# Study Protocol

A Randomised Placebo-Controlled Trial of Antenatal Corticosteroids for Planned Birth in Twins: STOPPIT-3.

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| Co-sponsors | The University of Edinburgh & Lothian Health Board<br>ACCORD<br>The Queen's Medical Research Institute<br>47 Little France Crescent<br>Edinburgh<br>EH16 4TJ |
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Academic and Clinical Central Office for Research and Development

# PROTOCOL APPROVAL SIGNATURE PAGE

A Randomised Placebo-Controlled Trial of Antenatal Corticosteroids for Planned Birth in Twins: STOPPIT-3.

## EudraCT

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

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| Sarah Murray | | | |
| **Chief Investigator** | **Signature** | | **Date** |
| Catriona Keerie | | | |
| **Trial Statistician** | **Signature** | | **Date** |
| Fiach O'Mahony | | | |
| **Lead Co-Sponsor Representative** | **Signature** | | **Date** |

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

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

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

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# LIST OF ABBREVIATIONS

| | |
|---|---|
| **ACCORD** | Academic and Clinical Central Office for Research & Development - Joint office for The University of Edinburgh and Lothian Health Board |
| **ACS** | Antenatal corticosteroids |
| **AE** | Adverse Event |
| **AR** | Adverse Reaction |
| **CI** | Chief Investigator |
| **CHI** | Community Healthcare Index |
| **CRF** | Case Report Form |
| **CSR** | Clinical Study Report |
| **CTA** | Clinical Trial Authorisation |
| **CTIMP** | Clinical Trial of Investigational Medicinal Product |
| **DMC** | Data Monitoring Committee |
| **DSUR** | Development Safety Update Report |
| **EudraCT** | European Clinical Trials Database |
| **EME** | Efficacy and Mechanism Evaluation |
| **GCP** | Good Clinical Practice |
| **GMP** | Good Manufacturing Practice |
| **IB** | Investigator Brochure |
| **ICC** | Intraclass correlation |
| **ICH** | International Conference on Harmonisation |
| **IMP** | Investigational Medicinal Product |
| **IOL** | Induction of Labour |
| **IQR** | Inter-quartile range |
| **ISF** | Investigator Site File |
| **ISRCTN** | International Standard Randomised Controlled Trials Number |
| **MHRA** | Medicines and Healthcare products Regulatory Agency |
| **PARCA-R** | Parent Report of Children's Abilities-Revised |

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|---|---|
| **PI** | Principal Investigator |
| **NIMP** | Non-Investigational Medicinal Product |
| **QA** | Quality Assurance |
| **REC** | Research Ethics Committee |
| **SAE** | Serious Adverse Event |
| **SAR** | Serious Adverse Reaction |
| **SD** | Standard deviation |
| **SDV** | Source Data Verification |
| **SPC** | Summary of Product Characteristics |
| **SOP** | Standard Operating Procedure |
| **SUSAR** | Suspected Unexpected Serious Adverse Reaction |
| **TMF** | Trial Master File |
| **TMG** | Trial Management Group |
| **TSC** | Trial Steering Committee |

# TRIAL SUMMARY

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|---|---|
| **Trial Title** | A Randomised Placebo-Controlled Trial of Antenatal Corticosteroids for Planned Birth in Twins: STOPPIT-3. |
| **Study Acronym** | STOPPIT-3 |
| **Clinical Phase** | III |
| **Trial Design** | Randomised Placebo-Controlled Trial |
| **Trial Participants** | Women with viable twin pregnancy, with planned delivery at $35^{+0}$-$38^{+6}$ weeks gestation |
| **Planned Number of Participants** | 1552 |
| **Planned Number of Sites** | 50 sites invited to participate |
| **Countries Anticipated to be Involved in Trial** | UK |
| **Treatment Duration** | 24 hours |
| **Follow up Duration** | 2 years after delivery |
| **Total Planned Trial Duration** | 4 years<br>01/11/2021 – 31/10/2025 |
| **Primary Objective** | To determine the effect of ACS on neonatal morbidity including the need for respiratory support within 72 hours of birth. |
| **Secondary Objectives** | To determine the effect of ACS on severe respiratory morbidity<br>To determine the effect of ACS on perinatal mortality<br>To determine the effect of ACS on maternal outcomes including infection and breastfeeding<br>To determine the cost-effectiveness of treatment with ACS compared to placebo<br>To explore the effects of ACS on childhood cognitive and language development at two years of age compared to placebo, in a subset of twins<br>Within the internal pilot, to confirm our sample size, recruitment and outcome frequency estimates |
| **Primary Endpoint** | Assessment of neonatal morbidity using neonatal and delivery records |
| **Secondary Endpoint** | Assessment of maternal outcomes using maternity records.<br>Assessment of cost-effectiveness<br>Assessment of childhood cognitive and language development at two years of age using PARCA-R questionnaire |
| **IMP(s)** | 6.6mg/2ml |
| **IMP Route of Administration** | Intramuscular injection |

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| **NIMP(s)** | N/A |
| **Lay Summary of Trial** | Admission rates of twins to neonatal units is high even among babies born to women who are recommended to have planned birth in the late preterm (35-36 weeks gestation) or early term (37 weeks gestation) period.<br><br>To reduce the risk of perinatal mortality (NICE guidance) Antenatal Corticosteroids (ACS) are often given to women at risk of preterm birth (24-34 weeks gestation) to help mature babies' lungs and reduce the need for high levels of respiratory support. These are administered to women at risk of an early delivery and has potential to reduce morbidity. However, there is currently little evidence of ACS effectiveness in twins.<br><br>We plan to recruit 1552 women from 50+ centres across the UK. We will invite women to consent to participate in the study who are expecting twins. We will ask the women to have a single course of dexamethasone 6.6mg/2ml (an antenatal corticosteroid) given in two divided doses by intramuscular (IM) injection 24 hours apart. We will follow women and their babies for two years after delivery.<br><br>The proposed research will generate much needed evidence on the use of ACS prior to a planned birth of twins. If ACS is clinically and cost-effective over placebo this will provide evidence to address the current uncertainty regarding its use in twin pregnancy. If ACS does not prove to be effective over placebo this will also be very important for clinical practice given we know the use of ACS is not devoid of harms and this may result in important cost savings to the NHS. |

# 1. INTRODUCTION

## 1.1 BACKGROUND

STOPPIT-3 will address the uncertainty regarding the effectiveness of Antenatal Corticosteroids (ACS) prior to a planned birth of twins. ACS are widely administered to women at risk of preterm birth (defined as birth less than 37 completed weeks gestation) to reduce morbidity and mortality in babies born to early. (1) There is currently little evidence that ACS work in twins, and little evidence that ACS are effective in the late preterm and early term period which is the period that NICE recommend that twins are born. (2) Nevertheless, ACS are widely given to women with twin pregnancy having planned birth, despite recognition that ACS may have adverse effects on growth and neurodevelopment. (3, 4)

ACS have been recommended since the 1990s to reduce neonatal mortality and morbidity in the context of preterm birth. ACS are administered by IM injection. A total of 24mg of either dexamethasone or betamethasone is administered in 2 to 4 divided doses over 24 hours. ACS are most effective if birth occurs 24 to 48 hours following administration, with little or no benefit seen if birth is seven days or more after administration. (1)

Twin pregnancy is common and associated with adverse outcomes for the babies, accounting for ~3% of live births but ~15-20% of all neonatal care admissions. (5) A recent Global Priority Setting Partnership, including nearly 1000 parents, identified ten research priorities for future health of multiples and their families. (6) Two of the top ten priorities will be addressed within STOPPIT-3:

i) How can we reduce multiples' (the babies) admission to neonatal care and can we reduce their length of stay in the neonatal care? and
ii) What are the short- and long-term outcomes in multiple pregnancies and are these outcomes affected by antenatal events and medical interventions?

