial outcomes.

6.2. Randomisation

Randomisation will be provided by a secure online randomisation system at the Birmingham Clinical Trials Unit (BCTU) (available at http://www.trials.bham.ac.uk/cape). Unique log-in usernames and passwords will be provided to those who wish to use the online system and who have been delegated the role of randomising participants into the trial as detailed on the CaPE Trial Signature and Delegation Log. These unique log-in details must not be shared with other staff and in no circumstances should staff at sites access either system using another person's login details.

The online randomisation system will be available **24 hours a day, 7 days a week**, apart from short periods of scheduled maintenance. A toll-free telephone randomisation service (0800 953 0274) is also available Monday to Friday, 09:00 to 17:00 UK time, except for bank holidays and University of Birmingham closed days.

After participant eligibility has been confirmed and informed consent has been given, the participant can be randomised into the trial. Randomisation forms will be provided to investigators at each site and will be used to collate the necessary information prior to randomisation. All required questions and data items on the Randomisation Notepad must be answered before a Trial Number can be given. If data items are missing, randomisation will be suspended, but can be resumed once the information is available. Only when all eligibility criteria and required baseline data items have been provided will a Trial Number be allocated.

Participants will be randomised at the level of the individual in a 1:1 ratio to either the equivalent of 2 grams per day of dietary calcium or placebo starting from between 12^{+0} and 22^{+0} weeks gestation and continuing up to delivery.

A minimisation algorithm will be used within the online randomisation system to ensure balance in the treatment allocation over the following variables:

- trial site
- risk factor for pre-eclampsia (either one or more high risk factor OR two or more moderate risk factors OR high risk on the FMF algorithm)
- intention to use aspirin for prevention of pre-eclampsia (yes / no)
- gestational age at randomisation (<16 weeks / ≥16+0 weeks);

Women may have a high-risk factor along with moderate risk factors; in this case women will be minimised based on the high-risk factor as they are likely to be in the group at highest risk of developing pre-eclampsia. Where the FMF algorithm has been used to ascertain high risk for pre-eclampsia, women will be minimised based on use of the FMF algorithm regardless of whether they have high or moderate risk factors based on NICE criteria, as women who are screen positive on the FMF algorithm have a higher probability of developing pre-eclampsia compared to use of the NICE criteria risk factors alone.

A 'random element' will be included in the minimisation algorithm, so that each participant has a probability (unspecified here), of being randomised to the opposite treatment that they would have otherwise received. Full details of the randomisation specification will be stored in a confidential document at BCTU.

Following randomisation, a confirmatory e-mail will be sent to the randomiser, the local PI, the trial manager, and the pharmacist, displaying the pack numbers to be dispensed to that participant alongside their unique trial number.

Investigators will keep their own trial file log which links patients with their allocated trial number in the CaPE **Patient Recruitment and Identification Log**. The Investigator must maintain this document, which is **not** for submission to the Trials Office. The Investigator will also keep and maintain the CaPE **Screening Log** which will be kept in the ISF and should be available to be sent to the CaPE Trials Office upon request. The CaPE **Patient Recruitment and Identification Log** and CaPE **Participant Screening/Enrolment Log** should be held in strict confidence.

6.3. Informing the participant's GP

If the participant has agreed on the ICF, the participant's GP should be notified by the trial centre that they are in the CaPE trial**.** The CaPE GP letter template provided must be used where applicable.

6.4. Blinding & Unblinding

This is a triple blind placebo-controlled trial. The participants, their medical/care teams, research team /investigators (including statistician) will be blinded to the treatment allocation (either calcium or placebo).

To maintain blinding, placebo tablets will be manufactured to match commercially licensed calcium 1g chewable tablets. The placebo tablets will contain no active ingredients.

Packaging Design and Labelling

All active and placebo tablets will be primarily packed in randomised labelled bottles each containing 105 active or placebo tablets. To ensure complete blinding, the active calcium 1g tablets will be rebottled into identical bottle packaging that is also used for the placebo.

Four bottles will be supplied (total IMP supply for the duration of the trial) at the time of randomisation. The bottles will be contained in a single kit. Each kit will have a unique number. Each kit and containing four bottles will be labelled according to Annex 13 guidelines.

Unblinding

Investigators will have access to unblinding of the treatment allocation in case of a medical emergency *via* the online code-brake system or by contacting the CaPE Trial office.

Should any Serious Adverse Event occur, the management and care of the participant will be initiated as though the woman is taking a calcium supplement.

Cases that are considered serious, unexpected and possibly, probably or definitely related will be unblinded only at the CaPE Trial Office by the CaPE Trial Manager (or other nominated individual), for reporting purposes. Members of the local care team, or the woman will not be made aware of the actual trial treatment allocation unless it is deemed clinically necessary by the Chief Investigator or the local clinical team.

In all other circumstances, the participant, the investigators and research midwives/nurses will remain blind to treatment allocation whilst the participant remains in the trial.

In the rare event that information about the woman's treatment allocation is required for the continued medical management of the woman or her child, care providers can contact the CaPE Trial Office or use the online CaPE code-break system (available 24 hours a day, seven days a week) to facilitate unblinding.

7. TRIAL TREATMENT / INTERVENTION

7.1. Treatment(s) and Dosing Schedule

Trial participants will be randomised to receive either an oral calcium supplement of 2 g per day plus usual care (including aspirin) or a placebo plus usual care (including aspirin), to be commenced anytime from 12^{+0} to 22^{+0} weeks' gestation and taken until delivery.

The calcium supplement group: Each tablet supplied contains the equivalent of 1 gram of calcium. Participants will be asked to take one of these tablets in the morning and one in the evening.

The placebo group: Participants in this group will receive matched chewable tablets that do not contain any calcium. They will be asked to take one of these tablets in the morning and one in the evening.

The regime of 1 tablet twice a day is the recommended regime, however if the participant is unable to take tablets in divided doses due to other medication they may be taking, they may be advised to take tablets at a more convenient frequency (i.e. at the same time).

Justification of dose and frequency

The recommended daily intake of calcium in pregnancy is 1 to 1.3 g/day (for ages 19 - 50 and 14-18 years respectively); however, the maximum daily intake unlikely to cause adverse health effects (Tolerable Upper Intake Level) is 2.5 to 3 g/day (for 19-50 and 14-18 years respectively) (27). The study dose of 2 g/day does not carry any additional risks to the woman or her baby as detailed in section 3.4 above.

Data from previous studies on efficacy suggest that there may be a dose-dependent relationship between calcium intake and reduction in the risk of pre-eclampsia. A dose of 2 g/day is the highest and most used dose among previous RCTs that show a significant reduction in risk of pre-eclampsia. Studies with lower doses either show smaller treatment effects, are of poorer quality or have evaluated calcium in combination with other nutrients (18). Moreover, one RCT directly comparing high dose calcium (2 g/day) with low dose (500 mg/day) found a greater reduction in the risk of pre-eclampsia with 2 g/day (25). Adherence has not been reported to be problematic at a dose of 2 g/day in previous studies (3 RCTs, 64% to 84% and 67% to 86% for the calcium and placebo groups respectively).

The dose of 2 g/day selected for this study will therefore optimise efficacy without compromising safety, based on best available evidence, and ensure the greatest likelihood of a definitive result for the trial.

Over 90% of women in previous calcium supplementation trials were randomised at or prior to 22 weeks (18). Commencing calcium between 12 and 22 weeks will avoid IMP exposure in the first trimester as well as randomising women at a time of increased pregnancy loss and improve adherence as nausea and vomiting subside. It

is still early enough to potentially benefit women who are at risk of developing severe early onset pre-eclampsia. Moreover, this timing will coincide with routine antenatal appointments (dating and anomaly scan), making it easier and more efficient for clinicians to recruit and less time consuming and inconvenient for women.

The 2 g dose of IMP will be administered in divided doses, as one tablet to be taken twice daily; this will help improve absorption of calcium and reduce potential gastrointestinal side effects but is an acceptable frequency so as not to be too inconvenient to the woman.

7.2. Drug Interaction or contraindications

Women commonly use other supplements or medications during their pregnancy that may impact or be impacted by calcium. The common ones include:

I. Iron: calcium can decrease iron absorption. Women will be advised to take the trial tablets more than two hours before or after any iron tablets.

II. Vitamin D: Vitamin D impacts calcium absorption. Severe deficiency can lead to rickets and osteomalacia while excessive amounts (toxicity) can lead to excessive calcium in the blood. The association between vitamin D deficiency and pregnancy outcomes, particularly risk of pre-eclampsia, is contentious and evidence is contradictory.

   For the CaPE trial, we will include women if they are on vitamin D supplements in a preventative dose (≤1000 IU) or short-term treatment doses of vitamin D (e.g., 20000 IU weekly for 6 weeks) as it would be inappropriate to withhold these. We will not provide routine supplementation with vitamin D as part of trial treatment to optimise calcium absorption as ensuring vitamin D is given to all participants or testing and treating for vitamin D deficiency will deviate from current clinical practice and introduce a parallel intervention. We will ask women not to use vitamin D supplements containing calcium.

