PITCHES

Phase III trial in IntrahepaTic CHolestasis of pregnancy (ICP) to Evaluate urSodeoxycholic acid (UDCA) in improving perinatal outcomes

PROTOCOL

Trial Identifier

EudraCT: 2014-004478-41
REC ref: 15/EE/0010
ISRCTN: 91918806

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1. Protocol Synopsis

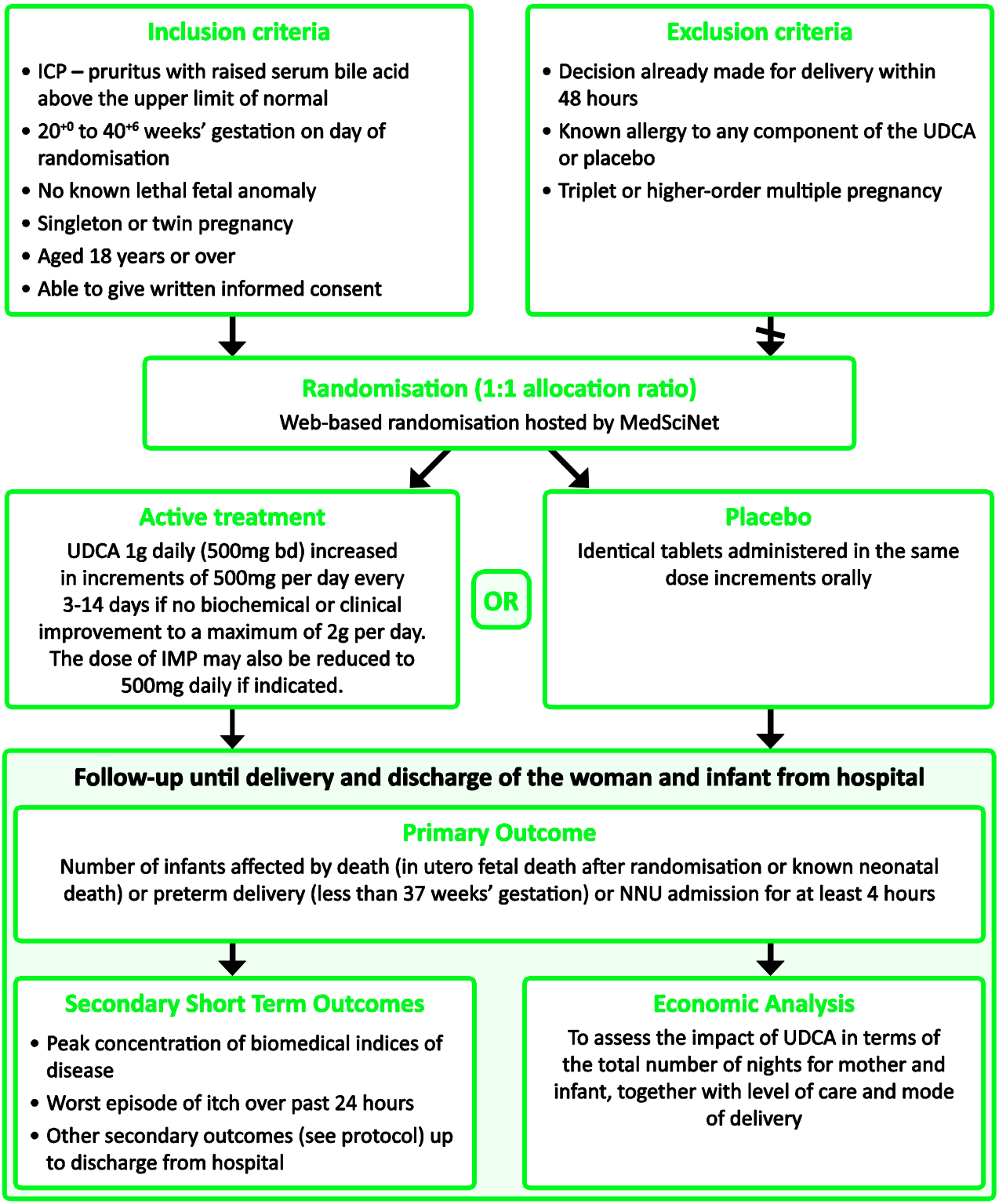
Title of Clinical Trial	Phase III trial in IntrahepaTic CHolestasis of pregnancy to Evaluate urSodeoxycholic acid (UDCA) in improving perinatal outcomes
Protocol Acronym	PITCHES
Sponsor Name	King's College London / Guy's and St Thomas' NHS Foundation Trust
Chief Investigator	Professor Lucy Chappell
ISRCTN	91918806
EudraCT number	2014-004478-41
REC number	15/EE/0010
Medical Condition	Intrahepatic Cholestasis of Pregnancy (ICP)
Purpose of Clinical Trial	To provide definitive evidence for (or against) a role for UDCA in ameliorating adverse perinatal outcomes.
Trial Design	This will be a masked placebo-controlled randomised trial, to evaluate UDCA vs. placebo in women with ICP between 20^{+0} to 40^{+6} weeks' gestation. The trial will be conducted at approximately 30 centres across UK. Recruitment will run for approximately 39 months in total.
Sample Size	580 women with ICP between 20^{+0} and 40^{+6} weeks' gestation (approximately 290 women randomised per group).
Maximum duration of treatment	22 weeks
Summary of Eligibility Criteria	<u>Inclusion criteria:</u> • ICP (pruritus with a raised serum bile acid above the upper limit of normal for the local laboratory) • 20^{+0} to 40^{+6} weeks' gestation on day of randomisation • No known lethal fetal anomaly • Singleton or twin pregnancy • Aged 18 years or over • Able to give written informed consent <u>Exclusion criteria:</u> • Decision already made for delivery within the next 48 hours • Known allergy to any component of the UDCA or placebo tablets • Triplet or higher-order multiple pregnancy
Primary Objective	The primary short term objective of the trial is to determine if UDCA treatment of women with ICP between 20^{+0} and 40^{+6} weeks of

	gestation reduces the following adverse perinatal outcomes up to infant hospital discharge: • In utero fetal death after randomisation • Known neonatal death up to 7 days • Preterm delivery (less than 37 weeks' gestation) • Neonatal unit admission for at least 4 hours
Outcomes	**Primary outcomes:** Primary short term perinatal outcomes: A composite of perinatal death (as defined by in utero fetal death after randomisation or known neonatal death up to 7 days) or preterm delivery (less than 37 weeks' gestation) or neonatal unit admission for at least 4 hours (between infant delivery and hospital discharge). Each infant will only be counted once within this composite. The time points of evaluation of this outcome measure are: - For death: between randomisation and 7 days post delivery - For preterm delivery: between randomisation and up to 37 weeks' gestation - For infant neonatal unit admission for at least 4 hours between infant delivery and hospital discharge **Secondary outcomes:** Secondary short term maternal outcomes: • Peak maternal serum concentration (between randomisation and delivery) of the following biochemical indices of disease: o Bile acids o Alanine transaminase o Aspartate transaminase o Bilirubin (total) o Gamma glutamyl transferase • Change of itch between randomisation and delivery, as measured by the worst episode of itch over past 24 hours (mm on visual analogue scale, assessed at clinic visits) • Maximum dose of trial medication required • Need for additional therapy for cholestasis • Gestational diabetes mellitus • Assessment of myometrial contractions by CTG approximately one week (3-14 days) post randomisation • Mode of onset of labour • Mode of delivery classified as spontaneous vaginal, instrumental vaginal or caesarean • Reason for induction or pre-labour caesarean section • Estimated blood loss after delivery • Maternal death Secondary short term perinatal outcomes: • In utero fetal death after randomisation • Preterm delivery (less than 37 weeks' gestation) • Known neonatal death up to 7 days • Known neonatal death up to 28 days • NNU admission for at least 4 hours