Reducing term (>37 weeks gestation) neonatal care admission is a UK national priority. It is costly and separation of mothers and babies is detrimental to maternal wellbeing, mother-infant bonding and breastfeeding. (7) The rate of twin pregnancy has risen since the advent of assisted reproduction technologies. (2) Recent NICE guidance gives clear recommendations that twins should be born in the late preterm or early term period but the benefits and harms of ACS in this population are unclear.

We surveyed the STOPPIT-2 network of twin specialists (a network of 56 UK sites created as part of the recently completed NIHR HTA funded STOPPIT-2 trial) (8) with 82 responses from twin specialist clinicians. The majority of sites follow NICE guidance regarding timing of birth, with planned birth of uncomplicated DC twins at 37 weeks gestation (53%), and MC twins at 36 weeks (68%). (2) However, there was considerable variation in use of ACS prior to planned birth, with 88% of respondents supporting a trial of ACS before planned birth in twins to address this uncertainty.

## 1.2 RATIONALE FOR STUDY

Evidence as to whether women having planned birth of twins should receive ACS is both conflicting and confusing. There is some evidence that ACS in singleton pregnancies in the late preterm period ($34^{+0}$ – $36^{+6}$ weeks) and/or prior to planned CS at term ($37^{+0}$ - $38^{+6}$ weeks gestation), (9) may have short term benefits reducing respiratory morbidity and neonatal care admission. This evidence is often extrapolated to twin pregnancy, however, there is almost no evidence showing benefits of ACS from women with twin pregnancies. Differences in the pharmacokinetics of ACS, (10) and

mechanisms of fetal maturation (which may be accelerated in twins), (11) may mean that ACS have different effectiveness at late preterm and early term gestations. 2019 NICE guidance for twin pregnancy recommends planned birth at $37^{+0}$ weeks gestation in uncomplicated dichorionic (DC) twins (twins that have separate placentae), and planned birth at $36^{+0}$ weeks gestation in uncomplicated monochorionic (MC) twins (twins that share a placenta [~20% of twins]). (2) Planned birth is by induction of labour or caesarean section (CS). These slightly earlier, non-spontaneous births are at increased risk of respiratory morbidity and needing respiratory support requiring neonatal care admission.

ACS are not devoid of harm. A large RCT of ACS in late preterm singletons demonstrated an increase in neonatal hypoglycaemia in the ACS group compared to placebo (number needed to harm 11). (12) ACS have well recognised detrimental effects on fetal growth (birthweight, length and head circumference) and neurodevelopment. (3, 4, 13) The balance of risk and benefit needs to be determined for twin pregnancies.

There is evidence that ACS reduce serious respiratory morbidity and neonatal unit admission but there is potential for short (e.g. hypoglycaemia) and long-term harms (e.g. neurodevelopment). Practice is highly variable regarding ACS administration at later preterm and early term gestations. Our survey of STOPPIT-2 twin specialists (see 1.1 Background) reflects uncertainty regarding best management, with high variation in rates of administration of ACS prior to planned birth in twins. Either currently a substantial number of babies miss a morbidity sparing treatment; or a substantial number receive a potentially harmful treatment unnecessarily. STOPPIT-3 will provide the evidence to address this uncertainty.

# 2. STUDY OBJECTIVES

## 2.1 OBJECTIVES

### 2.1.1 Primary Objective

The primary objective of this study is to test the hypothesis that ACS reduce neonatal morbidity including the need for respiratory support within 72 hours of birth.

### 2.1.2 Secondary Objectives

- To determine the effect of ACS on severe respiratory morbidity
- To determine the effect of ACS on other perinatal morbidity
- To determine the effect of ACS on perinatal mortality
- To determine the effect of ACS on maternal outcomes including infection and breastfeeding
- To determine the cost-effectiveness of treatment with ACS compared to placebo
- To explore the effects of ACS on childhood cognitive and language development at two years of age compared to placebo, in a subset of twins
- Within the internal pilot, to confirm our sample size, recruitment and outcome frequency estimates

## 2.2 ENDPOINTS

### 2.2.1 Primary Endpoint

Assessment of neonatal morbidity using neonatal and delivery records. The definition of the primary outcome of respiratory support within 72 hours of birth is a composite outcome encompassing a range of levels of support consisting of one or more of the following:

- Continuous positive airway pressure (CPAP)
- Supplemental oxygen by high-flow nasal cannulae for at least 2 consecutive hours
- Need for supplemental oxygen by low flow nasal cannulae or incubator oxygen for at least 4 continuous hours
- mechanical ventilation
- Extracorporeal membrane oxygenation (ECMO)
- Stillbirth or neonatal death within 72 hours of birth included as competing events

### 2.2.2 Secondary Endpoints

Assessment of neonatal morbidity using neonatal and delivery records, maternal morbidity using maternity records, childhood cognitive and language development at two years of age using PARCA-R questionnaire and cost-effectiveness assessment. The definitions for individual secondary outcomes are described below:

*(1) To determine the effect of ACS on severe respiratory morbidity*

Severe respiratory morbidity within 72 hours after birth, is a composite outcome of one or more of the following:

- CPAP or high-flow nasal cannula for at least 12 continuous hours
- Supplemental oxygen with a fraction of inspired oxygen of at least 0.30 for at least 24 continuous hours
- Mechanical ventilation
- ECMO
- Pneumothorax
- Stillbirth or Neonatal death within 72 hours of birth included as competing events

*(2) To determine the effect of ACS on other perinatal morbidity*

Other perinatal outcomes are:

- any admission to neonatal care (i.e. admission for any reason and for any duration)
- Neonatal care admission within 72 hours of birth for 48 hours or more or any Neonatal care admission (within 28 days of birth) or those requiring surfactant treatment or nitric oxide therapy
- Apgar score at 5 minutes
- umbilical arterial cord pH*
- umbilical arterial cord base excess*
- the number of newborns with hypoglycaemia diagnosed within 48 hours of birth (defined as blood glucose of less than 2.0 mmol per litre or treatment for hypoglycaemia administered).*
- the number of newborns with neonatal jaundice (defined as those requiring treatment with phototherapy according to NICE threshold for gestation and postnatal age)

- birthweight
- head circumference at birth
- all cause early onset sepsis within 72 hours of birth (defined as culture positive [pure growth from blood or CSF of a known bacterial pathogen] or culture negative [acute onset of illness with 3 or more predefined clinical signs])

**These are not mandated in all STOPPIT-3 twins and data will be collected for those newborns where these measurements were recorded as part of routine clinical care. Hypoglycaemia screening is performed according national guidance (British Association of Perinatal Medicine (BAPM) guidance on Identification and Management of Neonatal Hypoglycaemia). Umbilical cord base excess and pH are measured per local guidelines.*

*(3) To determine the effect of ACS on perinatal mortality*

Perinatal mortality outcomes are:

- extended perinatal mortality (stillbirth or neonatal death up to 28 days)
- stillbirth (death *in utero*)
- neonatal death (death within 28 days of birth)

*(4) To determine the effect of ACS on maternal outcomes*

The maternal outcomes included are:

- exclusive breastmilk nutrition at discharge
- confirmed or suspected postpartum infection during hospital admission (defined by a new prescription of antibiotics, confirmed systemic infection on culture, or endometritis as defined by the US Centers for Disease Control and Prevention)

*(5) To determine the cost-effectiveness of treatment with ACS compared to placebo*

We will assess cost-effectiveness of treatment with ACS compared to placebo, reported as incremental cost per reduction in respiratory support, over a 28 day time horizon.