   We will record the use of or intention to use vitamin D at the start of the pregnancy to confirm eligibility.

III. Multivitamins: During pregnancy women may routinely take multivitamins however whilst on trial they **must** avoid multivitamins containing calcium. We recommend that they use either the 'Healthy Start Vitamins' brand for pregnant women (containing Vit D 10 mcg, Vit C and Folic acid) that are freely available from many antenatal clinics, or Pregnacare without calcium. These are two of the most used preparations in pregnancy. Women will be provided with an information sheet at the beginning of the trial on which preparations are suitable to take and which are not.

IV. Antacids: women will be advised to take non-calcium-based antacids, such as aluminium or magnesium-based antacid (e.g., Maalox®). Recent evidence suggests that proton pump inhibitors (such as omeprazole) do not have a significant impact on calcium absorption so may be used.

V. Thyroxine and hydroxychloroquine: calcium may reduce their absorption so women will be advised to leave a period of at least four hours before taking their trial tablet if they use these medications.

VI. Folic acid: no known interaction with calcium, so women may take this as normal.

7.3. Accountability Procedures

The dispensing of the CaPE trial drugs will be recorded in the Pharmacy Drug Accountability Log. The Trial Manager will periodically request the trial drug chart to verify that the dispensing system is being followed. Any deviations from the protocol schedule should be logged locally and both the PI and the Trial Office informed.

At randomisation, the participant's unique trial number and drug kit number will be provided to the local hospital pharmacy. The pharmacist will receive notification of the name and trial number of the randomised woman and will prepare the trial treatment kit for dispensing. The trial treatment kits will consist of four bottles each containing 105 active or placebo tablets.

The local pharmacist should keep accurate records of trial drugs dispensed using a pharmacy log provided by the CaPE Trial Office. Trial drugs must be kept in the packaging supplied and under no circumstances used for other participants or non-participants.

7.4. Treatment Supply and Storage

7.4.1. Treatment Supplies

Procurement, manufacture, packaging and distribution of trial medication will be arranged by MODEPHARMA.

MODEPHARMA will arrange the supply of active calcium 1g tablets, placebo manufacture, randomised double-blind IMP packaging, final QP release, storage and distribution of the investigational medicinal products (IMPs). The IMPs will be shipped directly from the final QP releasing site to the trial sites following site initiation.

Please refer to the Summary of Product Characteristics for the calcium 1g chewable tablets and the Investigational Medicinal Product Dossier (IMPD) for more details about the active and placebo IMPs.

7.4.2. Packaging and Labelling

Each kit will be labelled with a unique number and be tamper-evident sealed. Four bottles will be supplied in each kit and each bottle will also be labelled with the unique number of the kit. The information on the labels will be compliant with Annex 13 guidelines.

7.4.3. Drug Storage

Following delivery to the hospital, the kits containing the IMP bottles will be stored in the Hospital Pharmacy at a temperature not exceeding 30°C. Sites will maintain temperature logs for all hospital stored IMP up to the point of dispensing the IMP to the participant. The sponsor must be notified of any temperature excursions. Sites will be required to complete a CaPE temperature excursion form and return it to the CaPE trial office for review. All affected stock should be quarantined until a response has been received from the CaPE trial office detailing stability of the stock.

Participants will be asked to return any unused medication to the trial team when they are admitted to hospital for delivery for the purpose of pill counting. Hospital trusts will be asked to destroy any unused trial medication at the end of the trial in accordance with their local procedure. A certificate of destruction must be sent to the CaPE trial office.

8. TRIAL PROCEDURES & OUTCOME MEASURES

Once the participant has provided informed consent and baseline data has been collected, the participant will be randomised into the trial and receive their allocated trial medication. The baseline information should be recorded for the participant within the randomisation form, and the participant should complete the calcium survey (to record current baseline calcium intake, please refer to Appendix 2 for more information).

A copy of the completed calcium survey should be added to the patient file within the ISF. Participants will be advised to follow the detailed treatment plan as per the trial prescription throughout their pregnancy (refer to Section 7 trial treatment).

Adherence to the IMP will be assessed by collecting data from participants via text message, where women have granted their permission to do so. Where permission to measure adherence via text message is not granted the site will contact the participant by phone to record adherence monthly. The text message will be sent by a specialist third party organisation (TextLocal) every four weeks enquiring about

adherence with the trial medication over the last week. The participant will be asked to respond to the text message as prompted. The message will be sent once every four weeks to mimic the frequency of routine antenatal clinic appointments. Text messages will be sent until the participant has completed the trial (or earlier if the participant's trial status changes).

Sites will be required to report any adverse events throughout the participation in the trial, from the day of commencement of trial treatment until the end of trial follow up (hospital discharge or up to 4 weeks post term, whichever is later). After hospital discharge, sites will not be actively following up patients for SAEs but should still report patient reported adverse events if they become aware.

The outcome CRF must be completed for all participants (providing trial status has not changed, any relevant data items recorded up until the change of status should be documented on the outcome CRF) after hospital discharge (for the woman and baby (or babies)) or estimated delivery date plus four weeks, whichever is sooner).

Participants will be asked to return any unused trial treatment back to the trials team, when they are admitted to hospital for delivery (or as close to this timepoint as possible). The research team will document the returned number of tablets within the outcome CRF

Women participating in the trial will receive all other treatments, investigations and procedures in accordance with the local centres antenatal care pathway.

Please refer to section 8.2 schedule of assessments for a visual representation of assessments.

8.1. Trial Outcomes

The following outcomes will be collected up to primary hospital discharge, or four weeks after estimated date of delivery, whichever is sooner.

8.1.1. Primary outcome

The primary outcome of the CaPE trial is a clinician diagnosis of pre-eclampsia, based on the ISSHP definition: a blood pressure ≥140/90mmHg **AND** either

1. significant proteinuria (protein/creatinine ratio (PCR) of 30 mg/mmol or more) OR
2. maternal multiorgan dysfunction:
    a. Acute kidney injury (AKI) (creatinine ≥90 µmol/L)
    b. Liver involvement (elevated transaminases e.g. alanine transaminase (ALT) or aspartate transaminase (AST) >40IU/L) with or without right upper quadrant or epigastric abdominal pain)
    c. neurological complications (including eclampsia, altered mental status, blindness, stroke, clonus, severe headaches, persistent visual scotomata)

d. haematological complications (thrombocytopenia – platelet count below 150,000/µL, DIC, haemolysis)
OR

3. uteroplacental insufficiency (fetal growth restriction, abnormal Umbilical artery doppler, stillbirth)

developing at or after 20 weeks gestation

8.1.2. Key secondary outcomes

The following will be considered key secondary outcomes for the analysis as they are clinically very important, and have a potential to be impacted by calcium based on data from previous trials:

- Severe pre-eclampsia index: any one of severe pre-eclampsia, early onset pre-eclampsia <32 weeks, eclampsia, placental abruption, HELLP, or severe gestational hypertension (20).

- Preterm birth <37 weeks

8.1.3. Other secondary outcomes

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

- Death
- Eclampsia
- Stroke
- Visual impairment: retinal detachment or cortical blindness
- Pulmonary oedema
- Acute kidney injury: creatinine ≥90 µmol/L
- Liver capsule haematoma or rupture (confirmed on ultrasound)
- Raised liver enzymes: ALT or AST >40IU/L.
- Low platelets < 150,000/µL
- Abruption
- Postpartum haemorrhage: estimated or measured blood loss ≥500 mls and ≥1000 after birth
- Admission to Intensive Treatment Unit (ITU)
    - Any admission
    - Days of admission
- Use of mechanical ventilation (for other than Caesarean section)

In addition to these COS, we will record.

- Gestational hypertension: new onset hypertension ≥140/90 (at least two measurements several hours apart) after 20 weeks gestation in the absence of proteinuria or other features of pre-eclampsia
- Severe hypertension: blood pressure ≥160 systolic and/or 110 mm Hg diastolic

- Severe gestational hypertension: new onset hypertension ≥160 systolic and/or 110 mm Hg diastolic after 20 weeks gestation in the absence of proteinuria or other features of pre-eclampsia
- Severe pre-eclampsia, defined as pre-eclampsia with severe features (ACOG definition) including severe hypertension or low platelets <100,000X10^9/L, or abnormal 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 mg/dl), or pulmonary edema or visual impairment or severe headache unresponsive to medication and no other cause found.
- 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 lactate dehydrogenase (LDH)enzyme or blood film)
- Early onset pre-eclampsia < 32 weeks
- Pre-eclampsia requiring delivery before 37 weeks.
- Use of magnesium sulphate for pre-eclampsia.
- Onset of birth: spontaneous, induction of labour or Caesarean section
- Mode of birth: vaginal birth, assisted vaginal birth, electivce pre-labour Caesarean section, emergency pre-labour Caesarean section, emergency Caesarean section in labour.
- Adverse effect: new diagnosis of maternal hypercalcaemia
- Adverse effect: renal stones (confirmed on imaging, after starting IMP)
- Adverse effect: stopping of medication due to adverse effects.