	• Number of nights in each category of care (intensive, high dependency, special, transitional and normal) • Total number of nights in hospital • Birth weight (g) • Birth weight centile • Gestational age at delivery • Presence of meconium • APGAR score at 5 minutes • Umbilical arterial pH at birth • Need for supplementary oxygen prior to discharge • Number of days when supplemental oxygen is required • Need for ventilation support (CPAP/high flow/endotracheal ventilation) • Abnormal cerebral ultrasound scan • Confirmed sepsis (positive blood or cerebrospinal fluid cultures) • Necrotising Enterocolitis (Bell's stage 2 and 3) • Seizures (confirmed by EEG or requiring anticonvulsant therapy) • Encephalopathy grade (worst at any time: mild, moderate, severe) • Other indications and main diagnoses resulting in neonatal unit admission for at least 4 hours The time points of evaluation of the secondary outcomes are taken at the clinic visits and during admission for delivery up to discharge of mother and infant. <u>Economic Analysis</u> The following health resource use post-randomisation will be captured: • Maternal: total number of nights (antenatal, intrapartum and postnatal) together with level of care including adult intensive care unit; mode of delivery • Infant: total number of nights for the infant length of stay in neonatal unit, together with level of care (e.g. neonatal ICU) • The cost of UDCA in the intervention group
IMP, Dosage and Route of Administration	UDCA 1g daily (500mg bd), increased in increments of 500mg per day every 3-14 days if there is no biochemical or clinical improvement, based on clinical decision, to a maximum of 2g per day. The dose of IMP may be reduced to 500mg daily. Administered orally as Ursofalk tablets each containing 500mg UDCA.
Active comparator product	Identical placebo tablets administered in the same dose increments orally.
Version and date of final protocol	Version 2.4, dated 14/03/16

2. Trial Flow Diagram

PITCHES Flow Diagram



3. Abbreviations

AE	Adverse event
AR	Adverse reaction
CI	Chief Investigator
CIG	Co-Investigator Group
CRN	Clinical Research Network
CT	Clinical Trial
CTG	Cardiotocography
CTU	Clinical Trial Unit
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
eCRF	Electronic Case Record Form
GCP	Good Clinical Practice
GP	General Practitioner
GSTFT	Guy's and St Thomas' NHS Foundation Trust
HTA	Health Technology Assessment
IB	Investigator Brochure
ICF	Informed Consent Form
ICP	Intrahepatic Cholestasis of Pregnancy
ICU	Intensive Care Unit
IMP	Investigational Medicinal Product
ISF	Investigator Site File
KCL	King's College London
KHP-CTO	King's Health Partners Clinical Trials Office
MHRA	Medicines and Healthcare products Regulatory Agency
NNU	Neonatal Unit
NPEU CTU	National Perinatal Epidemiological Unit Clinical Trials Unit
OC	Obstetric Cholestasis
PI	Principal Investigator
PIL	Participant Information Leaflet
PMG	Project Management Group
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SmPC	Summary of Medicinal Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reactions
TSC	Trial Steering Committee
UDCA	Ursodeoxycholic Acid

4. Background & Rationale

Intrahepatic cholestasis of pregnancy (ICP), also called obstetric cholestasis (OC), is the most common liver disorder specific to pregnancy. It presents with maternal pruritus, raised concentrations of serum bile acids and abnormal liver function tests. The maternal symptoms typically resolve postpartum, but affected women have an increased risk of hepatobiliary disease in later life (Marschall et al., 2013). ICP is associated with increased rates of spontaneous and iatrogenic preterm labour, fetal hypoxia, meconium-stained amniotic fluid (Glantz et al., 2004, Chappell et al., 2012, Geenes and Williamson 2009). There are also reports of increased rates of intrauterine death (Fisk et al., 1998, Davies et al., 1995, Williamson et al., 2004), although the incidence is low (Glantz et al., 2004, Geenes et al., 2014). Most clinicians treat ICP with ursodeoxycholic acid (UDCA) (Saleh et al., 2007, Zapata et al., 2005) to improve maternal pruritus and biochemical abnormalities.

However, there are currently no data to support the use of UDCA to improve pregnancy outcome as none of the trials performed to date have been powered to address this question.

UDCA is a naturally occurring bile acid that is present in small amounts in humans. It is relatively hydrophilic and has several actions that result in improvement of cholestasis. It increases biliary bile acid excretion by post-translational modification of hepatic bile acid transporters, enhances renal bile acid excretion and has anti-apoptotic effects (Roma MG et al., 2011). UDCA improves outcomes in primary biliary cirrhosis in addition to maternal symptoms in ICP (Carey and Lindor, 2012). Other therapeutic options in ICP include rifampicin, cholestyramine, S-adenosyl methionine, guar gum and dexamethasone, but the small studies of these drugs in women with ICP have not consistently shown that they improve maternal symptoms or serum bile acid concentrations (Geenes and Williamson, 2009).

The main clinical research question is whether adverse pregnancy outcomes can be reduced in women with ICP by treatment with UDCA. This is a subject of intense debate. The current RCOG Guideline on the management of OC describes the evidence relating to the use of UDCA and states that “UDCA improves pruritus and liver function in women with obstetric cholestasis” but “Women should be informed of the lack of robust data concerning protection against stillbirth and safety to the fetus or neonate”. The guideline concludes that, “As the pathophysiology of obstetric cholestasis and the mechanism of fetal demise are uncertain, the possible role of UDCA is unclear. Further larger studies are required to determine this”.

The controversy regarding the efficacy of UDCA treatment also extends across the spectrum of disease severity. Of the four well-conducted prospective studies of UDCA versus placebo, comprising a total of only 236 women, two have investigated the relationship between the maternal serum bile acid concentration and adverse perinatal outcomes. Subgroup analysis of the study by Glantz et al., (2005) suggested a differential effect of UDCA in the severe group (serum bile acids >40μmol/L) with an improvement in maternal symptoms and biochemistry, whilst no such effect was seen in the mild group (serum bile acids <40μmol/L); the study was not sufficiently powered to assess perinatal outcomes. Chappell et al., (2012) showed no differential effect of UDCA on maternal outcomes, but was not large enough to examine the impact on adverse fetal events. In relation to this uncertainty, the study design of the proposed trial includes women with a spectrum of disease severity to address this issue.

Small case series and a larger prospective cohort study have reported increased rates of adverse pregnancy outcome in ICP, but these were limited to women with severe disease, defined as

pregnancies where the maternal fasting serum bile acid level is ≥40μmol/L (Glantz et al., 2004). We confirmed this association in a much larger prospective study of severe ICP cases with non-fasting serum bile acid levels ≥40μmol/L (Geenes et al., 2014). We also demonstrated a significantly increased risk of stillbirth, a novel observation. Thus ICP impacts patients and healthcare due to increased perinatal mortality and morbidity.

Our recent PITCH pilot trial in 111 ICP women demonstrated that UDCA decreased maternal itching compared to placebo but by less than the difference pre-specified as clinically meaningful (Chappell et al., 2012). Specifically, UDCA reduced itching by -16 mm (95% CI -27 mm to -6 mm). However, we surveyed clinicians and women that had previously had ICP, and both groups indicated that a reduction of 30mm (from a median score of 60mm) would be a clinically important reduction in pruritus using an itch analogue scale (0-100mm). This demonstrates a limited use of UDCA for maternal symptoms only and highlights the need to establish potential perinatal benefits.

The latest updated Cochrane review (Gurung et al., 2013) judged many of the primary trials to be at moderate to high risk of bias. Trials to date have lacked power to demonstrate whether UDCA is fetoprotective, with numbers of participants and adverse events too small to enable recommendation of UDCA. The Cochrane review concluded that larger trials of UDCA to determine fetal benefits or risks are needed.