*(6) To explore the effects of ACS on childhood cognitive and language development at two years of age compared to placebo, in a subset of twins*

Determined by the Parent Report of Children's Abilities-Revised (PARCA-R) score. (14)

*(7) Within the internal pilot, to confirm our sample size, recruitment and outcome frequency estimates*

These will be determined in analysis of the internal pilot data (see section 10.2)

# 3. STUDY DESIGN

STOPPIT-3 is a multicentre, double blind randomised placebo-controlled trial of ACS versus placebo in women with a viable twin pregnancy with planned birth between $35^{+0}$ and $38^{+6}$ weeks gestation.

An internal pilot phase will take place to determine recruitment rates with robust criteria to assess continuation of the trial.

A nested economics analysis will assess cost-effectiveness of ACS versus placebo.

## 4. STUDY POPULATION

Women with a confirmed viable twin pregnancy and planned birth at $35^{+0}$-$38^{+6}$ weeks gestation

### 4.1 NUMBER OF PARTICIPANTS

We plan to recruit 1552 women who are pregnant with twins.

### 4.2 INCLUSION CRITERIA (all must apply)

- Women aged 16 years or older and able to provide electronic or written consent
- Women presenting with a viable twin pregnancy (monochorionic or dichorionic) with a planned birth* scheduled between $35^{+0}$ and $38^{+6}$ weeks gestation including women who have a planned birth due to logistic reasons (e.g. availability of beds or staff), parental preference or other maternal or fetal indications.
- Women with gestation established by scan at ≤16 weeks according to NICE guidelines and known chorionicity.
- ≥ 24 hours* and < 7 days until planned birth

*Birth planned to take place at 35 or more weeks gestation, after induction of labour (IOL) or CS. At the point of randomisation there must be ≥ 24 hours until the planned CS or IOL date to allow two doses of the study drug to be administered, at 24 hours (+/- 4 hours) apart prior to the planned birth.

### 4.3 EXCLUSION CRITERIA (none must apply)

- Women who are unable to give informed consent
- Women who have a known or suspected major congenital fetal anomaly at the time of inclusion (defined as any structural or chromosomal anomaly that would influence management at or around birth or in the immediate postnatal period. Suspected isolated minor anomalies with lesser medical, functional or cosmetic consequences; or isolated limb abnormalities such as talipes can be included).
- Women who have received ACS within the seven days prior to randomisation
- Women who have a sensitivity, contraindication or intolerance to any of the ACS or any of its excipients

- Women in whom chorionicity or gestational age are unknown

  Women with other serious pregnancy morbidities which indicate either birth before 35 weeks or urgent birth within 24 hours

## 4.4 CO-ENROLMENT

The importance of including pregnant women in research has been raised by our co-applicants, The Twins Trust and the Multiple Birth Foundation, and through parent representatives in our PAG and more widely by other parent organisations. Therefore, co-enrolment in another study does not automatically exclude participation in STOPPIT-3. Co-enrolment in STOPPIT-3 and another study (either non-CTIMP or CTIMP) will be considered in line with the sponsor's policy on co-enrolment.

Co-enrolment in STOPPIT-3 and another non-interventional research study (for example, sample only or questionnaire studies) is permitted and this does not require any formal written documentation. This includes the related but distinct protocol of the STOPPIT-3 mechanistic study sponsored by the NIHR Efficacy and Mechanism Evaluation (EME) programme (reference NIHR133388).

Co-enrolment in STOPPIT-3 and another CTIMP or interventional non-CTIMP (for example, diagnostic, device or surgical interventions) are permitted provided an assessment on the safety of study participants, interventions involved, participant burden and the potential impact on the study endpoints have been considered. This assessment will be performed and documented in line with the Sponsor policy on co-enrolment, and included within the site initiation visit (SIV) training during site set up.
During the set up phase sites should identify any studies that will be recruiting women who are also eligible for inclusion in STOPPIT-3. This will allow decisions on co-enrolment to be made ahead of the site opening to recruitment and this allows compliance to the allowed time windows for recruitment as described in section 5.

# 5. PARTICIPANT SELECTION AND ENROLMENT

## 5.1 IDENTIFYING PARTICIPANTS

Pregnant women who are booked for their delivery at one of the hospital sites participating in the study and who appear to meet the study eligibility criteria will be invited to participate. Medical records of women pregnant with twins will be reviewed by the maternity care teams for individual recruitment potential into the trial. This may include the research, medical and nursing staff where it is locally agreed that they are part of the clinical care team. We anticipate that all eligible women expecting twins and who are attending for antenatal care in each of the sites will be invited to participate.

## 5.2 SCREENING FOR ELIGIBILITY

Women who appear to fulfil the inclusion criteria for the trial will be approached by a member of the maternity care team and will be provided with written information about the study. This may be a member of the research, medical and nursing staff where it is locally agreed that they are part of the clinical care team. Potentially eligible women will normally be informed of the study at the first twin clinic appointment early in pregnancy.

However, due to Covid-19 this may be undertaken remotely and study information sent to the women electronically or by post.

A screening log will be maintained in each participating site of all potentially eligible women who have been approached and if (1) they are 32 weeks gestation or more, and (2) there is a clinical decision for planned delivery (a date for delivery is not needed). Where possible the reason for an eligible woman being excluded or declining participation will be recorded, for input into trial metrics as per the CONSORT statement. (15)

## 5.3 CONSENTING PARTICIPANTS

Women will be given information about the study and will be given adequate time to read the patient information sheet, with study information usually given at around 16-24 weeks gestation and again around 32-34 weeks (see section 7.2.1). The scheduling of antenatal appointments will vary between sites. The timings for giving women trial information should be followed if possible. Flexibility for approaching women is permitted and deviation from the timelines set out here will not be recorded as a protocol deviation. If the woman waives this opportunity for early information but still wishes to participate, consent may be taken after a shorter time interval.

Women will be asked to complete a consent form. Details of the consent process, including the name of the doctor confirming eligibility, will be recorded in the woman's medical records and on the consent log. Consent should be provided within 7 days of randomisation/IMP administration.

It is permitted to consent women remotely over the telephone/video call in advance of giving written consent. This allows for randomisation and dispensing of the study drug pack ahead of the clinic visit to avoid delays with trial procedures. This should only be used when there are known or predicted delays to the randomisation/IMP administration. Remote consent should always be followed up with written consent, and the process should be clearly documented in the patient notes.

### 5.3.1 Ineligible and non-recruited participants

Women who consent to participate in the study, but who spontaneously deliver or undergo induction or CS prior to randomisation will not be eligible for randomisation. Such women who did consent to participate will be withdrawn but will remain on the eCRF system and reported in recruitment metrics as ineligible post consent. No delivery outcomes will be collected and they will continue receiving standard care under the management of a clinician, as per current medical practice. The woman's care will not be affected due to non-trial participation.