For the baby: COS outcomes namely:

- Any death in the baby up to hospital discharge. We will collect data separately for:
    - Fetal loss <24 weeks gestation (miscarriage)
    - Fetal loss ≥24 weeks' gestation (stillbirth)
    - Neonatal death (from birth up to 28 days)
        - Early neonatal death (up to 7 days after birth)
        - Late neonatal death (from 7 days up to 28 days)
    - Perinatal death – stillbirth or neonatal death up to 7 days
    - Termination of pregnancy
- Gestational age at delivery (median, <28 weeks, <32 weeks, <37 weeks)
- Birthweight (mean, <3rd centile, <10th centile)
- Admission to NNU
    - any admission
    - level of neonatal care (admission to NICU /HDU/SCBU/Transitional Care)
    - days of admission
- Respiratory support morbidity

    - use of surfactant
    - use of mechanical ventilation.
    - use of non-invasive ventilation: (NIV, BPAP, CPAP, high flow oxygen
    - use of supplementary oxygen.
    - duration of respiratory support
- Neonatal seizures
- Neonatal brain injury:
    - hypoxic ischaemic encephalopathy requiring therapeutic hypothermia.
    - neonatal stroke,
    - severe intraventricular haemorrhage (IVH) grade III/IV and / or cystic periventricular leukomalacia

In addition to these COS outcomes, we will record:

- Chronic lung disease (CLD) requiring oxygen therapy at 36 weeks post-menstrual age.
- Necrotising enterocolitis (NEC) requiring surgery.
- Retinopathy of prematurity (ROP) requiring treatment with laser or anti-VEGF injection.
- Composite of death or serious morbidity: death or CLD, IVH grade III/IV, NEC requiring surgery or ROP requiring treatment.
- Adverse effects: neonatal hypocalcaemia requiring treatment.

Longer term outcomes for the woman and the baby: we will seek consent from trial participants to be approached for long term data linkage studies in the future (requiring additional and separate funding and ethical approval). This could include assessment of cardiovascular health for both women and babies. This approach has been used in similar trials recruiting in pregnancy and was not found to impact on recruitment.

8.1.4. Internal pilot

The trial includes an internal pilot during the first 12 months of recruitment. Outcomes for the internal pilot are listed below and the ability to achieve appropriate targets will determine whether the trial will proceed to the full trial.

<u>1.Recruitment</u>
We aim to recruit a minimum of 1157 women at the end of the pilot. This is based on the assumption that approximately 3 sites per month are opened through the pilot phase with a staggered start and individual recruitment targets. If recruitment is 100% of expected (green), we will proceed to the main trial; if 60% to 99% of expected (amber), we will explore and implement methods to improve recruitment; if <60% of expected (red), and there are no obvious remedial factors, we will discuss with the TSC and consider stopping the trial.

2. Adherence to the trial IMP

Adherence to trial treatment will be measured via women's responses to adherence text messages (where consent is provided) sent on a four-weekly basis (refer to Section 8 trial procedures). Good adherence is defined as women taking 75% or more of the IMP. If there is good adherence in ≥75% of responders (green), we will proceed to the main trial; if 50%-74% (amber) of responders report good adherence, we will explore and implement methods to improve adherence; if <50% (red) of responders report good adherence, and there are no obvious remedial factors, we will discuss with the TSC and consider stopping the trial.

3. Primary outcome

Primary outcome data will be collected throughout the pilot. If outcome data are available for ≥95% of participants (green) that have given birth and reached the trial endpoint, we will proceed to the main trial; if available for 80%-94% (amber) we will explore and implement methods to improve adherence; if available for <80% or participants (red) and there are no obvious remedial factors, we will discuss with the TSC and consider stopping the trial.

Internal pilot outcome table

	Red	Dark Amber	Light Amber	Green
Recruitment				
Sites open (Pilot target =34)	<60% of target	60-79% of target	80-99% of target	100% of target
Women recruited (Pilot target=1157)	<60% of target	60-79% of target	80-99% of target	100% of target
Action	Discuss with TSC: stop trial if no obvious remedial factors	1.Explore/implement tested methods to improve recruitment 2. Open new sites 3.Discuss with TSC: consider stopping trial	Explore/implement tested methods to improve recruitment, proceed to main trial	Proceed to main trial
Adherence				
Women reporting good adherence (defined as taking ≥75% of tablets)	<50%	50-59%	60-74%	≥75%
Action	Discuss with TSC: stop trial if no obvious remedial factors.	1.Explore/implement methods to improve adherence. 2.Discuss with TSC: consider stopping trial	Explore/implement tested methods to improve adherence, proceed to main trial	Proceed to main trial
Primary outcome				
Data collected	<80%	80-90%		≥95%
Action	Discuss with TSC: stop trial if no obvious remedial factors	Explore and implement methods to improve completeness of data, proceed to main trial		Proceed to main trial

8.2. Schedule of Assessments

			From randomisation			
Visit	**Screening**	**Baseline**	**After recruitment- as identified**	**Every 4 weeks until delivery**	**Admission for delivery**	**hospital discharge/ estimated delivery date plus four weeks**
Eligibility check	x	x				
Dietary calcium intake survey		x				
Intention to take or taking Vitamin D		x				
Intention to take or taking aspirin		x				
Valid informed consent		x				
Randomisation		x				
Dispensing of IMP		x				
Adherence text message (automated)				x		
Outcome CRF Completion						x
Serious Adverse Events (SAE)			x			x *
Return un-used medication (Pill counting)					X**	

** Any events meeting the trial definition of an SAE should be reported to the CaPE trial office at the point of becoming aware. Sites will be required to report any adverse events throughout the participation in the trial, from the day of commencement of trial treatment until the end of trial follow up (hospital discharge or up to 4 weeks post term, whichever is later). After hospital discharge, sites will not be actively following up patients for SAEs but should still report patient reported adverse events if they become aware.*

*** at point of admission for delivery or as close to as possible*

8.3. Participant withdrawal & discontinuation

Participants should be aware at the beginning that they can freely withdraw from the trial at any time.

Withdrawal is defined as:

- The participant would like to withdraw from trial treatment and is not willing to be followed up in any way for the purposes of the trial and for no further data to be collected (i.e. only data collected prior to the withdrawal can be used in the trial analysis)

Participants that stop trial treatment as defined below will be recorded as a treatment discontinuation only:

- The participant would like to discontinue from trial treatment, but is willing to be followed up in accordance with the schedule of assessments and if applicable using any central UK NHS bodies for long-term outcomes (i.e. the participant has agreed that data can be collected and used in the trial analysis)

The details of withdrawal or discontinuation (date and reason (if provided)) must be clearly documented in the source data and a change of status CRF must be completed.

9. ADVERSE EVENT REPORTING

9.1. Definitions

Table 1: Adverse event reporting definitions

Severity Definitions	Mild Moderate Severe	Awareness of signs or symptoms that do not interfere with the participant's usual activity or are transient and resolved without treatment and with no sequelae. A sign or symptom, which interferes with the participant's usual activity. Incapacity with inability to do work or perform usual activities.
Adverse Event	AE	Any untoward medical occurrence in a participant administered a medicinal product and which does not necessarily have a causal relationship with this intervention. Comment: An AE can therefore be any unfavourable and unintended sign (including abnormal laboratory findings), symptom or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product.
Adverse Reaction	AR	All untoward and unintended responses to an IMP related to any dose administered. Comment: An AE judged by either the reporting Investigator or Sponsor as having causal relationship to the IMP qualifies as an AR. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.
Serious Adverse Event	SAE	Any untoward medical occurrence or effect that: Results in death Is life-threatening* Requires hospitalisation or prolongation of existing hospitalisation. Results in persistent or significant disability or incapacity Is a congenital anomaly/birth defect? Or is otherwise considered medically significant by the Investigator**
Serious Adverse Reaction	SAR	An AR which also meets the definition of a SAE.
Unexpected Adverse Reaction	UAR	An AR, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator Brochure for an unapproved IMP or (compendium of) Summary of Product Characteristics (SPC) for a licensed product). When the outcome of an AR is not consistent with the applicable product information the AR should be considered unexpected.
Suspected Unexpected Serious Adverse Reaction	SUSAR	A SAR that is unexpected i.e., the nature, or severity of the event is not consistent with the applicable product information. A SUSAR should meet the definition of an AR, UAR and SAR.

* The term life-threatening is defined as diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted.
** Medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed in the definitions above.

9.2. Adverse event recording – general

The recording and reporting of Adverse Events (AEs) will be in accordance with the UK Policy Framework for Health and Social Care Research, the Principles of GCP as set out in the UK Statutory Instrument (2004/1031; and subsequent amendments) and the requirements of the Health Research Authority (HRA) and, The Medicines for Human Use (Clinical Trials) Regulations 2004 and amendments thereof. Definitions for adverse event reporting are listed in Table 1: Adverse event reporting definitions in Section 9.