If UDCA is found to be beneficial in ameliorating adverse perinatal outcomes, once published these results would be highly likely to lead to an immediate change in clinical practice, through individual choice of clinicians and women, and through changing national/international guidelines.

5. Trial Objectives

5.1. Primary Objective

The primary short term objective of the trial is to determine if UDCA treatment of women with ICP between 20^{+0} and 40^{+6} weeks' gestation reduces the following adverse perinatal outcomes up to infant hospital discharge:

- In utero fetal death after randomisation
- Known neonatal death up to 7 days
- Preterm delivery (less than 37 weeks' gestation)
- NNU admission for at least 4 hours

5.2. Primary Outcomes

The primary short term perinatal outcome is a composite of perinatal death (as defined by in utero fetal death after randomisation or known neonatal death up to 7 days) or preterm delivery (less than 37 weeks' gestation) or NNU admission for at least 4 hours (from infant delivery until hospital discharge).

Each infant will only be counted once within this composite.

The time points of evaluation of this outcome measure are:

- For death: between randomisation and 7 days post delivery
- For preterm delivery: between randomisation and up to 37 weeks' gestation
- For infant neonatal unit admission between randomisation and infant discharge from hospital

5.3. Secondary Objectives

The secondary objectives of the trial are:

- To investigate the effect of UDCA on other short term outcomes for both mother and infant
- To assess the impact of UDCA on health care resource use: in terms of the total number of nights for mother and infant, together with level of care

5.4. Secondary Outcomes

The secondary short term maternal outcomes are as shown below. The statistical analysis plan will delineate those for formal statistical comparisons and those provided descriptively.

- Peak maternal serum concentration (between randomisation and delivery) of following biochemical indices of disease:
    - Bile acids
    - Alanine transaminase
    - Aspartate transaminase
    - Bilirubin (total)
    - Gamma glutamyl transferase
- Change of itch between randomisation and delivery, measured by the worst episode of itch over past 24 hours (mm on visual analogue scale, assessed at clinic visits)
- Maximum dose of trial medication required
- Need for additional therapy for cholestasis
- Gestational diabetes mellitus

- Assessment of myometrial contractions by CTG approximately one week (3-14 days) post randomisation
- Mode of onset of labour
- Mode of delivery classified as spontaneous vaginal, instrumental vaginal or caesarean
- Reason for induction or pre-labour caesarean section
- Estimated blood loss after delivery
- Maternal death

The secondary short term perinatal outcomes are:

- In utero fetal death after randomisation
- Preterm delivery (less than 37 weeks' gestation)
- Known neonatal death up to 7 days
- Known neonatal death up to 28 days
- NNU admission for at least 4 hours until infant hospital discharge
- Number of nights in each category of care (intensive, high dependency, special, transitional and normal)
- Total number of nights in hospital
- Birth weight (g)
- Birth weight centile
- Gestational age at delivery
- Presence of meconium
- APGAR score at 5 minutes
- Umbilical arterial pH at birth
- Need for supplementary oxygen prior to discharge
- Number of days when supplemental oxygen is required
- Need for ventilation support (CPAP/high flow/endotracheal ventilation)
- Abnormal cerebral ultrasound scan
- Confirmed sepsis (positive blood or cerebrospinal fluid cultures)
- Necrotising Enterocolitis (Bell's stage 2 and 3)
- Seizures (confirmed by EEG or requiring anticonvulsant therapy)
- Encephalopathy grade (worst at any time: mild, moderate, severe)
- Other indications and main diagnoses resulting in neonatal unit admission for at least 4 hours

The time points of evaluation of the secondary outcomes are taken at the clinic visits and during admission for delivery up to discharge of mother and infant.

The following health resource use post enrolment will be captured for economic analysis:

- Maternal: total number of nights (antenatal, intrapartum and postnatal) together with level of care including adult ICU; mode of delivery
- Infant: total number of nights for the infant in neonatal unit, together with level of care (e.g. neonatal ICU)
- The cost of UDCA in the intervention group

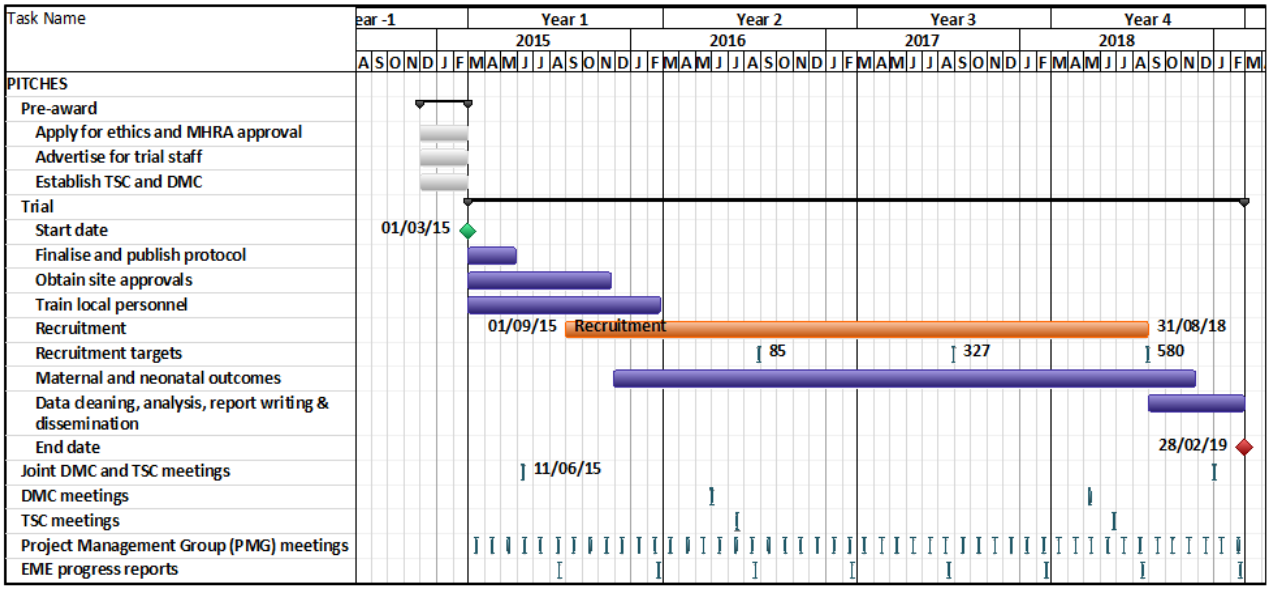
All primary and secondary outcomes will be considered up to infant discharge home (from the hospital where delivered) or transfer to another hospital.

6. Trial Design

This will be a masked placebo-controlled randomised trial, to evaluate UDCA vs. placebo in women with ICP between 20^{+0} to 40^{+6} weeks' gestation. The study will be conducted with 580 women at approximately 30 centres across the UK.

It is anticipated that the trial will last four years. Recruitment will run for approximately 39 months. Recruitment will be rolled out to centres, with a staggered start. Following recruitment of the final participant we will allow six months for completion of pregnancy of all remaining participants and for their infants to be discharged home. This will be followed by data cleaning and analysis.

PITCHES Timeline



In parallel to this trial, under separate ethics approval (ref. 08/H0707/21), we are running a prospective observational study to evaluate mechanisms of action of UDCA in women with ICP. Women in a small proportion of the centres, who participate in the trial, will be approached separately and invited to give maternal and fetal samples to explore the mechanism of UDCA. They will be given a separate PIL, and sign a separate consent form if they agree to take part.

We will investigate the hypotheses that UDCA acts by:

i. attenuating myometrial contractility through inhibition of pathways leading to parturition;
ii. reversing altered placental bile acid transporter expression and function;
iii. ameliorating impaired fetal lung maturity induced by raised amniotic fluid bile acids secondary to meconium passage.