## 5.4 RANDOMISATION

### 5.4.1 Randomisation Procedures

Randomisation to treatment will be performed immediately prior to IMP administration*, 24 hours to 5 days (120 hours before the planned CS or IOL date). Randomisation will be performed using a web-based randomisation system managed by ECTU via a web portal. Users (research staff) will be assigned a unique study identifier and will be required to enter some baseline participant details prior to randomisation (e.g.

demographics, pregnancy information, inclusion /exclusion criteria; see section 7.2.2). As this is a large trial (1552 women), group imbalances are extremely unlikely. We will therefore use a simple allocation sequence with no minimisation criteria. The participants' medical records will be annotated to show they are participating in the STOPPIT-3 trial.

Further details will be put in to a separate randomisation specification. Study participants, trial investigators and medical staff providing care will remain blinded to treatment allocation.

*except when consent is permitted over the telephone/video call in advance of written consent so randomisation and dispensing of the study drug pack can proceed ahead of the clinic visit due to known or predicted delays with the clinic appointments.

### 5.4.2 Treatment Allocation

Women will be asked to attend the hospital for administration of the IMP where it will be administered by a health care professional trained and delegated to give the IMP. The first dose of IMP should be given immediately following randomisation (with randomisation being performed 24 hours to 5 days (120 hours) before the planned CS or IOL date). Randomisation and IMP administration should be performed contiguously to minimise the chance of spontaneous labour or delivery between randomisation and IMP*. The timing of randomisation /IMP administration is to maximise administration of both doses of IMP within 24 – 7 days of actual birth, as this is when antenatal corticosteroids are most effective.

Dispensing will be undertaken by the local site clinical trial pharmacist or pharmacy technician in accordance with local SOPs. Detailed guidance is provided in the supplementary documentation for pharmacy and the trial team contained in the site file.

Dexamethasone and visually matching placebo injections of sodium chloride 0.9% will be prepared by Sharp healthcare and packaged in ampoules. Sharp healthcare is not involved in the recruitment or administration of the drug, and will apply the trial labels before shipment to site. Drugs will be stored at each recruiting site and prepared for administration according to the study SOP for drug administration.

*except when consent is permitted over the telephone/video call in advance of written consent so randomisation and dispensing of the study drug pack can proceed due to known or predicted delays with the clinic appointments.

### 5.4.3 Emergency Unblinding Procedures

Breaking of the trial blind should only be performed where knowledge of the treatment is essential for the clinical management of the woman or neonate(s). Where possible, members of the local research team should remain blinded. It is anticipated that in the majority of instances, appropriate clinical management can proceed with the assumption that the patient is being treated with a trial drug without the need to unblind the participant. Unblinding should not take place at participant request, even if they have withdrawn from trial treatment.

The facility to perform emergency unblinding will be available 24 hours per day, 7 days a week. Participant unblinding can be completed by following the unblinding instructions below which are also detailed within a trial working practice document (WPD) which will

be filed in the investigator site file (ISF) and training given during the site initiation visits (SIV).

All recruited participants will be given a card with an emergency contact number for unblinding. The site PI, research team or anyone involved in the care and management of the participant will be able to call this number to unblind. This mobile number will be managed 24 hours a day, 7 days a week by members of the central trial team with access to the 24 hour web-based trial randomisation system to unblind. The name and email address of the person requesting the unblinding along with the reason for unblinding will be used to complete the unblinding page within the database. Unblinding will be immediately performed, with an email showing the treatment allocation sent directly to the person requesting the unblinding from the web-based randomisation system. Treatment allocation will not be revealed to the trial team member performing the unblind. The person requesting the unblinding can discuss the trial with the central trial team however any decision to unblind remains their own.

The unblinding system is a secure page held within the trial database (REDCap) and access to the unblinding page is restricted via user access rights. A record of activity, e.g., who requested it and when it was requested, will be stored in the database and available for audit purposes. However, this unblinding page will not hold the unblinding data as this is emailed directly to the person who requested it. The process is GCP compliant and the system is owned by the Edinburgh Clinical Trials Unit (ECTU).

As part of the consent discussions, it will be explained to women that they will not be able to find out what treatment they received during the trial, so as not to jeopardise validity of future long term follow up trials. Ensuring women understand this forms part of the assessment of suitability for inclusion in the trial which is performed by suitably qualified clinicians.

Reasons for unblinding will be collected and reported to the DMC. Unless there is a clinical requirement, the blind will not be broken until after data entry is complete, the validity of the data is checked, all queries are resolved and the patient populations agreed.

## 5.5 WITHDRAWAL OF STUDY PARTICIPANTS

Participants are free to withdraw from the study at any point or a participant can be withdrawn by the Investigator. If withdrawal occurs, the primary reason for withdrawal will be documented in the participant's eCRF and medical records. The participant will have the option of withdrawal from:

(i) study medication with continued study procedures and collection of clinical and safety data;

(ii) all aspects of the trial but continued use of data collected up to that point. To safeguard rights, the minimum personally-identifiable information possible will be collected.

(iii) follow-up of themselves and their babies, if they withdraw following delivery.

Randomised patients who wish to be withdrawn from the study before they have undertaken any study related procedures will be withdrawn. Data on the participant and babies' outcomes will be requested and retained on the database, if the participant agrees to this.

If a participant withdraws after randomisation, all data collected up until that point will be retained. This will be explained within the participant information sheet.

# 6. INVESTIGATIONAL MEDICINAL PRODUCT AND PLACEBO

## 6.1 STUDY DRUG

### 6.1.1 Study Drug Identification

Dexamethasone (corticosteroid) 6.6 mg/2ml solution for injection

### 6.1.2 Study Drug Manufacturer

Panpharma UK Ltd, Sharp Clinical Services (UK) Ltd. Unit 28, Heads of the Valleys,

Industrial Estate, Heol Klockner, Rhymney, NP22 5RL, UK.

### 6.1.3 Marketing Authorisation Holder

PAN PHARMA

Z.I. du Clairay

35133 Luitre

France

MA number : PL 44124/0015

via

Sharp Clinical Services

Unit 28, Heol Klockner

Heads of the Valleys Industrial Estate

Rhymney

NP22 5RL

### 6.1.4 Labelling and Packaging

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

### 6.1.5 Regulatory Release to Site

The sponsor or their representative (ACCORD) are responsible for the regulatory release to site following the Qualified Person certification of the blind labelled supplies by Sharp (the technical release).

### 6.1.6 Destruction of Trial Drug

Used ampoules will be destroyed and recorded as such at ward level.

Unused IMP and placebo will be returned to pharmacy for destruction. Returned and unused IMP and placebo but must recorded on the destruction log which must be

submitted for approval by the Sponsor. The Sponsor must give approval in writing prior to destruction. Further details are given in the STOPPIT-3 pharmacy manual.

#### 6.1.7 Summary of Product Characteristics (SPC) Booklet or Investigators Brochure

The Dexamethasone Summary of Product Characteristics (SPC) is provided in a separate document (SPC Booklet) with a cover sheet and signature page (signed and verified by the CI and Sponsor) and is filed in the Trial Master File (TMF).