It is routine practice to record AEs in the participant's medical notes and it is also recommended that this includes the documentation of the assessment of severity and seriousness and also of causality (relatedness) in relation to the intervention(s) in accordance with the protocol.

9.3. Adverse event reporting in CaPE

Sites will be required to report any adverse events throughout the participation in the trial, from the day of commencement of trial treatment until the end of trial follow up (hospital discharge or up to 4 weeks post term, whichever is later). After hospital discharge, sites will not be actively following up patients for SAEs but should still report patient reported adverse events if they become aware.

Adverse Events

AEs are rarely encountered in participants taking additional dietary calcium and previous trials in pregnant women have consistently shown no increase in AEs. As the safety profiles of the IMPs used in this trial are well characterised and mild side effects have significant overlap with pregnancy symptoms (nausea, dyspepsia, abdominal pain, itching, etc), we will only be collecting AEs and ARs that have a higher probability of being related to calcium intake on the outcome CRF. These include:

1. new diagnosis of maternal hypercalcaemia
2. new diagnosis of renal stones in the woman (confirmed on imaging, after starting of IMP)
3. neonatal hypocalcaemia requiring treatment

9.4. Serious Adverse Advents (SAE) reporting in CaPE

For all SAEs, the PI or delegate must do one of the following:

1. **Record safety reporting-exempt SAEs** in the medical notes but do **not report** them to the trial's office on an SAE form as per Section 9.5 Serious Adverse Events not requiring reporting to the Trial .

2. **Report SAEs to the trial office in an expedited manner** (within 24 hours of the site research team becoming aware of the event). All SAEs not covered by the above category must be reported as per Section 9.7 SAE Reporting process.

Note: when an SAE occurs at the same hospital at which the participant is receiving trial intervention or is being followed up for trial purposes, processes must be in place to make the trial team at the hospital aware of any SAEs, regardless of which department first becomes aware of the event, in an expedited manner.

9.5. Serious Adverse Events not requiring reporting to the Trial Office.

At whatever time they occur during an individual's participation the following are not considered to be critical to evaluations of the safety of the trial:

- Pre-planned hospitalisation
- Hospitalisation for pregnancy bleeding
- Hospitalisation for the management of pregnancy loss
- Hospitalisation for rest in pregnancy
- Hospitalisation for observation or monitoring of pregnancy.
- Hospitalisation for maternal discomfort in pregnancy
- Hospitalisation for complications of pregnancy e.g. urinary tract infection, pyelonephritis
- Hospitalisation for birth (including caesarean section)
- Prolonged hospitalisation for post-natal care
- Neonatal hospitalisation for sepsis
- Neonatal hospitalisation for prematurity

All events which meet the definition of serious must be recorded in the participant notes, including the causality and severity, throughout the participant's time on trial, including follow-up, but for trial purposes these events do not require reporting on the SAE Form. Such events are "safety reporting exempt".

9.6. Serious Adverse Events requiring expedited reporting to the Trial Office.

All SAEs not listed in Sections 9.5 must be reported to the Trial Office on a trial specific SAE form within 24 hours of the site research team becoming aware of the event.

The following AEs related to calcium must be reported as SAEs/SARs:

1. maternal hypercalcaemia which is severe (>3 mmol/l) or symptomatic

2. symptomatic neonatal hypocalcaemia (usually presenting as neonatal seizures) secondary to maternal hypercalcaemia

3. milk alkali syndrome (hypercalcaemia, alkalosis, and biochemical evidence of renal impairment)

9.7. SAE Reporting process

On becoming aware that a participant has experienced an SAE which requires reporting on an SAE form, the PI or delegate should report the SAE to their own Trust in accordance with local practice and to the Trial Office.

To report an SAE to the Trial Office, the PI "or delegate" must complete, date and sign the SAE form the completed form together with any other relevant, appropriately anonymised, data should be submitted to the Trial Office using the information below in accordance with the timelines given in Section 9.4.

To report an SAE, submit the SAE Form to:

CaPE@trials.bham.ac.uk

Where an SAE Form has been completed by someone other than the PI initially, the original SAE form must be countersigned by the PI (or medically qualified delegate) to confirm agreement with the causality and severity assessments.

On receipt of an SAE form, the Trial Office will allocate each SAE a unique reference number and notify the site via email to the site as proof of receipt. The site and the Trial Office should ensure that the SAE reference number is quoted on all correspondence and follow-up reports regarding the SAE and filed with the SAE in the ISF.

If the site has not received confirmation of receipt of the SAE or if the SAE has not been assigned a unique SAE identification number within 1 working day of reporting, the site should contact the Trial Office.

9.8. Assessment of causality of an SAE

When completing the SAE form, the PI (or, throughout this section, a medically qualified delegate) will be asked to define the nature of the seriousness and causality (relatedness; see **Table 2**: Categories of causality) of the event.

In defining the causality the PI must consider if any concomitant events or medications may have contributed to the event and, where this is so, these events or medications should be reported on the SAE form. It is not necessary to report concomitant events or medications which did not contribute to the event.

As per **Table 2**: Categories of causality, all events considered to be 'possibly', 'probably', or 'definitely' related to the intervention will be reported by the trial office as 'related'; all events considered at site to be 'unlikely' or 'unrelated' to the intervention will be reported by the trial's office as 'unrelated'. The same categorisation should be used when describing AEs and protocol-exempt SAEs in the source data.

Table 2: Categories of causality

Category	Definition	Causality
Definitely	There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.	Related
Probably	There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.	
Possibly	There is some evidence to suggest a causal relationship. However, the influence of other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events or medication)	
Unlikely	There is little evidence to suggest there is a causal relationship. There is another reasonable explanation for the event (e.g., the participant's clinical condition, other concomitant events or medication).	Unrelated
Not related	There is no evidence of any causal relationship.	

On receipt of an SAE Form, the Trial Office will forward it, with the unique reference number, to the Chief Investigator (CI) "or delegate(s)" who will independently* review the causality of the SAE. An SAE judged by the PI or CI "or delegate(s)" to have a reasonable causal relationship ("Related" as per Table 2: Categories of causality) with the intervention will be regarded as a related SAE (i.e., SAR). The severity and causality assessment given by the PI will not be downgraded by the CI "or delegate(s)". If the CI "or delegate(s)" disagrees with the PI's causality assessment, the opinion of both parties will be documented, and where the event requires further reporting, the opinion will be provided with the report. *Where the CI is also the reporting PI an independent clinical causality review will be performed.

9.9. Assessment of expectedness of an SAE by the CI

The CI "or delegate(s)" will also assess all related SAEs for expectedness with reference to the criteria in **Table 3**: Categories of expectedness.

Table 3: Categories of expectedness

Category	Definition
Expected	An adverse event that is consistent with known information about the trial related procedures or that is clearly defined in the Reference safety information document
Unexpected	An adverse event that is not consistent with known information about the trial related procedures.

If the event is unexpected (i.e., it is not defined in the approved version of the RSI) it will be classified as a Suspected Unexpected Serious Adverse Reaction (SUSAR).

The CI will undertake review of all SAEs and may request further information from the clinical team at site for any given event(s) to assist in this.

9.10. Provision of SAE follow-up information

Following reporting of an SAE for a participant, the participant should be followed up until resolution or stabilisation of the event. Follow-up information should be provided using the SAE reference number provided by the Trial Office. Once the SAE has been resolved, all critical follow-up information has been received and the paperwork is complete, a copy of the final version of the completed SAE form must be submitted to the Trial Office and the original kept in the ISF.

9.11. Reporting SAEs to third parties

The independent Data Monitoring Committee (DMC) may review any SAEs at their meetings. The Trial Office will report details of all SARs (including SUSARs) to the MHRA, Research Ethics Committee (REC), annually from the date of the Clinical Trial Authorisation, in the form of a Development Safety Update Report (DSUR). Additionally, the Trial Office will report a minimal data set of all individual events categorised as a fatal or life threatening SUSAR to the MHRA and REC within 7 days of being notified. Follow-up information will be provided within an additional 8 days.

All other events categorised as SUSARs will be reported within 15 days of being notified.

9.12. Urgent Safety Measures

If any urgent safety measures are taken, the Trial Office shall immediately, and in any event no later than 3 days from the date the measures are taken, give written notice to the REC and MHRA of the measures taken and the reason why they have been taken.

9.13. Follow-up of pregnancy outcomes for potential SAEs

Calcium is not known to be associated with a teratogenic risk, however as there is a potential unknown risk with any medication taken in earlier stages of pregnancy, any reportable congenital abnormalities (as defined by the EUROCAT guideline (51)) detected will be documented on a SAE form.

10. DATA HANDLING AND RECORD KEEPING

10.1. Source Data

In order to allow for the accurate reconstruction of the trial and clinical management of the woman, source data will be accessible and maintained. The source date for all data will be stored in either the woman's hospital notes, the neonatal notes or at the BCTU (Text local adherence reports). Where required for audit purposes information not held at the BCTU may be reviewed by the sponsor at the site.