7. Statistics

7.1. Sample Size

We will recruit 580 women in total; this will allow for the possibility of 5% of infants being lost to follow-up and is a conservative estimate given that some women will have twin pregnancies.

The primary outcome measure will be a composite of perinatal death or preterm delivery (less than 37 weeks' gestation) or NNU admission. The sample size is informed by the most recent Cochrane meta-analysis (Gurung et al., 2013). This includes the trials reported in the previous meta-analysis (Bacq et al., 2012) with the addition of the largest trial published in 2012 by our group (Chappell et al., 2012).

From these data, we can estimate the event rate for infants of untreated women as 40% with a plausible and relevant reduction to 27% for infants of women treated with UDCA, corresponding to an absolute risk reduction of 13% and a risk ratio (RR) of 0.675. This is conservative compared with the effect sizes seen in the Cochrane meta-analysis (Gurung et al., 2013) for the three individual endpoints (RR 0.31, 0.46 and 0.48 for perinatal death, preterm delivery and NNU admission respectively). 550 infants of women with ICP (275 per group) are required to have a 90% chance of detecting, as significant at the 2-sided 5% level, a reduction in the primary outcome measure from 40% in the control group to 27% in the treated group. Allowing for 5% lost to follow-up requires a total sample size of 580 infants (290 per group). We are uncertain as to the proportion of women that have twin pregnancies in this target population. Office for National Statistics data indicate that around 1.5% of mothers have twin deliveries (ONS Birth Statistics, 2008). Recruiting 580 women to achieve a sample size of 580 infants is, therefore, a conservative estimate of the sample size required to address the primary (short term) objective.

This number will also allow us to look at the components of the composite endpoints: a trial assessing 550 infants will have 89% power to demonstrate a reduction in NNU admission rates from 17% to 8%, and 99% power for a reduction in prematurity from 41% to 23% (based on the Cochrane meta-analysis – Gurung et al., 2013), both effect sizes of the same magnitude as that demonstrated in our previous trial (Chappell et al., 2012). We do not anticipate enough perinatal deaths to detect reliably any plausible treatment effect but we have included this due to its clinical importance and will report it separately.

7.2. Randomisation

The allocation ratio of intervention (ursodeoxycholic acid) to control (placebo) arms will be 1:1. Randomisation will be managed via a secure web-based randomisation facility hosted by MedSciNet with telephone back-up available A minimisation algorithm will be used to ensure balance between the groups with respect to study centre (approximately 30 centres), gestational age at randomisation (<34, 34 to <37, ≥37 weeks' gestation), single vs. multi-fetal pregnancy, and serum bile acid concentration prior to randomisation (< 40µmol/L, ≥40µmol/L). MedSciNet will hold the allocation code.

7.2.1. Emergency Code Break

Clinicians requesting unmasking must be satisfied that it is a genuine emergency and that knowledge of the treatment allocation (either UDCA or placebo) is needed to guide the appropriate clinical management of the participant. In some cases this may be achieved without unblinding, by stopping the allocated treatment and treating the participant with UDCA.

In the event of an emergency, where the clinician needs to know the allocation, a participant may be unblinded by the clinician at site by logging into the PITCHES randomisation website via the Study Product Page using the "request to unblind" button. The reason for unblinding will be requested. The PI or requesting clinician will then press the unblind button which will provide allocation details. Alternatively, a participant may be unblinded by the PI or requesting clinician, contacting the NPEU CTU during working hours. The contact details for the NPEU CTU are below:

9:00 am to 5.00 pm NPEU CTU: 01865 289 735

Details of contact numbers will also be filed in the Investigator Site File.

Details of the person requesting unmasking and the reason for the request will be recorded.

Wherever possible, the unmasking of a woman's treatment allocation will be discussed with the CI or their safety delegate in advance through the telephone contacts given above.

As it is best practice to not unblind participants until follow-up is completed, all other requests for unblinding must be made in writing to the NPEU CTU, who along with the Chief Investigator and the Principal Investigator will consider the request.

7.3. Analysis

A detailed Statistical Analysis Plan (SAP) will be developed in-house and agreed by the Trial Steering Committee (TSC) before the analysis is undertaken. The analysis and presentation of results will follow the most up-to-date recommendations of the CONSORT group. Analyses will be completed in STATA® version 13.0 or later.

All analyses will follow the intention to treat principle, i.e. all randomised women (and infants) will be analysed according to the treatment they were allocated to irrespective of the treatment they received or whether they received any treatment at all.

Demographic and clinical data will be summarised with counts and percentages for categorical variables, means (standard deviations) for normally distributed continuous variables and medians (with interquartile or simple ranges) for other continuous variables.

All comparative analyses will be performed adjusting for minimisation factors at randomisation (Kahan and Morris, 2012), and baseline measures of the outcome where relevant. Binary outcomes will be analysed using log binomial regression models. Results will be presented as adjusted risk ratios plus confidence intervals. If the model does not converge, centre will be removed from the model as a factor in the first instance. If the model is still unstable log Poisson regression models with robust variance estimation will be used (Zou, 2004). Continuous outcomes will be analysed using linear regression models and results will be presented as adjusted differences in means (with confidence intervals). Unadjusted median differences (with confidence intervals) for skewed continuous variables will be presented (unless the data can be transformed to Normality). Analysis of outcomes that are measured repeatedly over time (severity of itch and biochemistry measures) will use repeated measures analysis techniques.

Perinatal outcomes will include all infants born to a randomised mother, the denominator being the number of infants. For these outcomes, correlations between multiples will be accounted for in the adjusted model.

7.3.1. Pre-specified subgroup analysis

Pre-specified subgroup analyses will use the statistical test of interaction (or test for trend) and where appropriate, results will be presented as risk ratios with confidence intervals. Pre-specified subgroups will be based on:

- Serum bile acid concentrations at baseline (10-39 μmol/L/ ≥40 μmol/L)
- Gestational age (participants recruited before/after 36+6 weeks' gestation)
- Singletons and twins

7.3.2. Level of Statistical Significance

95% confidence intervals will be used for all primary outcome comparisons including subgroup analysis; to take account of the multiplicity of secondary outcomes, 99% confidence intervals will be presented.

7.3.3. Dealing with missing data

Missing data as a result of women or infants being lost to follow-up are expected to be minimal. A sensitivity analysis will be conducted on the primary outcome using multiple imputation methods to impute missing data, assuming that the outcome is not linked to the reason for being lost to follow-up (i.e. missing at random).

7.4. Interim Analysis

An independent Data Monitoring Committee (DMC) will be established, whose remit is to review the trial's progress. The DMC is independent of the trial organisers. Interim analyses will be supplied, in strict confidence, to the DMC, as frequently as its Chair requests. The terms of reference for the DMC will be agreed at their first meeting. A DMC charter will be completed following the recommendations of the DAMOCLES Study (Foresterhill, 2005). Meetings of the committee will be arranged periodically, as considered appropriate by the Chair. In the light of interim data on the trial's outcomes, adverse event data, accumulating evidence from other trials (see below) and any other relevant evidence (including updated overviews of the relevant randomised controlled trials), the DMC will inform the Trial Steering Committee (TSC) if in their view there is proof beyond reasonable doubt that the data indicate that any part of the protocol under investigation is either clearly indicated or contra-indicated, either for all infants or for a particular subgroup of trial participants. Unless modification or cessation of the trial is recommended by the DMC, the TSC, investigators, collaborators and administrative staff (except those who supply the confidential information) will remain ignorant of the results of the interim analysis. Collaborators and all others associated with the study may write to the DMC via NPEU CTU, to draw attention to any concern they may have about the possibility of harm arising from the treatment under study.