### 6.2 PLACEBO

Sodium Chloride Injection 0.9%

#### 6.2.1 Labelling and Packaging

Sharp Clinical Services
Unit 28 Heads of The Valley Ind Est,
Tredegar
NP22 5RL

Sharp will prepare the Placebo and provide medication labels in English which will comply with the legal requirements of Annex 13 of the European Union's Good Manufacturing Practice (GMP). They will include storage conditions for the drug, but no information about the patient.

#### 6.2.2 Storage

The Placebo and IMP will be prepared and shipped to site by Sharp and stored at site.

There are no temperature ranges for the placebo or IMP but it should be stored at room temperature and protected from excessive heat or freezing. The temperature will be monitored in transit and details of transport conditions provided to the team at site upon receipt.

Monitoring of IMP storage temperature at site pharmacies will be according to normal clinical practice. Any temperature excursions identified by pharmacy staff will be escalated to the Sponsor.

The IMP and placebo will not be further diluted before administration.

### 6.3 DOSING REGIME

The IMP or placebo will be supplied in a clear glass ampoule and prepared by the maternity care team following the study SOP for study drug administration. The women will be given two doses of the study drug by intramuscular injection to the thigh or buttock by appropriately qualified clinical or research staff at the study site. The first dose of IMP should be given immediately following randomisation* (with randomisation being performed 24 hours to 5 days (120 hours) before the planned CS or IOL date), with the second dose administered 24 hours (+/- 4 hours) after the first dose. A total dose of 24mg will be administered after which the study treatment is complete.
*except when consent is permitted over the telephone/video call in advance of written consent so randomisation and dispensing of the study drug pack can proceed due to known or predicted delays with the clinic appointments.

## 6.4 DOSE CHANGES

Dose changes are not permitted. This is a recognised dosing regimen.

## 6.5 PARTICIPANT COMPLIANCE

Two doses of the study drug will be administered 24 hours apart +/- 4 hours (i.e 20-28 hours). If the date/time of the participant's planned delivery is brought forward and/or labour commences spontaneously before the second dose has been administered it should still be administered as long as it is ≥20 hours following the first dose. If the birth is imminent and it is <20 hours since the first dose the second dose should not be given. There is no minimum timeframe between the second dose and the planned birth. The timing of each dose and compliance will be recorded in the eCRF.

If birth occurs before the second scheduled dose it should be withheld.

## 6.6 OVERDOSE

Reports of overdose of ACS are rare and we would not anticipate this to be a problem as only two doses will be administered, and these will be given intramuscularly by a healthcare professional. No antidote is available so in the case of an overdose symptomatic treatment should be administered as necessary.

## 6.7 OTHER MEDICATIONS

### 6.7.1 Non-Investigational Medicinal Products

Not applicable.

### 6.7.2 Permitted Medications

No restrictions.

There are no reported safety concerns regarding interactions between the IMP and the COVID-19 vaccines.

### 6.7.3 Prohibited Medications

There will be no restrictions on other medications.

# 7. STUDY ASSESSMENTS

## 7.1 SAFETY ASSESSMENTS

There are no specific safety assessments for women who have been given ACS for fetal lung maturity in standard maternity care.

Women with pre-existing and gestational diabetes should have their serum glucose monitored according to the local protocol. These participants should be treated as if they have received ACS.

We will be monitoring the blood glucose in newborns (as described on page 15 of the trial protocol).

## 7.2 STUDY ASSESSMENTS

### 7.2.1 Eligibility assessments conducted between 32-36 weeks gestation

A member of the maternity care team will provide all potentially eligible women with a short trial summary after confirmation of a viable twin pregnancy at an appropriate antenatal clinic or ultrasound visit, usually between 16 and 24 weeks gestation.

A member of the maternity care team will assess eligibility at a later routine antenatal appointment when birth plans are finalised (anticipated to be between 30 and 34 weeks gestation, but may differ between sites). Women considered eligible at this stage, and who are interested in taking part, will be given the full PIL and consent form.

Women will be given the opportunity to discuss the study and to ask questions during a follow-up clinic appointment or telephone call between 32-36 weeks gestation (this may differ between sites and should fit with normal scheduling of appointments). The inclusion / exclusion checklist will be used as a guide to eligibility at this stage and only minimal data will be collected i.e. initials, date identified, EDD, date of planned delivery and date of discussion/ date of sending the study information. Information will be recorded on the screening log and in the medical notes.

It is anticipated that women will be contacted to ascertain their interest in participation. Women who decline will be recorded on the screening log with their reasons, where possible.

### 7.2.2 Consent, Baseline Assessment, Randomisation

Consent, baseline assessment and randomisation will be conducted before the planned birth.

The consent, baseline assessment and randomisation for STOPPIT-3 are anticipated to be combined and conducted as a single visit and will wherever possible coincide with routine pre-admission appointments to help minimise additional visits.

It is usual practice for pregnant women who require a planned birth to attend antenatal services in the days prior, for a pre-admission appointment. Combining the study visit with the pre-admission visit may require a longer visit duration and women will be advised to anticipate this. This means that for the majority of participants, consent, baseline and randomisation will not require any additional hospital attendance. Aspects of this may also be conducted remotely prior to attendance in person using technology where permitted locally i.e. near me or other remote secure system.

**CONSENT:** Women who have verbally agreed to participation will be invited to attend hospital to give written informed consent. Consent will be taken by a member of the maternity care team (this may be a doctor, Research Midwife/ Nurse or suitably trained individual as delegated by the local PI). Consent should be provided within 7 days of randomisation/IMP administration.

Consent can be given on paper or electronically. If consent is given on paper, the original written consent form(s) will be stored as in the Investigator Site File (ISF) file, a copy will be given to the woman and a copy added to the medical notes. Allowance for consent to be taken electronically has been included in the protocol. The software to

be used for this will be reviewed and agreed with the sponsor, and necessary amendment approvals sought where required.

**BASELINE:** The women's demographics, medical history, obstetric history, current pregnancy information and inclusion /exclusion criteria will be collected and entered on the eCRF by a member of the trial team. The inclusion/ exclusion criteria will be further assessed by a doctor (delegated by the PI) and they will complete and sign the eligibility form confirming the woman meets the study criteria to participate and is suitable for randomisation.

**RANDOMISATION:** Using the eCRF staff will enter data sought at the baseline and note eligibility confirmation has been obtained. Women will then be randomised to the corticosteroid group or the placebo group.

The randomisation process will assign each participant with a study drug treatment pack number. The system will only allocate treatment packs assigned to and available at the individual recruiting site.

All of the above activities should be completed prior to the first dose being administered. IMP procedures for making up the syringes should be followed.

Women will be randomised to one of two groups:

1. Corticosteroid group – two doses of 12mg dexamethasone by intramuscular injection 24 hours (+/- 4 hours) apart. The first dose of IMP should be given immediately following randomisation* (with randomisation being performed 24 hours to 5 days (120 hours) before the planned CS or IOL date).

2. Placebo group – two doses of matching placebo (sodium chloride 0.9%) by intramuscular injection 24 hours (+/- 4 hours) apart. The first dose of placebo should be given immediately following randomisation* (with randomisation being performed 24 hours to 5 days (120 hours) before the planned CS or IOL date).

Study participants, trial investigators and medical staff delivering care will remain blinded to treatment allocation**.** The first dose of IMP should be given immediately following randomisation (with randomisation being performed 24 hours to 5 days (120 hours) before the planned CS or IOL date), with the second dose administered 24 hours (+/- 4 hours) after the first dose.