Data	Source
Clinical event data	The original clinical annotation is the source data. This may be found on clinical correspondence, or electronic or paper participant records. Clinical events reported by the participant, either in or out of clinic (e.g., phone calls), must be documented in the source data.
Recruitment	The original record of the randomisation is the source. It is held on the CaPE trial database as part of the randomisation and data entry system.
Drop out	Where a participant expresses a wish to withdraw, the conversation must be recorded in the patient's hospital records (electronic or paper).

10.2. Case Report Form (CRF) Completion

Data reported on each CRF form will be consistent with the source data and any discrepancies will need to be clarified by site staff. All missing and ambiguous data will be queried by the BCTU staff with site staff. Staff delegated to complete CRFs will be trained to adhere to procedures for:

- CRF completion and corrections;
- Date format and partial dates;
- Time format and unknown times;
- Rounding conventions;
- Trial-specific interpretation of data fields;
- Entry requirements for concomitant medications (generic or brand names);
- Which forms to complete and when;
- What to do in certain scenarios, e.g. when a woman withdraws from the trial;
- Missing/incomplete data;
- Completing SAE forms and reporting SAEs; and
- Protocol and GCP non-compliances.

In all cases it remains the responsibility of the site's PI to ensure that the CRF has been completed correctly and that the data are accurate. This will be evidenced by the signature of the site's PI (or delegate), on the CRF. The Site Signature & Delegation Log will identify all those personnel with responsibilities for data collection.

10.3. Data Management

Processes will be employed to ensure the accuracy of the data included in the final report. These processes will be detailed in the trial specific data management plan. Coding and validation will be agreed between the trial manager, statistician and programmer and the trial database will be signed off once the implementation of these has been agreed.

Data entry will be completed by the sites via a bespoke BCTU trial database at www.trials.bham.ac.uk/CAPE. Authorised staff will require an individual secure login username and password to access this online data entry system. Those entering data will receive written work instructions on the process (a copy of which should be filed in the ISF and TMF).

If changes need to be made to a CRF that has already been entered and submitted onto the database, the site should contact the CaPE trial office so that the form can be made available for the site to edit and an explanation of the errors entered.

Data reported on each CRF should be consistent with the source data or the discrepancies should be explained. If information is unknown, this must be clearly indicated on the CRF. All missing and ambiguous data will be queried. Queries will be raised using data clarification forms (DCFs) via the trial database. These will be generated on a regular basis by CaPE trial office staff and reported to the site for clarification. The process of entering data on to the database itself forms a data quality check, as ranges are put in place to ensure that only viable data values can be input. It will be the responsibility of the PI to ensure the accuracy of all data entered in the CRFs on behalf of their site. The Site Signature and Delegation Log will identify all those personnel with responsibilities for data collection.

CRFs may be amended and the versions updated by the CaPE trial office, as appropriate, throughout the duration of the trial. Whilst this may not constitute a protocol amendment, new versions of the CRFs must be implemented by participating sites immediately on receipt, in some circumstances sites will be asked to update previously completed CRF where additional information is now being requested.

10.4. Data Security

The security of the system is governed by the policies of the University of Birmingham. The University's Data Protection Policy and the Conditions of Use of Computing and Network Facilities set out the security arrangements under which sensitive data should be processed and stored. All studies at the University of Birmingham must be registered with the Data Protection Officer and data held in accordance with the Data Protection Act. The University will designate a Data Protection Officer upon registration of the trial. The Trial Centre has arrangements in place for the secure storage and processing of the trial data which comply with the University of Birmingham policies.

10.5. Archiving

It is the responsibility of the PI to ensure all essential trial documentation and source documents (e.g. signed ICFs, Investigator Site Files, Pharmacy Files, participants' hospital notes, copies of CRFs etc.) at their site are securely retained for at least 25 years. Archiving will be authorised by BCTU on behalf of UoB following submission of the end of trial report. No documents should be destroyed without prior approval from the BCTU Director or their delegate.. Electronic and paper documents will be archived as per the applicable policies of BCTU and the University of Birmingham.

11. QUALITY CONTROL AND QUALITY ASSURANCE

11.1. Site Set-up and Initiation

The CI is required to sign a UoB CI agreement to document the expectations of both parties. The UoB CI agreement document must be completed prior to participation. The CI is required to sign a Clinical Trials Task Delegation Log which documents the agreements between the CI and BCTU. All PIs will be asked to sign the necessary agreements including a Site Signature & Delegation Log between the PI and the BCTU and supply a current CV and GCP certificate to BCTU. All site staff who are performing trial specific tasks are required to sign the Site Signature and Delegation Log, which details all tasks that have been delegated to them by the PI.

Prior to commencing recruitment, each recruiting site will undergo a process of initiation, either a meeting or a tele/videoconference, at which key members of the site research team (PI and responsible pharmacist are a minimum requirement) are

required to attend, covering aspects of the trial design, protocol procedures, adverse event reporting, collection and reporting of data and record keeping. Sites will be provided with an ISF and a Pharmacy File containing essential documentation, instructions, and other documentation required for the conduct of the trial. The BCTU trials team must be informed immediately of any change in the site research team.

11.2. Monitoring

The monitoring requirements for this trial have been developed following a trial specific risk assessment by BCTU and are documented in the trial specific monitoring plan.

11.3. Onsite Monitoring

For this trial we will monitor sites in accordance with the trial risk assessment and monitoring plan. Any monitoring activities will be reported to the trials team and any issues noted will be followed up to resolution. Additional on-site monitoring visits may be triggered, for example due to poor CRF return, poor data quality, low SAE reporting rates, excessive number of participant withdrawals or deviations (also defined in the monitoring plan). Investigators will allow the CaPE trial staff access to source documents as requested. The monitoring will be conducted by BCTU/UoB staff.

11.4. Central Monitoring

Trials staff will be in regular contact with the site research team to check on progress and address any queries that they may have. Trials staff will check incoming ICFs and CRFs for compliance with the protocol, data consistency, missing data and timing. Sites will be sent DCFs requesting missing data or clarification of inconsistencies or discrepancies.

Sites will be requested to send in copies of signed consent forms and other documentation for in-house review for all participants providing explicit consent. This will be detailed in the monitoring plan.

11.5. Audit and Inspection

The Investigator will permit trial-related monitoring, audits, ethical review, and regulatory inspection(s) at their site, providing direct access to source data/documents. The investigator will comply with these visits and any required follow up. Sites are also requested to notify BCTU of any relevant inspections.

11.6. Notification of Serious Breaches

In accordance with the Medicines for Human Use (Clinical Trials) Regulations 2004 and its amendments, the Sponsor of the trial is responsible for notifying the licensing authority in writing of any serious breach of the conditions and principles of GCP in

connection with that trial or the protocol relating to that trial, within 7 days of becoming aware of that breach.

For the purposes of this regulation, a “serious breach” is a breach which is likely to affect:

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

Sites are therefore requested to notify the Trials Office of any suspected trial-related serious breach of GCP and/or the trial protocol as soon as they become aware. Where the Trials Office is investigating whether or not a serious breach has occurred, sites are also requested to cooperate with the Trials Office in providing sufficient information to report the breach to the MHRA where required and in undertaking any corrective and/or preventive action.

Sites may be suspended from further recruitment in the event of serious and persistent non-compliance with the protocol and/or GCP, and/or poor recruitment. Any major problems identified during monitoring may be reported to the Trial Management Group, Trial Steering Committee, the site’s R&D Department, and the REC. This includes reporting serious breaches of GCP and/or the trial protocol to the REC and MHRA.

A copy of the documentation relating to serious breaches will be sent to the sponsor and University of Birmingham Clinical Research Compliance Team at the time of reporting to the REC and/or relevant regulatory bodies.

12.END OF TRIAL DEFINITION

The end of trial will be the date of the last data capture including resolution of DCFs. This will allow sufficient time for the completion of protocol procedures, data collection and input and data cleaning. The Trial Office will notify the REC and MHRA within 90 days of the end of trial. Where the trial has terminated early, the Trial Office will notify the MHRA and REC within 15 days of the end of trial. The Trial Office will provide the REC and MHRA with a summary of the clinical trial report within 12 months of the end of trial.

13.STATISTICAL CONSIDERATIONS

13.1. Sample Size

The trial will recruit women at high risk of pre-eclampsia based on a combination of (1) women with a single high-risk factor and (2) women with two or more moderate risk factors. The control group event rate of pre-eclampsia in women with a single high-risk factor on aspirin has been estimated to be 15% from the PARIS IPD meta-analysis of antiplatelet agents for prevention of preeclampsia (37). For women with two or more moderate risk factors, the control rate is estimated to be 8% from a retrospective trial conducted at a tertiary referral unit (findings presented at British Maternal Fetal Medicine Society Conference 2011) (47). We estimated the ratio of the two risk factor groups to be approximately 50:50 (data taken from ongoing BUMP clinical trial), giving an overall control group event rate of 11.5%.