7.5. Economic Analysis

Data on mother and infant inpatient care and mode of delivery will be costed using nationally published sources. The cost of UDCA will also be included for women randomised to receive the intervention. Descriptive statistics will be reported including mean cost per participant and 95% confidence intervals constructed using bootstrapping. Missing data will be handled in the same way as the other statistical analyses.

8. Participant Identification

Potentially eligible participants will be identified by PIs, members of their clinical team or by CLN research midwives who will be part of the clinical team. They will be identified via antenatal clinics, antenatal assessment units and antenatal wards and by review of laboratory bile acid results.

8.1. Inclusion Criteria

Women will be considered eligible for inclusion into the trial if they fit the following criteria:

- ICP (pruritus with a raised serum bile acid above the upper limit of normal for the local laboratory)
- 20^{+0} to 40^{+6} weeks' gestation on day of randomisation (see note below on gestational age)
- No known lethal fetal anomaly
- Singleton or twin pregnancy
- Aged 18 years or over
- Able to give written informed consent

Determination of gestational age: for all calculations relating to gestational age (eligibility for enrolment, gestational age at delivery), gestational age will be calculated based on the following hierarchical model, as set out in the NICE guidelines for antenatal care:

- From crown-rump length measurement on early ultrasound scan between 10^{+0} weeks and 13^{+6} weeks
- From head circumference on ultrasound scan if crown–rump length is above 84 mm

8.2. Exclusion Criteria

Women will be excluded from the trial if:

- Decision has already made for delivery within the next 48 hours
- Known allergy to any component of the UDCA or placebo tablets
- Triplet or higher-order multiple pregnancy

9. Trial Procedures

9.1. Trial Assessments

Procedure	Screening[1]	Trial Entry and treatment	Weekly ± four days[2]	Delivery	At hospital discharge to home
Demography		✓			✓
Confirmation of Eligibility	✓				
Consent[3]		✓			
Randomisation		✓			
Blood samples for bile acids/ALT/[4]	✓	✓	✓		
IMP dosing[5]		✓	✓		
CTG[6]			(✓) (first visit after randomisation only)		
Pruritus score on itching chart		(✓)	(✓)		
SAEs[7]		✓	✓	✓	✓
Concomitant Medication[8]		✓	✓	✓	✓
Tablet adherence assessment			✓		
Post-delivery outcome form					✓

1. All screening assessments are part of routine clinical practice.
2. Weekly visits are recommended but not mandatory; normal hospital clinical practice is acceptable.
3. No trial specific procedures before consent.
4. These blood tests are taken as per routine clinical practice and are not trial specific.
5. IMP started after randomisation. IMP dose altered by PI if indicated by symptoms and/or blood tests taken during normal clinical practice.
6. CTG only measured 1 week after randomisation or as per routine clinical practice.
7. All unexpected AEs occurring during the trial that are observed by the PI or reported by the participant will be recorded in the eCRF, whether or not attributed to the IMP. Unexpected SAEs will be expeditiously reported.
8. All prescribed concomitant medication only.

9.2. Informed Consent

Potential participants will be approached at a routine visit or by phone as appropriate. Written informed consent will be sought from the woman only after she has been given a full verbal explanation and written description (via the latest and approved version of the Participant Information Leaflet). She will be given sufficient time to consider the information, and the opportunity to question the PI or their delegate, to decide whether she will participate in the trial. Women who do not speak English will only be approached if an interpreter is available. Relatives may not interpret.

Written informed consent will be obtained using the informed consent form (ICF) completed, signed and dated by the woman (with countersignature by an interpreter where required) and signed by the person taking consent. A copy of the signed ICF will be given to the woman; a further copy will be retained in the woman's medical notes; a copy will be retained in the Investigator's Site File (ISF), and the original will be sent to the NPEU CTU.

At all visits it will be made clear to the woman that she is free to stop study medication at any time with no obligation to give the reason for stopping, and without prejudice to future care. Participants will be made aware that this decision will have no impact on any aspect of their continuing care.

9.3. Baseline Assessments

The trial baseline data, including all demography, serum bile acid concentrations and LFTs, and itch chart results will be entered on the web-based MedSciNet database. The itch chart is a visual analogue score where the woman is asked to score her worst itch in the previous 24 hours.

On completion of these details, the database will issue a pack number to the local hospital pharmacy. A prescription for the IMP will be written by the recruiting PI or their delegate and the participant will collect the IMP from the local hospital pharmacy.

9.4. Subsequent visits

Participants will be reviewed at clinic visits until delivery. The Co-Investigators recommend that the participating sites undertake weekly monitoring of liver function tests (including serum bile acids) as recommended by the Green Top guidelines from the Royal College of Obstetricians and Gynaecologists.

At the first visit after randomisation, and only once 28 weeks' gestation is reached, a CTG may be performed by a qualified member of the clinical or research team (assessed as one of the secondary outcomes. CTGs may be performed at other times at the discretion of the clinical team as per normal clinical practice.)

At all visits after randomisation, serum bile acids (and LFTs) will be repeated and monitored as per normal clinical practice. The woman may also be asked for a value of the worst itch she felt during the previous 24 hours. The IMP dose will be altered at the discretion of the responsible clinician. If maximal doses of the IMP have been reached, consideration can be given to the addition of other therapy, e.g. rifampicin, in addition to the trial therapy, without breaking the allocation code.

Visit data will be entered on the MedSciNet database by local CRN research midwife.

The remainder of antenatal care, in particular the timing and mode of delivery will be left to the discretion of the responsible clinician.

The post-delivery outcome form will be completed after the woman and her infant(s) have been discharged from hospital.

9.5. Laboratory Tests

Routine biochemical testing will be undertaken as per local maternity unit guidelines (commonly liver function tests including bile acids).

All laboratory staff are trained in GLP according to local guidelines.

9.6. Withdrawal of Participants

At all stages it will be made clear to the woman that she will remain free to withdraw from the clinical trial at any time without the need to provide any reason or explanation; and that this decision will not impact on any aspect of her ongoing clinical care. The investigator will be able to withdraw participants from the clinical trial in the event that they judge that UDCA is either mandated or contraindicated, and other additional therapy is not being considered. Participants will not be withdrawn for self-reported low or non-adherence.

Should a participant decide to withdraw from the CT, all efforts will be made to report the reason for withdrawal as thoroughly as possible. Permission will be sought to complete and use data up to the point of withdrawal including both:

- trial specific data
- data collected as per routine clinical practice

Permission will also be sought to ascertain and record subsequent perinatal outcome data.
The reason for withdrawal will be recorded in the eCRF, and if it was due to an AE, the investigator will follow up to resolution/stability. There is no requirement to enrol extra participants to replace women who do not complete the study.

9.7. End of Trial

The end of the trial will be defined as the date when the trial database is locked. An end of trial declaration will be made to MHRA and the approving REC.

10. Investigational Medicinal Product (IMP)

The Investigational Medicinal Product (IMP) is ursodeoxycholic acid (UDCA) or matching placebo, manufactured and supplied in bulk by Dr. Falk Pharma, GmBH.

The most recent Summary of Product Characteristics for ursodeoxycholic acid can be found at http://www.medicines.org.uk/emc/medicine/27444.

10.1. IMP Risks

Possible side-effects:

- Gastrointestinal disorders: In clinical trials, reports of pasty stools or diarrhoea during UDCA therapy were common *(≥ 1/100 to <1/10 patients).*
- Skin and subcutaneous disorders: Very rarely *(< 1/10,000 patients)*, urticaria can occur.

The reference documents are the SmPC.

10.2. Formulation and Packaging

Treatment arm: Each film-coated tablet contains the active ingredient: 500 mg ursodeoxycholic acid and the inactive ingredients of magnesium stearate, polysorbate 80, providone K 25, microcrystalline cellulose, colloidal anhydrous silica, crospovidone (Type A) and talc. The coating ingredients are talc, hypromellose and macrogol 6000.