*except when consent is permitted over the telephone/video call in advance of written consent so randomisation and dispensing of the study drug pack can proceed due to known or predicted delays with the clinic appointments.

### 7.2.3 Birth and Neonatal Information

Birth and neonatal information will be extracted from the woman's +/- babies' medical notes and information recorded in the eCRF by a member of the maternity care team.

### 7.2.4 Study Visits

There are no other specific study visits planned other than attendance for the study drug administration.

## 7.3 COMPLIANCE ASSESSMENTS

The study drug will be administered by an appropriately qualified clinical or research staff at the study site as described in section 6.5. The timing of each dose and compliance will be recorded on the CRF.

## 7.4 LONG TERM FOLLOW UP ASSESSMENTS

STOPPIT-3 participants will be asked to complete the PARCA-R questionnaire (online or on a paper copy) at 2 years (to assess the cognitive and language development). Before sending the questionnaire, sites will be asked to complete a status check on each twin to ensure it is appropriate to send the questionnaire.

A letter or email (depending parent preference) will be sent at 2 years with details of how to complete the questionnaire. If there is no response to the first request to complete the questionnaire, this will be followed up by a second email or letter. If no response is received after the second request, the questionnaire will be marked as "missed". Missed follow-up will not be documented as protocol non-compliance.

Paper copies of completed questionnaires will be stored in a locked, fireproof filing cabinet within ECTU with access restricted to members of the team only. Participants will receive a high street shopping voucher on completion and return of the questionnaire.

## 7.5 STORAGE AND ANALYSIS OF SAMPLES

There are no biological samples involved in this study however participants with planned CS will be invited to participate in the STOPPIT-3 mechanistic study sponsored by EME (reference NIHR13388).

# 8. DATA COLLECTION

Trial data will be collected by members of the maternity care team delegated by the PI. Information which will fulfil the requirements of the study primary and secondary endpoints will be collected. Data is primarily collected from source and entered in to the eCRF (REDCap database), once available.

A unique trial identifier will be allocated to each participating woman at randomisation and this unique number will be used for data collection within the trial. Identifiers are stored in separate tables from the main data tables within the trial database and only delegated members of the team will be granted access to these tables.

Data will be reviewed regularly by the Central Trial Team for completeness and data queries sent for missing information. Data collection points are described in Table 1,

***Table 1: Data collection points***

Data will be collected at the following time points: Screening, Consent, Baseline, Randomisation, Delivery, Neonatal and Childhood periods.

| **Study activities** | **Screening**<br>*Identification of Viable twin pregnancy until 24 weeks* | **Consent**<br>*Within 7 days of randomisation* | **Baseline**<br>*24- 120 hours prior to planned birth* | **Randomisation**<br>*24 -120 hours prior to planned birth* | **IMP Administration 1**<br>*Immediately following randomisation*.* | **IMP Administration 2**<br>*24 hours (+/- 4hrs after IMP administration 1)* | **Delivery** | **Neonatal**<br>*Neonatal period* | **Childhood**<br>*2 years after delivery* |
|---|---|---|---|---|---|---|---|---|---|
| **ASSESSMENT ID** | Pre Study | i) | i) | i) | i) | ii) | iii) | iv) | v) |
| Screening log | x | | | | | | | | |
| Consent log | | x | | | | | | | |
| Date of consent | | x | | | | | | | |
| Person who took consent | | x | | | | | | | |
| Contact details of patient | | x | | | | | | | |
| GP details | | x | | | | | | | |
| GP letter issued | | x | | | | | | | |
| Demographics | | | x | | | | | | |
| Medical History, | | | x | | | | | | |
| Obstetric history, | | | x | | | | | | |
| Current pregnancy History | | | x | | | | | | |
| Current Medications | | | x | | | | | | |
| Eligibility confirmation | | | | x | | | | | |
| Randomisation date and assignment | | | | x | | | | | |
| Prescription issued | | | | x | | | | | |
| IMP administered within 7 days before delivery | | | | | x | x | | | |
| IMP Administered 20-28 hours after first dose | | | | | x | x | | | |

| | | | | | |
|---|---|---|---|---|---|
| Delivery outcomes | | | x | | |
| Neonatal outcomes | | | | x | |
| Safety information SAE | x | x | x | x | x |
| PARCA_R | | | | | x |

*except when consent is permitted over the telephone/video call in advance of written consent so randomisation and dispensing of the study drug pack can proceed due to known or predicted delays with the clinic appointments.

## 8.1 SOURCE DATA DOCUMENTATION

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

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

In STOPPIT-3:

For each participant, the Investigator will indicate in the medical source records that the participant is in this trial and the date of obtaining the informed consent.

The records should enable verification of eligibility at enrolment. Signed and dated informed consent will be stored and archived according to local requirements. In addition, the following information, at the minimum, will also be recorded in the maternal maternity source records for each participant:

- Documentation of signed and dated Informed Consent
- Participant's name and date of birth
- Screening/randomisation number (Study ID)
- Dosing of IMP – date and time of first and second doses
- Occurrence of any adverse events/SAEs (including description and duration)
- Medical history
- Obstetric history
- Estimated date of delivery
- Chorionicity
- Date of delivery
- Any concomitant therapy
- Reason for discontinuation/withdrawal, if applicable

The following information will also be recorded in the neonatal/baby source records for each twin:

- Any concomitant therapy

The following documents collected during the trial should be stored and archived together with the patient's hospital/medical records or in the Investigator File as agreed upon prior to the trial start at each trial site:

- Patient dispensing logs of IMP
- Demographics

For withdrawals, data will be monitored as per source data verification (SDV) plan.

We will collect the following characteristics from all participants: maternal age at birth of twins, ethnicity, height and weight at pregnancy booking, smoking, alcohol and substance use at booking, obstetric history (parity, previous mode of birth), medical conditions (hypertension, respiratory disease, cardiac disease), pregnancy conditions (pre-eclampsia), medications (antihypertensives, steroids; oral/topical/inhaled) , previous ACS, chorionicity, twin complications (if there was ever suspected twin to twin transfusion syndrome [yes/no], fetoscopic laser ablation of placental anastomoses in

pregnancy, suspected twin anaemia-polycythaemia sequence), indication for scheduled birth and mode of birth of each twin.

## 8.2 CASE REPORT FORMS

An e-CRF system (REDCap) will be used for data capture. The system is validated and access at all levels to the system is granted/revoked following ECTU procedures, in accordance with regulatory and system requirements.

Data should be entered into the eCRF timely after the patient has attended a visit or after the data become available, as applicable. Data will be entered by research staff at study sites.

All case report forms must be reviewed and approved by the ACCORD Monitor prior to use (see ACCORD SOP CR013 CRF Design and Implementation) and all electronic case report forms are subject to sponsor approval. The eCRF will be developed by the Data Management & Programming Team at ECTU. The eCRF will include range checks to enhance data quality and tools to check for completeness of data.

Errors occurring in the e-CRF will be corrected electronically. Such corrections/modifications will be automatically tracked by an audit trail detailing the date and time of the correction and the name of the person making the correction.

## 8.3 TRIAL DATABASE

The trial database will be created and maintained by ECTU. Trained and delegated members of the study team will be given password-protected logins to the database to complete data entry. The data will be stored on a secure server in the University of Edinburgh for the minimum retention period for the study.