N=7756 women will be recruited (approximately 3878 in each group). This will allow us to detect with 90% power (p=0.05) a 20% relative risk reduction in pre-eclampsia from 11.5% down to 9.2%, allowing for a 5% loss to follow up (total 7368 women after attrition). A 20% reduction is considered plausible given the 55% reduction observed in the Cochrane review (18), albeit in a population distinct from that considered in CaPE. It is also likely to be considered clinically meaningful by clinicians and policy makers given aspirin was adopted into clinical practice based on a 17% reduction (8).

13.2. Analysis of Outcome Measures

A separate Statistical Analysis Plan will be produced and will provide a more comprehensive description of the planned statistical analyses. A brief outline of these analyses is given below.

The primary comparison groups will be composed of those randomised to usual care plus an additional dietary calcium supplement of 2 grams per day versus those randomised to usual care plus a placebo (the randomised groups).

In the first instance, all analyses will be based on the intention to treat principle, i.e. all participants will be analysed in the treatment group to which they were randomised, irrespective of e.g. adherence or other protocol deviation. For all outcome measures, appropriate summary statistics will be presented by group (e.g. proportions/percentages, mean/standard deviation or median/interquartile range). All outcomes will be presented with point estimates (e.g. relative risks, incident rate ratios, hazard ratios, mean differences) and 95% confidence intervals.

13.2.1. Primary Outcome Measure

We will use a mixed effects log-binomial regression model to calculate the risk difference and relative risk with 95% confidence intervals for the primary outcome (pre-eclampsia), adjusting for the variables listed in section 6.2. The p-value relating to the intervention group parameter as generated by the model estimating the relative risk will be presented.

13.2.2. Secondary Outcome Measures

Secondary maternal outcomes are all dichotomous (e.g. eclampsia occurred or not) and will be analysed using risk ratios and 95% confidence intervals, generated using a

log-binomial regression model, adjusting for the variables listed in section 6.2. Dichotomous secondary outcomes for the baby (e.g. small for gestational age <10th centile) will be analysed in the same fashion. Continuous outcomes for the baby (e.g. birthweight) will be analysed using a linear regression model, adjusting for the same factors to obtain a mean difference between groups, and 95% confidence interval. Secondary outcomes will not be subject to hypothesis testing and confidence intervals will be interpreted cautiously given the potential for multiplicity.

13.3. Subgroup Analyses

Subgroup analyses will be restricted to the primary outcome only. Adequate vs inadequate baseline dietary calcium intake (to be defined in the Statistical Analysis Plan) is the main subgroup of interest. This is based on a previous systematic review (18) which suggested greater efficacy in those women with inadequate intake. Analysis will be carried out using a test for statistical heterogeneity, i.e. by including the treatment group by subgroup interaction parameter in the regression model to produce a p-value. 95% confidence intervals will be produced for estimates within each subgroup and will be presented using forest plots.

Other subgroup analyses as follows will be considered exploratory:

- At least one high risk factor for pre-eclampsia vs two or more moderate risk factors
- Women deemed eligible based on NICE criteria vs FMF algorithm
- Gestational age at Randomisation (<16 weeks / ≥16+0 weeks)
- Aspirin intake of 150mg vs aspirin intake of 75mg vs no aspirin
- Vitamin D supplement vs no vitamin D supplement

Analysis will be performed in the same manner as the main subgroup of interest, but confidence interval widths will be interpreted cautiously given the potential for multiplicity.

13.4. Missing Data and Sensitivity Analyses

Every attempt will be made to collect full follow-up data on all trial participants; it is thus anticipated that missing data will be minimal. Participants with missing primary outcome data will not be included in the primary analysis in the first instance. This presents a risk of bias, and sensitivity analyses will be undertaken to assess the possible impact of the risk. This will include imputing missing data using multiple imputation techniques. Further sensitivity analysis will include an assessment of efficacy with those who had good adherence to treatment (as defined in section 8) using a CACE (Complier Average Causal Effects) approach. Full details will be included in the Statistical Analysis Plan.

13.5. Planned Interim Analysis

Interim analyses of safety and efficacy for presentation to the independent DMC will take place during the trial. The committee will agree the manner and timing of such analyses, but this is likely to include the analysis of the primary and major secondary outcomes and full assessment of safety (SAEs) at least at annual intervals. Criteria for

stopping or modifying the trial based on this information will be ratified by the DMC. Details of the agreed plan will be written into the Statistical Analysis Plan and DMC Charter.

13.6. Planned Final Analyses

The primary analysis for the trial will occur once all participants have either been discharged or reach four weeks after their estimated date of delivery and corresponding outcome data has been entered onto the trial database and validated as being ready for analysis. This analysis will include data items up to and including the point of hospital discharge or four weeks after estimated date of delivery (whichever is sooner) and no further.

14. Health Economics Analysis

A trial based economic evaluation will explore the cost-effectiveness of a calcium regime to prevent pre-eclampsia in expectant mothers compared to the current standard of care i.e. no calcium supplementation. The cost differences between the intervention and control groups will be measured, valued and combined with the clinical effectiveness data from the trial to generate Incremental Cost Effectiveness Ratios (ICERs). The main health economics outcome will be the cost per case of pre-eclampsia prevented.

14.1 Economic data collection

In line with existing recommendations, the economic analysis will adopt a health care system (payer's) perspective by considering costs incurred by the NHS (NICE 2013). The analysis will use the individual level data on all health-related resource use collected during the trial by research midwives at each centre. The main resource categories related to each participant that will be monitored include:

1. Drug administration
2. Resource use of standard care.
3. Resource use associated with adverse events and complications.
4. Resource use associated with outpatient or emergency visits and hospital admissions.

In order to value health care resource use to estimate the overall cost of each trial-arm, unit costs will be applied to each resource item. Information on unit costs will be obtained from key UK national sources, such as the NHS reference costs, the Unit Costs of Health and Social Care, the British National Formulary, and the Office for National Statistics. Variations in the unit cost of items and services across settings will be explored in sensitivity analyses.

14.2 Health Economics sensitivity analysis

The results of these economic analyses will be presented firstly using a cost consequences table and secondly using cost-effectiveness acceptability curves (CEAC) to reflect decision uncertainty across different thresholds of willingness-to-pay per additional unit of outcome. Deterministic and probabilistic sensitivity analyses will be undertaken to explore the robustness of the findings to plausible variations in key

assumptions and analytical methods used, and to consider the broader issue of generalisability of the trial's results. The probabilities of compliance with the calcium regimen, risk ratio for the prevention of pre-eclampsia with calcium supplementation, and hospitalisation will all be varied. The distribution of costs and outcomes and missing data, censoring and correlations between costs and outcomes will be explored. Results of the analysis will be presented in terms of the cost per pre-eclampsia case prevented, the main clinical outcome on which calcium has an effect.

A probabilistic sensitivity analysis (PSA) will also be conducted to demonstrate the impact of a change in the parameters on the Incremental Cost Effectiveness Ratios.

15.TRIAL ORGANISATIONAL STRUCTURE

15.1. Sponsor

The Sponsor for this trial is the University of Birmingham. The Head Organisation (i.e. the contracting party with the funder) is Birmingham Women's and Children's NHS Foundation Trust.

15.2. Coordinating Centre

The trial coordinating centre (Trial Office) is the Birmingham Clinical Trials Unit (BCTU), based at the University of Birmingham.

15.3. Trial Management Group

The Trial Management Group will take responsibility for the day-to-day management of the trial and will include (but is not limited to) the CI, co-applicants, statistician, team leader and trial manager. The role of the group is to monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself.

15.4. Trial Steering Committee (TSC)

A TSC will be created for the CaPE trial.

Membership and duties/responsibilities are outlined in the TSC Charter. In summary, the TSC will:

- provide overall oversight of the trial, including the practical aspects of the trial, as well as ensuring that the trial is run in a way which is both safe for the participants and
- provides appropriate feasibility data to the sponsor and investigators.

The CaPE contract with the IMP Supplier (Modepharma) contains break points based around the campaign provision to allow termination, and thus minimise expenditure, if the trial proves to be futile. The TSC will meet at least one month before each break point to review recruitment and trial progress and recommend to the TMG if they believe that continuation of the trial is futile and whether the next manufacturing campaign is needed.

15.5. Data Monitoring Committee

Data analyses will be supplied in confidence to an independent Data Monitoring Committee (DMC)), which will be asked to give advice on whether the accumulated data from the trial, together with the results from other relevant research, justifies the continuing recruitment of further participants. The DMEC will operate in accordance with a trial specific charter. The DMEC will meet at least annually as agreed by the Committee and documented in the Charter. More frequent meetings may be required for a specific reason (e.g. safety) and will be recorded in minutes.

Additional meetings may be called if recruitment is much faster than anticipated and the DMC may, at their discretion, request to meet more frequently or continue to meet following completion of recruitment. An emergency meeting may also be convened if a safety issue is identified. The DMC will report directly to the Trial Steering Committee who will convey the findings of the DMC to the TMG, The DMC may consider recommending the discontinuation of the trial if the recruitment rate or data quality are unacceptable or if any issues are identified which may compromise participant safety. The trial would stop early if the interim analyses showed differences between treatments that were deemed to be convincing to the clinical community.