Control arm: A matching placebo tablet, identical in colour and shape to the treatment arm containing the inactive ingredients: magnesium stearate, polysorbate 80, providone K 25, microcrystalline cellulose, colloidal anhydrous silica, crospovidone (Type A) and talc. The coating ingredients are talc, hypromellose and macrogol 6000.

Guy's and St Thomas' NHS Foundation Trust (GSTFT) Pharmacy Manufacturing Unit will package, label, store and distribute the blinded bottles to the UK sites that are participating in the trial.

The IMP will be packaged into High Density Polyethylene (HDPE) bottles, with 32 tablets per bottle.

10.3. Labelling

Each bottle will be labelled in accordance with regulatory requirements (Annex 13). A medication dosing card will be provided.

10.4. Dosing Regimen

The IMP will be administered orally.

The starting dose will be 1,000 mg daily (500 mg bd), increased in increments of 500 mg per day every 3-14 days if there is no biochemical or clinical improvement, based on clinical decision, to a maximum of 2,000 mg per day. The dose of IMP may be reduced to 500mg daily

IMP will be continued until delivery. The duration of treatment will range from 1 day to a maximum of 22 weeks, for a participant randomised at 20 weeks' gestation who does not deliver until 42

weeks. In the previous trial (Chappell et al., 2012) the mean length of treatment with IMP was 4 weeks.

Divided doses will be spread evenly throughout the day. There is no need to take with or without food. This will be left to participant preference.

10.5. Dispensing and Accountability

Pharmacy will maintain an overall inventory of stock received, dispensed, returned, destroyed and quarantined.

The IMP will be dispensed by the site pharmacy against a trial specific prescription. A Prescription template will be provided in the ISF. The number of dispensings required during the pregnancy will vary between participants.

Full drug accountability of dispensed IMP must be maintained. These records must be available for inspection by representatives of the NPEU CTU, sponsor or MHRA at any time. An Investigational Product Accountability Log template will be provided in the Investigator Site File to maintain such accountability.

Drug supplies are to be used only in accordance with this protocol and under the supervision of the PI.

10.6. Returns and Adherence with Trial Treatment

Women will be asked to bring in their IMP bottle at each visit and at delivery. The research team will be responsible for returning the participant's IMP bottles and medication dosing card to pharmacy for reconciliation. Pharmacy staff will count the number of tablets remaining in the bottle and update the Investigational Product Accountability Log against the corresponding dispensing entry. The trial pharmacist will verify the IMP returns before on-site destruction can occur.

10.7. Destruction of IMP

The trial drugs must not be destroyed until the trial pharmacist verifies the quantities to destroy and gives permission to do so. The trial drugs must be destroyed on site following local waste disposal procedures.

10.8. Ordering

The initial shipment of IMP will be automatically shipped by the GSTFT pharmacy manufacturing unit. Sufficient supplies of IMP will be provided to each site. The process for re-supply is automatic through the MedSciNet database.

10.9. Receipt

GSTFT pharmacy manufacturing unit will send the IMP with a delivery note and a receipt document to confirm that everything is in order. A QP release certificate will be included with each supply of IMP distributed to the sites.

10.10. Costs

The trial drug will be provided to sites free-of-charge. The cost of UDCA and placebo is covered by the PITCHES trial funding.

10.11. Storage of IMP

The IMP does not require any special storage conditions.

10.12. Compliance with Trial Treatment

Tablet adherence will be measured by a self-report at each visit.

10.13. Concomitant Medication

All prescribed medications deemed necessary by the PI to provide adequate supportive care to the women are permitted during the CT. The medications must be recorded in the participant's eCRF.

For management of concomitant therapies, please refer to the Ursofalk SmPC at http://www.medicines.org.uk/emc/medicine/27444.

11. Assessment of Safety and Reporting

11.1. Specification, Timing and Recording of Safety Parameters

At each clinic visit, a member of the clinical or research team will ask the woman if she has had any adverse events, and will ensure that she has clinical monitoring (e.g. liver function tests and fetal monitoring) as routinely performed in each maternity unit.

11.2. Definitions

Adverse Event (AE)
Any untoward medical occurrence in a participant to whom a medicinal product has been administered including occurrences which do not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of the trial medication, whether or not considered related to the trial medication.

Adverse Reaction (AR)
Any untoward and unintended response in a participant to an IMP which is related to any dose administered to that participant. The phrase "response to an IMP" means that a causal relationship between trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

Serious Adverse Event (SAE)
A serious adverse event is any untoward medical occurrence that:

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- consists of a congenital anomaly/birth defect

The term 'severe' is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance. This is not the same as 'serious', which is based on participant/event outcome or action criteria usually associated with events that pose a threat to a participant's life or functioning.

Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences.

The term 'life-threatening' in the definition of serious refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

Medical and scientific judgement will be exercised by the PI at each site in deciding whether an adverse event is serious in other situations.

Serious Adverse Reaction (SAR)
A SAR is a SAE which is in the opinion of the Investigator believed with reasonable probability to be due to the IMP, based on the information provided.

Expected AEs and SAEs
The following are considered to be expected in this population of pregnant women or a result of the routine care/treatment of a participant and as such do not need to be recorded.

- Worsening pruritus
- Admission in active labour
- Admission for cervical ripening or induction of labour
- Admission for caesarean section
- Admission for assessment for suspected fetal compromise, including poor growth, or reduced fetal movements
- Admission for monitoring for hypertension, antepartum haemorrhage, suspected preterm labour, pre-labour rupture of the membranes or other reasons for monitoring
- Admission for psychiatric or social reasons
- Admission for unstable lie or external cephalic version

The following fetal/neonatal outcomes are pre-specified outcomes and as such will be recorded on the eCRFs but not expeditiously reported:

- NNU admission
- Stillbirth & Perinatal death (within 7 days)
- Preterm delivery (<37 completed weeks' gestation)
- Meconium staining of the amniotic fluid or placenta
- Small for gestational age
- Seizures
- Encephalopathy treated with hypothermia
- Need for respiratory support – Ventilation via an ETT or nasal CPAP
- Sepsis requiring antibiotics with symptoms or confirmed blood or CSF culture

Unexpected Serious Adverse Event
An unexpected SAE is any event that meets the definition of a SAE and is not detailed in the list above as expected, including:

- Maternal death
- Maternal acute hepatic failure resulting in admission to an intensive care setting or requiring liver transplant
- Any unexpected fetal or perinatal death unrelated to ICP

These events should be reported on the trial SAE form provided following the procedures detailed in section 11.5.

Suspected Unexpected Adverse Reaction (SUSAR)
This is a SAR, the nature or severity of which is not consistent with the known safety profile of the trial medication in the SmPC. See reporting procedures as detailed in section 11.7.

11.3. Causality

The relationship of each adverse event to the IMP must be determined by a medically qualified individual according to the following definitions:

Unrelated – where an event is not considered to be related to the IMP
Possibly – although a relationship to the IMP cannot be completely ruled out, the nature of the event, the underlying disease, concomitant medication or temporal relationship make other explanations possible
Probably – the temporal relationship and absence of a more likely explanation suggest the event could be related to the IMP
Definitely – the known effects of the active IMP, its therapeutic class or based on challenge testing suggest that the active IMP is the most likely cause

All AEs (SAEs) labelled possibly, probably or definitely will be considered as related to the IMP.

11.4. Procedures for Recording Unexpected AEs

All unexpected AEs occurring during the trial that are observed by the PI or reported by the participant will be recorded in the eCRF, whether or not attributed to the IMP. The following information will be recorded: description, date of onset and end date, severity, assessment of relatedness to IMP and action taken. The severity of events will be assessed on the following scale: 1=mild, 2=moderate, 3=severe. AEs considered related to the IMP, as judged by the CI or the Sponsor, will be followed either to resolution, or until the event is considered stable. It will be left to the PIs clinical judgement to decide whether or not an AE is of sufficient severity to require the participant's removal from the trial. A participant may also voluntarily withdraw from treatment due to what she perceives to be an intolerable AE. If either of these occurs, the participant must be given appropriate care until symptoms cease or the condition becomes stable.