# 9. DATA MANAGEMENT

### 9.1.1 Personal Data

The following personal data will be collected and stored on University of Edinburgh servers as part of the research:

- CHI/ NHS number (woman and child)
- Ethnicity to help ensure the project is representative of ethnic minority groups
- Full address and postcode for follow up questionnaires and childhood assessments
- Email address and IP for women who provide e-consent

Personal data will be stored by the research team in the Edinburgh Clinical Trials Unit, The University of Edinburgh for a minimum of 25 years. Study reports will contain only summary data. Identifiable data will not be released to any third party.

Personal data collected as part of this trial will be retained (with consent) to enable future studies into the long term outcomes of ACS. It is necessary to keep personal information for both woman and baby to allow record linking of trial data (treatment group) to long term outcome data in healthcare and education data. Any future studies

would be subject to separate funding, and the relevant research governance approvals would be obtained.

Consent will be obtained to allow anonymised data with other organisations running future related studies, providing appropriate approvals are in place. The CI is responsible for reviewing and authorising requests for anonymised data.

### 9.1.2 Data Information Flow

The collection, use and deletion of personal data is shown in the example diagram below.

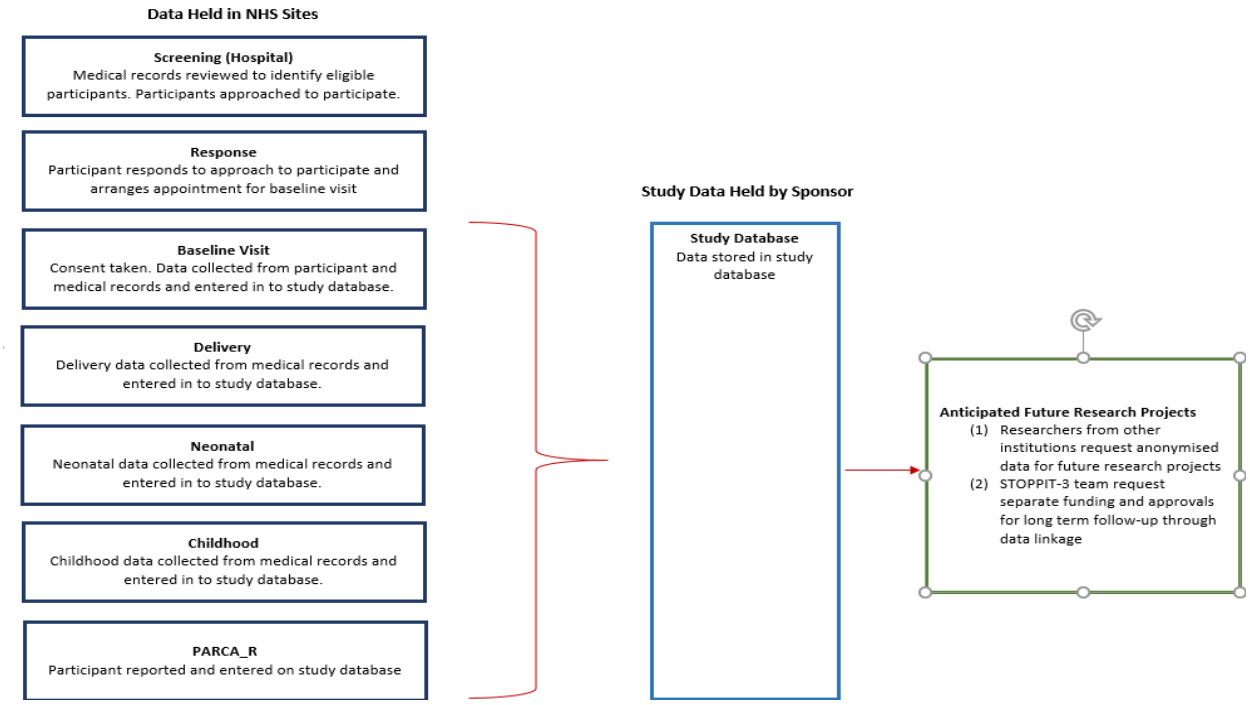


**Figure 1: Example of data flow**

### 9.1.3 Transfer of Data

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

The dataset will be retained and access may be given to other researchers from other institutions providing appropriate approvals are in place.

Personal data collected as part of this trial will be retained (with consent) for use in future studies into the long term outcomes of ACS. It is necessary to keep personal information for both woman and baby to allow record linking of trial data (treatment group) to long term outcome data in healthcare and education data. Any future studies

would be subject to separate funding, and the relevant research governance approvals would be obtained.

The University of Edinburgh and NHS Lothian are joint data controllers along with any other entities involved in delivering the study that may be a data controller in accordance with applicable laws (e.g. the site)

#### 9.1.4 Data Breaches

Any data breaches will be reported to the University of Edinburgh and NHS Lothian Data Protection Officers who will onward report to the relevant authority according to the appropriate timelines if required.

## 10. DATA ANALYSIS

### 10.1 SAMPLE SIZE CALCULATION

1552 women randomised at 1:1 to ACS or placebo prior to planned birth will have 90% power at the 5% significance level to detect a relative difference in the neonatal primary outcome of respiratory support within 72 hours of birth between the groups of 33% (absolute difference of 4%) assuming an event rate of 12% in the placebo group and an ICC of 0.3, assuming 1% of missing data for the primary outcome.

### 10.2 INTERNAL PILOT

We will include an internal pilot phase to determine recruitment rates with robust criteria to assess continuation of the trial. The criteria and timelines will be agreed with the funder as necessary.

### 10.3 PROPOSED ANALYSES

#### 10.3.1 Statistical Analysis

The statistical analysis will be according to the intention to treat principle (i.e. all participants will remain in their allocated group for analysis). Statistical significance will be at the 5% level with corresponding 95% confidence intervals (CI) presented. Randomised groups will be described at baseline and follow-up using mean (SD), median (IQR) and counts (with percentages) as appropriate

A comprehensive statistical analysis plan will be finalised before the data is released for the final analysis. For the primary outcome (respiratory support within 72 hours of birth) we will estimate the odds ratio (and 95% CI) for the treatment effect of ACS adjusting for mode of delivery, treatment centre (if appropriate) and chorionicity with logistic regression. To account for the clustering effect within twin pairs, a random effects logistic regression model will be used by fitting pregnant woman as a random effect.

Continuous secondary outcomes will be analysed using linear regression, and binary categorical secondary outcomes will be analysed using logistic regression as per the primary outcome. Secondary outcomes with more than two categories will be analysed using multinomial logistic regression.

In the specific case of death of either or both twin babies (apart from the primary outcome that includes stillbirth/neonatal death in the first 72 hours) we will examine the robustness of the findings on all the outcomes to these deaths using statistical approaches appropriate to the magnitude of the deaths and how balanced they are between the two randomised groups.

Subgroup analyses, for example by sex of twins, chorionicity and presence of maternal co-morbidity (e.g. hypertension) will be considered.