15.6. Finance

The research costs of the trial are funded by a National Institute for Health Research (NIHR) Health Technology Assessment (HTA), reference 17/116/01, awarded to Dr Shireen Meher at Birmingham Women's and Children's Hospital. The trial has been designed to minimise extra 'service support' costs for participating hospitals as far as possible. Additional costs, service support costs and excess treatment costs associated with the trial, e.g. gaining consent, are estimated in the SoECAT form. These costs should be met by accessing the Trust's Support for Science budget via the Local Comprehensive Research Network.

16.ETHICAL CONSIDERATIONS

The trial will be conducted in accordance with the UK Policy Framework for Health and Social Care Research and applicable UK Acts of Parliament and Statutory Instruments (and relevant subsequent amendments), which include, but are not limited to, the Medicines for Human Use Clinical Trials 2004, Data Protection Act 2018; Human Tissue Act 2004"; "Mental Capacity Act 2005"; "Medical devices Regulations 2002" as appropriate>).

This trial will be carried out under a Clinical Trial Authorisation in accordance with the Medicines for Human Use Clinical Trials regulations and according to the Principles of GCP as set out in the UK Statutory Instrument (2004/1031; and subsequent amendments).

The protocol will be submitted to and approved by the REC prior to the start of the trial. All correspondence with the MHRA and/or REC will be retained in the TMF/ISF, and an annual progress report will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given by the REC, and annually until the trial is declared ended. A trial-specific risk assessment and monitoring plan will be developed before submission to the REC and will be reviewed regularly during the trial.

Before any participants are enrolled into the trial, the PI at each site is required to obtain the necessary local approval.

It is the responsibility of the PI to ensure that all subsequent amendments gain the necessary local approval. This does not affect the individual clinicians' responsibility to take immediate action if thought necessary to protect the health and interest of individual participants.

17.CONFIDENTIALITY AND DATA PROTECTION

Personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the General Data Protection Regulation, 2018.

Participants will always be identified using their unique trial identification number and partial date of birth on the CRFs and on any correspondence between members of the BCTU and site research team. Participants will give their explicit consent for a copy their consent form to be sent to and stored at BCTU. This will be used to perform in-house monitoring of the consent process.

The PI must maintain documents not for submission to BCTU (e.g. Participant Identification Logs) in strict confidence. In the case of specific issues and/or queries from the regulatory authorities, it will be necessary to have access to the complete trial records, provided that participant confidentiality is protected.

BCTU will maintain the confidentiality of all participant's data and will not disclose information by which participants may be identified to any third party other than those organisations for which the participant has given explicit consent for data transfer (e.g. the transfer of their mobile phone number to Text local so the participant can receive texts measuring their adherence). Representatives of the CaPE trial team and sponsor may be required to have access to participant's notes for quality assurance purposes, but participants should be reassured that their confidentiality will be respected at all times.

18.Financial and other competing interests

Members of the TMG and trial oversight committees will be required to declare any financial or other competing interests. These will be recorded in specific documents recording any competing interests based upon the DAMOCLES declaration.

19.Insurance and Indemnity

The University of Birmingham has in place Clinical Trials indemnity coverage for this trial which provides cover to the University for harm which comes about through the University's, or its staff's, negligence in relation to the design or management of the trial and may alternatively, and at the University's discretion provide cover for non-negligent harm to participants. With respect to the conduct of the trial at Site and other clinical care of the patient, responsibility for the care of the patients remains with the NHS organisation responsible for the Clinical Site and is therefore indemnified through the NHS Litigation Authority. The University of Birmingham is independent of any pharmaceutical company, and as such it is not covered by the Association of the British Pharmaceutical Industry (ABPI) guidelines for participant compensation.

20.Amendments

The decision to amend the protocol and associated trial documentation will be initiated by the TMG.

As sponsor, the University of Birmingham will be responsible for deciding whether an amendment is substantial or non-substantial. Substantive changes will be submitted to MHRA REC and HRA for approval as appropriate. Once this has been received, R&D departments will be notified of the amendment and requested to provide their approval. If no response is received within 35 days, an assumption will be made that the site has no objection to the amendment, and it will be implemented at the site. All amendments will be tracked in the 'Protocol Amendments' section of the protocol.

21.Post-trial care

The intervention (a calcium supplement or placebo) will only be given whilst the woman is pregnant and will cease with the end of pregnancy. All participants will continue to receive standard medical care following participation in the clinical trial. There are no interventions that participants will be prevented from accessing after their participation in the trial has been completed.

22.Access to the final trial dataset

The final dataset will be available to members of the Trial Management and co-applicant group who need access to the data to undertake the final analyses. Following publication of the trial, the final trial dataset will be made available to external researchers upon request and with approval from the trial management group and the BCTU data sharing committee in line with standard data sharing practices for clinical trial data sets.

If the participant has consented, data collected from this trial may be used for future related studies. Permission will be sought, via written consent, to contact the participants at a later date to collect further data on the women participating in this

study and their children. This is included in the participant information sheet and the informed consent form.

23.Publication Policy

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

Any secondary publications and presentations prepared by Investigators must be reviewed and approved by the TMG. Manuscripts must be submitted to the TMG in a timely fashion and in advance of being submitted for publication, to allow time for review and resolution of any outstanding issues. Authors must acknowledge that the trial was performed with the support of National Institute for Health Research Health Technology Assessment Programme, and the University of Birmingham. Intellectual property rights will be addressed in the CI agreement Clinical Trial Site Agreement between Sponsor and site.

24.Patient and Public Involvement

A range of PPI activities including surveys and focus groups with women and clinicians have guided our protocol development. They have helped refine our research question, and choice of participant population, design, intervention, and outcomes. Specific input has been provided from the Action on Pre-eclampsia Charity (APEC).

25.Reference List

1. Tan MY, Wright D, Syngelaki A, et al. Comparison of diagnostic accuracy of early screening for pre-eclampsia by NICE guidelines and a method combining maternal factorsand
biomarkers: results of SPREE. Ultrasound Obstet Gynecol. 2018;51(6):743-750.

2. Brown MA, Magee LA, Kenny LC, et al. Hypertensive Disorders of Pregnancy: ISSHP Classification, Diagnosis, and Management. Recommendations for International Practice. Hypertension. 2018;72:24-43.

3. DH, editor. Confidential Enquiry into Maternal and Child Health (CEMACH). Perinatal Mortality 2006: England, Wales, and Northern Ireland. London: CEMACH; 2008.

4. Ananth CV, Vintzileos AM. Maternal-fetal conditions necessitating a medical intervention resulting in preterm birth. Am J Obstet Gynecol. 2006 Dec;195(6):1557-63.

5. Meads CA, Cnossen JS, Meher S, et al. Methods of prediction and prevention of pre-eclampsia: systematic reviews of accuracy and effectiveness literature with economic modelling. Health technology assessment (Winchester, England) 2008;12(6):iii-iv, 1-270.

6. Redman CW, Sargent IL. Latest advances in understanding preeclampsia. Science. 2005;308(5728):1592-4.

7. Wen SW, White RR, Rybk N, et al. Effect of high dose folic acid supplementation in pregnancy on pre-eclampsia (FACT): double blind, phase III, randomised controlled, international, multicentre trial. BMJ. 2018;362:k3478.

8. Duley L, Meher S, Hunter KE, Seidler AL, Askie LM. Antiplatelet agents for preventing pre-eclampsia and its complications. Cochrane Database of Systematic Reviews 2019, Issue 10. Art. No.: CD004659. DOI: 10.1002/14651858.CD004659.pub3. Accessed 07 December 2020.

9. Hypertension in pregnancy:diagnosis and management. NICE Guideline 2019. Available from www.nice.org.uk/guidance/ng133 [Accessed 08 December 2020].

10. Duckitt K, Harrington D. Risk factors for pre-eclampsia at antenatal booking: systematic review of controlled studies. BMJ. 2005; 330(7491): 565.

11. Bartsch E, Medcalf KE, Par AL et al. High Risk of Pre-eclampsia Identification Group. Clinical risk factors for pre-eclampsia determined in early pregnancy: systematic review and meta-analysis of large cohort studies. BMJ. 2016;353:i1753.

12. Belizan JM, Villar J. The relationship between calcium intake and edema-, proteinuria-, and hypertension-getosis: an hypothesis. Am J Clin Nutr. 1980;33(10):2202-10.

13. Villar J, Belizan JM, Fischer PJ. Epidemiologic observations on the relationship between calcium intake and eclampsia. Int J Gynaecol Obstet. 1983;21(4):271-8.

14. RHJ H. Prevention of pre-eclampsia. Lancet. 1962;1:864-5.

15. Weigel MM, Narvaez WM, Lopez A, et al. Prenatal diet, nutrient intake and pregnancy outcome in urban Ecuadorian primiparas. Arch Latinoam Nutr. 1991;41(1):21-37.

16. Belizan JM, Villar J, Repke J. The relationship between calcium intake and pregnancy-induced hypertension: up-to-date evidence. Am J Obstet Gynecol. 1988;158(4):898-902.