The period for safety reporting will be from first dose of IMP until discharge of mother and discharge of infant.

11.5. Reporting Procedures for Serious Adverse Events

Unexpected SAEs will be reported to the NPEU CTU within 24 hours of staff at the site becoming aware of the event.

Details will be recorded on an SAE form (filed in the Investigator Site File) and the form faxed or emailed back to the NPEU CTU. SAEs can also be reported using the MedSciNet database. Only staff with access to the PITCHES database may report SAEs in this way. Site staff will be required to print off the PITCHES database SAE form and obtain the information and signature of the Study Clinician carrying out the causality assessment. If this is not possible, the unexpected SAE may be reported by telephone and the SAE form completed by staff at the NPEU CTU. Follow-up information should be reported on a new SAE form and this forwarded to the NPEU CTU by fax or email. Follow-up information should be provided as necessary to resolution/stability.

Review of SAEs must be timely. NPEU CTU will ensure it is informed by the CI or safety delegate within the reporting timelines. All SAEs will also be reviewed by the DMC at regular intervals. The CI will inform all PIs concerned of relevant information that would adversely affect the safety of the participants.

11.6. Expectedness

Expectedness will be determined according to the SmPC for UDCA.

11.7. SUSAR Reporting

All SUSARs will be reported by the co-sponsors, in collaboration with the NPEU CTU, to the MHRA and REC. For fatal and life-threatening SUSARs, this will be done no later than 7 calendar days after the CI is first aware of the reaction. Any additional relevant information will be reported within 8 calendar days of the initial report. All other SUSARs will be reported within 15 calendar days.

Treatment codes will be un-blinded for specific participants.

11.8. Development Safety Update Report (DSUR)

In addition to the expedited reporting detailed above, the CI and NPEU CTU will prepare a Development Safety Update Report (DSUR) once a year throughout the duration of the trial. The co-sponsors will submit the DSUR to the MHRA and REC.

11.9. Trial Stopping Rules

A Data Monitoring Committee (DMC) will be established to ensure the wellbeing of study participants. The DMC will periodically review study progress and outcomes as well as reports of unexpected SAEs. In the light of interim data and other evidence from relevant studies, the DMC will inform the TSC if, in its view, there is proof beyond reasonable doubt that the data indicate that the trial should be terminated. A decision to inform the TSC of such a finding will in part be based on statistical considerations. Appropriate proof beyond reasonable doubt cannot be specified precisely. A difference of at least 3 standard errors in the interim analysis of a major endpoint may be needed to justify halting or modifying the trial prematurely, for the superiority hypothesis.

The TSC will have ultimate responsibility for deciding whether a trial should be stopped on safety grounds.

Should adequate evidence be gathered before the end of the trial, the DMC will inform the TSC. If the TSC are in agreement they will inform the co-sponsors, CI and NPEU CTU, who will in turn inform the PIs. The study will be stopped and a final close out visit will be arranged at all sites.

If the trial is prematurely discontinued, active participants will be informed and no further participant data will be collected. The Competent Authority (CA) and REC will be informed within 15 days of the early termination of the trial.

12. Quality Control and Assurance

12.1. Site Initiation and Training

Initiation of each participating centre will be performed by the CI or their delegate and a research midwife once all appropriate approvals are in place and the IMP has been shipped to the site.

The site PI, research midwife and their delegates, from each recruiting centre will be fully trained in protocol adherence and able to deal with site specific issues. They will then be responsible for delivering this training to all relevant site staff, to make sure that they are conversant with the trial's procedures prior to opening their centre for recruitment. The PI and research midwife will also promote the trial, and ensure that all appropriate site staff, are kept fully appraised of issues such as recruitment status, informed consent, data collection, follow-up and changing regulations, so that the necessary recruitment targets are reached within the timescale.

12.2. Site Monitoring and Auditing

The PI and research midwife, with support from the PITCHES trial co-ordinator, based at the NPEU CTU, will be responsible for the day-to-day smooth running of the trial at each participating centre. The trial co-ordinator will monitor recruitment against targets, and monitor data collection completeness and quality.

Trial monitoring will be conducted in accordance with the monitoring plan developed from the trial specific risk assessment. Training in the trial protocol and procedures will be delivered either at site or centrally (before recruitment begins), to ensure staff are confident and competent to recruit women to the trial; establish good working relationships with site staff; and identify any sites that may need extra support and monitoring during the trial.

Throughout the trial, there will be central monitoring, overseen by the PMG, DMC, TSC and Quality Assurance team, ensuring good communication between NPEU trial team and the site staff. The monitor will visit sites where anomalies are identified through central monitoring. Sites that are identified as requiring additional support will be visited by a member of the trial team or the monitor as appropriate to the particular issues.

The DMC will look regularly at protocol adherence by site and by trial arm, including randomisation processes and patterns of allocation.

13. Serious Breach of Good Clinical Practice or the Trial Protocol

The MHRA require that they be informed of all serious breaches in GCP or the trial protocol within 7 days of the Sponsor becoming aware of the breach.

A serious breach is defined as a breach of GCP or the trial protocol which is likely to affect to a significant degree:

- The safety or physical or mental integrity of the participant on the trial or
- The scientific value of the trial

In the event that a serious breach is suspected, the NPEU CTU should be contacted within 1 working day. The NPEU CTU will refer the serious breach onto the Sponsor immediately.

In collaboration with the CI, the serious breach will be reviewed by the Sponsor and appropriately reported to the REC and MHRA within 7 calendar days.

14. Ethics & Regulatory Approvals

14.1. Declaration of Helsinki and Guidelines for Good Clinical Practice

The trial will be conducted in compliance with the principles of the Declaration of Helsinki (1996), Good Clinical Practice (GCP) and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework and the Medicines for Human Use (Clinical Trial) Regulations 2004, as amended in 2006 and any subsequent amendments.

14.2. Approvals

The trial will only start after gaining approval from the MHRA for Clinical Trial Authorisation (CTA) and a registered REC. Additionally, approval of the appropriate NHS Trust Research and Development Office (R&D) will be sought for individual trial sites.

Applications will be submitted through the Integrated Research Application System (IRAS).

A copy of the protocol, Participant Information Leaflet, Informed Consent Form and GP letter will be submitted to the MHRA and REC for approval. The CI or their delegate will submit, and where necessary, obtain approval from the MHRA and REC for any substantial amendments. Substantial amendments are defined as those that affect:

- The safety, physical or mental integrity of the participants in the trial;
- The scientific value of the trial;
- The conduct or management of the trial; or
- The quality or safety of any IMP used in the trial

14.3. Participant Confidentiality, Data Handling and Record Keeping

Overall responsibility for ensuring that each participant's information is kept confidential will lie with the trial sponsor. All paper documents will be stored securely and kept in strict confidence in compliance with the Data Protection Act (1998) and all trial data will be stored in line with the Medicines for Human Use (Clinical Trials) Amended Regulations 2006.

Data entered onto the eCRFs will be automatically transferred for storage in an electronic database held by MedSciNet on behalf of the co-sponsors in which the participant will be identified only by a trial specific number and their initials. The participant's name and any other identifying details will be stored in a separate database which will be linked by the study identifier. This information will be collected and retained with the participant's explicit consent to enable the participant to be followed through the trial.