17. Carroli G, Merialdi M, Wojdyla D, et al. Effects of calcium supplementation on uteroplacental and fetoplacental blood flow in low-calcium-intake mothers: a randomized controlled trial. Am J Obstet Gynecol. 2010;202(1):45 e1-9.

18. Hofmeyr GJ, Lawrie TA, Atallah ÁN, Torloni MR. Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems. Cochrane Database of Systematic Reviews 2018, Issue 10. Art. No.: CD001059. DOI: 10.1002/14651858.CD001059.pub5. Accessed 08 December 2020

19. Belizan JM, Villar J, Bergel E, et al. Long term effect of calcium supplementation during pregnancy on the blood pressure of offspring: follow up of a randomised controlled trial. BMJ. 1997;315:281– 5.

20. World Health Organization Recommendations for Prevention and Treatment of Pre-eclampsia and Eclampsia. Available from: http://apps.who.int/iris/bitstream/handle/10665/44703/9789241548335_eng.pdf;jsessionid=F334CA D17BBF60BA16516D4ADAB59DA0?sequence=1 [Accessed 1st August 2018].

21. Villar J, Abdel-Aleem H, Merialdi M, et al. World Health Organization randomized trial of calcium supplementation among low calcium intake pregnant women. Am J Obstet Gynecol. 2006;194(3):639-49.

22. Levine RJ, Hauth JC, Curet LB, Sibai BM, Catalano PM, Morris CD, et al. Trial of calcium to prevent preeclampsia. N Engl J Med. 1997;337(2):69-76.

23. De Souza E, Sass, N. Aspirin and calcium to prevent preeclampsia in chronic hypertensive women with abnormal uterine artery Doppler ultrasound. Rev Bras Ginecol Obstet. 2006;28(2):136.

24. Crowther CA, Hiller JE, Pridmore B, et al. Calcium supplementation in nulliparous women for the prevention of pregnancy-induced hypertension, preeclampsia and preterm birth: an Australian randomized trial. Aust N Z J Obstet Gynaecol 1999;39(1):12-8.

25. Villar J, Repke J, Belizan JM, et al. Calcium supplementation reduces blood pressure during pregnancy: results of a randomized controlled clinical trial. Obstet Gynecol. 1987;70(3 Pt 1):317- 22.

26. Khan A, Mandal SK, Pal A. Role of high dose calcium in the prevention of preeclampsia. Bangladesh J of Obstet and Gynecol 2013;28(2):66-70.

27. US Department of Health and Human Services. National Institutes of Health, Office of Dietary Supplements. Calcium Fact Sheet for Professionals. Available from:

https://ods.od.nih.gov/factsheets/Calcium-HealthProfessional/. [Accessed 3rd July 2018].

28. REPROTOX® Calcium monograph, 2018. Reproductive Toxicology Centre. Available from: https://www.micromedexsolutions.com (subscription required) [accessed and provided by the UK Teratology Information Service 20th August 2018].

29. TERIS® Calcium salts monograph, 2018. Teris. Available from: https://www.micromedexsolutions.com (subscription required) [accessed and provided by the UK Teratology Information Service 20th August 2018].

30. Villar J, Repke JT. Calcium supplementation during pregnancy may reduce preterm delivery in high-risk populations. Am J Obstet Gynecol. 1990;163:11243

31. Patel AM, Goldfarb S. Got calcium? Welcome to the calcium-alkali syndrome. J Am Soc Nephrol. 2010 21(9):1440-3.

32. Roth DE, Morris SK, Zlotkin S, et al. Vitamin D Supplementation in Pregnancy and Lactation and Infant Growth. N Engl J Med. 2018;379(6):535-546.

33. Roth DE, Leung M, Mesfin E, et al. Vitamin D supplementation during pregnancy: state of the evidence from a systematic review of randomised trials. BMJ. 2017;359:j5237.

34. Antenatal care for uncomplicated pregnancies. NICE Clinical Guideline: Royal College of Obstetricians and Gynaecologists, 2008 (updated 2017). Available from: https://www.nice.org.uk/Guidance/CG62. Accessed 1st July 2018].

35. Vitamin D in Pregnancy. Scientific Impact Paper No.43. June 2014. The RCOG. Available from: https://www.rcog.org.uk/globalassets/documents/guidelines/scientific-impact-papers/vitamin_d_sip43_june14.pdf [Accessed 1st August 2018].

36. BNF: National Institute of Clinical Excellence. Available from: https://bnf.nice.org.uk/interaction/calcium-carbonate-2.html [Accessed 15th May, 2018].

37. Askie LM, Duley L, Henderson-Smart DJ, et al. Antiplatelet agents for prevention of pre-eclampsia: a meta-analysis of individual patient data. Lancet. 2007;369(9575):1791-8.

38. Poston L, Briley A, Seed P, et al. Vitamin C and vitamin E in pregnant women at risk for pre- eclampsia (VIP trial): randomised placebo-controlled trial. Lancet. 2006;367(9517):1145-54.

39. McCance DR, Holmes VA, Maresh MJ, et al. Vitamins C and E for prevention of pre-eclampsia in women with type 1 diabetes (DAPIT): a randomised placebo-controlled trial. Lancet. 2010;376(9737):259-66.

40. The BUMP Trial - Blood pressure monitoring in pregnancy. Available from: https://www.phc.ox.ac.uk/research/participate/bump-trial [Accessed 1st August 2018].

41. Core Outcome Set for Prevention of Pre-eclampsia (awaiting publication - personal communication). Email to James Duffy (james.duffy@balliol.ox.ac.uk) 11th April 2018.

42. Koop A, Mösges R. The use of handheld computers in clinical trials. Control Clin Trials. 2002;23(5):469-80.

43. Matsui D. Strategies to measure and improve patient adherence in clinical trials. Pharm Med. 2009; 23 (5-6): 289-297.

44. National Institute for Health and Care Excellence (NICE) (2013). Guide to the methods of technology appraisal. London, NICE.

45. Curtis, L. & Burns, A. (2017) Unit Costs of Health and Social Care 2017, Personal Social Services Research Unit, University of Kent, Canterbury. Available from: https://doi.org/10.22024/UniKent/01.02/65559 [Accessed 1st June 2018].

46. Running your maternity liaison services. National Childbirth Trust, 2015. Available from: https://www.nct.org.uk/sites/default/files/related_documents/457-NCT-MSLC-practical-guide-to- troubleshooting%20PROOFED%20AND%20FINAL.pdf

47. External validation of prognostic models predicting pre-eclampsia: individual participant data meta-analysis. Snell KIE, Allotey J, Smuk M, Hooper R, Chan C, Ahmed A, **Chappell LC**, Von Dadelszen P, Green M, Kenny L, Khalil A, Khan KS, Mol BW, Myers J, Poston L, Thilaganathan B, Staff AC, Smith GCS, Ganzevoort W, Laivuori H, Odibo AO, Arenas Ramírez J, Kingdom J, Daskalakis G, Farrar D, Baschat AA, Seed PT, Prefumo F, da Silva Costa F, Groen H, Audibert F, Masse J, Skråstad RB, Salvesen KÅ, Haavaldsen C, Nagata C, Rumbold AR, Heinonen S, Askie LM, Smits LJM, Vinter CA, Magnus P, Eero K, Villa PM, Jenum AK, Andersen LB, Norman JE, Ohkuchi A, Eskild A, Bhattacharya S, McAuliffe FM, Galindo A, Herraiz I, Carbillon L, Klipstein-Grobusch K, Yeo SA, Browne JL, Moons KGM, Riley RD, Thangaratinam S; IPPIC Collaborative Network.BMC Med. 2020 Nov 2;18(1):302. doi: 10.1186/s12916-020-01766-9.

48. **S Meher**, S Walkinshaw, J Neilson. Risk of pre-eclampsia in women with two moderate risk factors. Archives of Disease in Childhood-Fetal and Neonatal Edition 2011; 96 (Supp 1): Fa102-Fa103.

49. Fetal Medicine Foundation Algorithm: Risk Assessment for Pre-eclampsia, available from https://fetalmedicine.org/research/assess/preeclampsia/first-trimester [accessed 10th May 2021].

50. Poon LC, Wright D, Thornton S, Akolekar R, Brocklehurst P, Nicolaides KH. Mini-combined test compared with NICE guidelines for early risk-assessment for pre-eclampsia: the SPREE diagnostic accuracy study. Southampton (UK): NIHR Journals Library; 2020 Nov. PMID: 33226739.

51. https://eu-rd-platform.jrc.ec.europa.eu/eurocat/eurocat-data/prevalence_en

52. (NICE guideline [NG133] Published date: 25 June 2019)

26. APPENDICES

Appendix 1 Calcium survey website link

Please follow the link below to access the Calcium survey, the survey must be completed at baseline for all patients participating in the trial. A Pdf copy of the completed form from the website must be printed and returned the CaPE trials office along with the eligibility checklist and Informed consent form.

https://www.cgem.ed.ac.uk/research/rheumatological/calcium-calculator/