After the trial has been completed, and the reports published, the data will be archived on a file server in a secure physical and electronic location with controlled access, restricted to a few named individuals. This is in line with the Medicines for Human Use (Clinical Trials) Amended Regulations 2006 as defined in the KHP-CTO Archiving Standard Operating Procedure (SOP). Authorisation to access restricted areas of the MedSciNet network is as described in the MedSciNet security policy. Data will be processed on a workstation by authorised staff. The computer workstations access the network via a login name and password (changed regularly). No data are stored on individual workstations. Backing up is done automatically overnight to an offsite storage area. The location of the back-up computer is in a separate department which has electronic tag access. Access to the room in which the back-up machine is located is via a key-pad system.

14.4. Retention of Personal Data

Personal data will be needed to disseminate the results of the trial to the participants. Due to the nature of pregnancy research, data will be kept for a period of no fewer than 25 years in order to follow-up on health related issues which may become relevant in the future. At all times the personal data will be held securely and will not be used for any other purpose.

15. Trial Governance

15.1. Site Research and Development Approval

Individual sites will only commence recruiting participants once they receive approval from NHS Trust Research and Development (R&D) Offices. Applications to R&D offices will be submitted through the NIHR Co-Ordinated System for gaining NHS permission.

15.2. Coordinating Centre

The Trial Coordinating Centre will be at the NPEU CTU, University of Oxford where the Trial Co-ordinator will be based.

15.3. Project Management Group (PMG)

The trial will be supervised on a day-to-day basis by the Project Management Group. This group reports to the Trial Steering Committee (TSC) which is responsible to the trial sponsor. At each participating centre, a local PI will report to the PMG via the staff based at the NPEU CTU.

The core PMG will meet at least monthly and consist of the CI and NPEU CTU staff including:

- CTU Director
- Senior Trials Manager
- Trial Co-ordinator
- Trial Statistician
- Data Manager

15.4. Co-Investigator Group (CIG)

The CIG will meet (in person or by teleconference) at least twice a year. This will comprise all co-applicants and the members of the core PMG.

15.5. Trial Steering Committee (TSC)

The trial will be overseen by a TSC consisting of an independent chair and at least two other independent members. Committee members will be deemed independent if they are not involved in trial recruitment and are not employed by any organisation directly involved in the trial conduct.

Representatives from relevant Patient/Public Involvement groups, the CI, other investigators/co-applicants will be joined by observers from the NPEU CTU; they will be required to declare any competing interests they may have prior to participating in the meeting.

The role of the TSC is to provide overall supervision of the trial. The TSC should monitor the progress and conduct of the trial, and advise on its scientific credibility. The TSC will consider and act, as appropriate, upon the recommendations of the DMC and ultimately carries the responsibility for deciding whether a trial needs to be stopped on grounds of safety or efficacy.

A TSC charter will be prepared and agreed at the first TSC meeting to document how the committee will operate.

15.6. Data Monitoring Committee (DMC)

A DMC, independent of the applicants and of the TSC, will review the progress of the trial at least annually and provide advice on the conduct of the trial to the TSC and (via the TSC) to the funder. The committee will periodically review trial progress and outcomes. The content and timings of the DMC reviews will be detailed in a DMC Charter, which will be agreed at its first meeting.

Members of the committee, and any observers to the meetings, will be required to declare any competing interests they may have prior to participating.

16. Acknowledgement of Contribution / Publication Policy

The success of the trial depends on a large number of midwives, obstetricians and participants. Credit for the trial findings will be given to all those who have collaborated and participated in the clinical trial including all local coordinators and collaborators, members of trial committees and clinical trial staff.

16.1. Study Website

After REC approval has been obtained, this protocol will be submitted for publication and will be available for download via the PITCHES NPEU website at https://www.npeu.ox.ac.uk/pitches.

This website will provide information regarding the study to recruiting centres, participants and their families. Copies of all eCRFs, the study protocol, participant information leaflet and training literature will be available along with information on centres participating in the study and contact details for the NPEU CTU. The participant's page will also provide links to other websites that may provide advice and support to women and their families affected by ICP.

16.2. Publication Policy

Primary responsibility for preparing publications will lie with the CI, Professor Lucy Chappell, who will liaise with the NPEU CTU to deliver effective dissemination. All publications using data from this trial to undertake original analyses will be submitted to the TSC for review before release. The NPEU CTU has extensive experience of interpreting and disseminating research findings, employing up-to-date innovative methods such as podcasts for PIs unable to attend the planned 'final results' meeting, and bespoke newsletters to parents with a summary explaining the final study results and the implications.

The research will be published in high impact, peer reviewed, scientific journals. More general dissemination of the results will be achieved through publication of summary findings. There are no commercial or intellectual rights issues that would delay publication of results. The writing will be the responsibility of a writing committee drawn from the co-investigators (trial grant holders), trial co-ordinators and others substantially involved in execution, analysis and interpretation, and will be named authors on the principal publications arising from the trial provided they meet the authorship criteria used by most high impact peer reviewed journals see http://www.icmje.org.

Local PIs will be named formally as collaborators on the publication; PIs in non-recruiting centres and other trial personnel with significant input to the running of the trial will be named in the acknowledgements in publications. The CI will nominate and agree appropriate authorship on all publications prior to commencement of writing.

Participants will be sent a summary of trial publications if they wish, with a reference to the final paper and a copy of the journal article will be available on request from the CI. This material will be offered to all the women recruited, including those whose infants ultimately did not survive, although this group will first be asked if they wish to receive this information. As a policy, written dissemination will be in a style that is understandable and useable for all stakeholders including NHS commissioners, clinicians, funding bodies, service users, ICP charities and the general public.

In order to target the clinical community, the results of this research will be disseminated by conventional academic outputs, including presentations at prominent national and international conferences. The results will be included in the relevant Cochrane review and in national and international guidelines, specifically the following: RCOG Greentop guidelines for Obstetric

Cholestasis (last published 2011); Cochrane Database of Systematic Reviews (last updated 2013 - see Gurung et al., 2013).

Joint press releases will be coordinated by the NPEU with the University of Oxford, King's College London and GSTFT.

Information will be made available on the trial website including the final report and any publications when available. Links will also be placed or be encouraged to be placed on other relevant web sites such as the University of Oxford, King's College London and GSTFT, the NIHR and research user groups. Furthermore we will ensure there is wider dissemination of the results via the participant support group (ICPSupport) and appropriate social networks.

17. Insurance / Indemnity

Kings College London/ Guy's and St Thomas' NHS Foundation Trust, as co-sponsors of the study, have a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research. NHS indemnity operates in respect of the clinical treatment which is provided.

18. Financial Aspects

Funding to conduct the trial is provided by the National Institute of Health Research (NIHR) Efficacy Mechanisms & Evaluation (EME) programme (ref.12/164/16).

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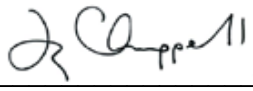
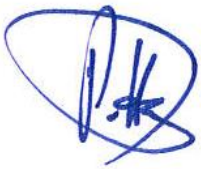
19. Protocol Signatures

19.1. Protocol Approval Signatures

The signatures below constitute approval of this protocol and provide assurance that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to ethical and regulatory requirements, other applicable regulations and GCP guidelines.



Chief Investigator — Date: 14/03/2016
Professor Lucy Chappell



Statistician — Date: 14/03/2016
Pollyanna Hardy

19.2. Principal Investigator Signatures

By signing the protocol signature page, I agree to:

- Conduct the trial in accordance with the protocol and only make changes in order to protect the safety, rights or welfare of the participants.
- Personally conduct or supervise the trial and ensure that all associates, colleagues and employees assisting in the conduct of the trial trained in GCP and are informed about their obligations.
- Ensure requirements with regard to obtaining informed consent are adhered to.
- Report AEs/SAEs that occur during the course of the trial and maintain adequate and accurate records to enable representatives of the co-sponsors or MHRA to confirm adherence with the protocol.

_____ _____

Principal Investigator's Signature Date

_____

Print name

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