No interim analyses are planned other than re-estimation of the intraclass correlation (ICC) following the internal pilot. We will follow the recommendations of Chuang-Stein in checking the assumption around the intraclass correlation coefficient. (16) This will use a blinded approach (i.e. assessed by the TSC, and not the DMC, so avoiding any suggestion that unblinded data might have been consulted). This is sample size re-estimation of a nuisance parameter, and since it does not use any information on the emerging treatment effect, the original simple analysis of all the data to estimate that treatment effect at study end can proceed without adjustment (i.e. there is no need to weight the data before and after any sample size adjustment takes place). We will use the standard ANOVA approach, (17) but may explore modelling approaches that adjust the estimated ICC for important baseline covariates (for example, by chorionicity). Re-estimating the sample size at 200 women with babies with outcome data is an appropriate trade-off between a sufficient sample to allow reasonably precise estimation of the ICC, and sufficiently early that it leaves enough time to implement any required change in sample size. We have purposefully chosen this n=200 to be after the conclusion of the internal pilot – primarily designed to demonstrate recruitment feasibility.

We will also check the other blinded assumptions of the original sample size at this n=200 women sample size re-estimation point – namely (a) the proportion of missing data (1%) and (b) the blinded (aggregated) event rate (12% expected in the control group and 8% expected in the active group, giving an average of 10%). At 200 women with complete data, ignoring clustering and analysing at the woman level, we would expect 20 primary events (95% CI 12 to 28). So, if there are fewer than 12 events or more than 28 events in the first 200 women we will need to reassess whether looking for an absolute treatment effect of 4% (relative 33%, from 12% to 8%) remains clinically worthwhile, or whether a smaller (or larger) absolute effect is justified. We would expect to have 202 women providing full data on the first 200, if the missing proportion is 1%. The upper 95% CI would be 5 or more with missing data – we would make a simple adjustment to the sample size calculation, inflating by the observed proportion missing, if this was the case.

In terms of the ICC, we have assumed an ICC of 0.3. We will, as per the event rate, estimate the 95% CI (without, and possibly with, adjustment for covariates) around the observed ICC at 200 women with complete data, and if this 95% CI does not contain 0.3 we will take corrective action. The design effect (DE) formula for sample size inflation in the case of twins simplifies to just 1+ICC. So, for example,
our chosen sample size of 1552 (with an assumed ICC of 0.3) would increase by around 8% to 1672 total if we observed an ICC of 0.4, and reduce to 1432 (a reduction of around 8%) if the observed ICC were 0.2 – and either of these (ICC of 0.2 or ICC of 0.4) was outside the confidence interval of the observed ICC at n=200 women. We think it is highly unlikely, given the experience in the STOPPIT- 2 study that was used to inform the assumption of ICC=0.3, that the observed ICC will be greater than 0.4.

The sample size re-estimation will simultaneously consider the impact of the observed ICC, the observed blinded (aggregated) primary event rate, and the observed level of missingness, and the discussions will be with the TSC, the funder, the research group, and the clinical investigators. If there is a decision to change the sample size, this will trigger a change to the protocol, and be fully documented in a revised Statistical Analysis Plan.

### 10.3.2 Economic Analysis: Measurement of costs and outcomes

The economic analysis will determine the cost-effectiveness of ACS compared to placebo, both within-trial and in the longer term, following recommended economic methods guidance. The cost-effectiveness analysis will adopt the perspective of the NHS and Public Social services, and will adhere to standard methodological and reporting guidelines.

A systematic literature review will be undertaken and an economic conceptual model will be developed to identify and represent the clinical short, medium and long term outcomes of relevance (e.g. hypoglycaemia; neonatal health; mortality; cognitive development; metabolic disease), and the relevant costs which are likely to be associated to the intervention and control. Causal pathways linking short and long term costs and outcomes associated with ACS and the control will be highlighted and the conceptual model will inform development of the Health Economic Analysis Plan which will be developed in conjunction with the trial statistical analysis plan to facilitate consistency between analytic approaches.

*Within trial analysis*
The primary within trial analysis will be a cost-effectiveness analysis (CEA) which will estimate the incremental cost per reduction in respiratory support (initiated within 72 hours after birth, i.e. the study primary outcome), with the time horizon spanning from birth to child hospital discharge or 28 days, whichever is sooner.

The costs of the intervention will be calculated as the daily cost of ACS medication and the associated administration costs. Hospital attendances required to administer ACS will be included. The direct medical costs post birth will be calculated based on resource utilisation accruing for the care of new born (after birth respiratory treatment; admission to neonatal care) and women (type of delivery, inpatient stays; hospital transfers etc.) including adverse events. Resource utilisation for woman and child will be collected from the clinical hospital records up to 28 days post birth. Resource use will be valuated using national databases including NHS reference costs, the British National Formulary and the PSSRU costs of health and social care, relative to the reference year.

The mean cost and mean outcome associated to the intervention and the control arm will be estimated using generalised linear model (GLM), which will tackle non-normality of data, adjusting for relevant covariates (e.g. type of delivery; monochorionic/dichorionic twins). Following best practice, and in line with the efficacy analysis, a multiple imputation procedure using chained equations (MICE) will be used to impute missing outcomes and resource use separately for each arm of the trial and predictive mean matching will allow dealing with non-normality of cost and outcome data. Clustering at twin level will be tackled with appropriate econometric techniques (e.g multilevel models).Within trial results will be reported and presented as mean cost, mean effect and incremental cost-effectiveness ratio (ICER). Non-parametric bootstrapping techniques will explore uncertainty around estimated costs, outcome

and the ICER. A cost-effectiveness acceptability curve (CEAC) will show the probability that ACS administration is cost-effective over the short term for different Willingness to Pay thresholds. Net monetary benefit will also be calculated. Subgroup analyses will be undertaken on relevant groups identified a priori, e.g. sex of twins, chorionicity and presence of maternal co-morbidity (e.g. hypertension or diabetes) if found to have an impact on costs and effects.

*Long term model*
If evidence of differences between the treatment arms in terms of effectiveness, costs or cost-effectiveness are found in the trial, a decision analytic model will be developed to explore the cost-effectiveness of ACS administration over a medium (2 year) and longer term (lifetime)horizon. The medium term analysis will utilise data from the final trial follow-up period in childhood (e.g. PARCA-R, any medical records available etc), to account for costs and consequences which are associated with ACS treatment over the neonatal period (hypoglycaemia; neonatal health) and childhood (mortality; cognitive development metabolic illness). Deterministic, one and two -way sensitivity analysis will examine the impact that the change of key parameters will have on the model results. Model parameter uncertainty will be addressed using probabilistic sensitivity analysis, undertaken using Monte Carlo simulation techniques and summarised using the cost-effectiveness acceptability curve at differing willingness to pay thresholds.

## 11. PHARMACOVIGILANCE

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

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

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

### 11.1 DEFINITIONS

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

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

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

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

*Life-threatening in the definition of an SAE or SAR refers to an event where the participant was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe.

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

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

### 11.1.1 Reportable and non-reportable events

For clarity, and to ensure meaningful safety reporting and signalling, the events listed below are not required to be reported in an expedited manner. The following events are collected on the eCRF as outcomes and do not need to be recorded and reported on AE logs, or reported to the sponsor as described in section 11.6. .

**Non-reportable AEs**

- Admission to neonatal care
- Respiratory support required within 72 hrs of birth
- Surfactant Used
- Nitric Oxide Used
- Neonatal jaundice (requiring treatment with phototherapy according to NICE threshold for gestation and postnatal age)
- Early onset sepsis within 72 hours of birth
- Blood glucose of less than 2.0 mmol/L

**Reportable AEs**

The following AEs will also be reported as SAEs if they meet the criteria considered to be “serious”

- Antepartum (pre-birth) haemorrhage, after the time of randomisation (Grade II moderate ie Blood loss of 50 to <250ml with no signs of clinical shock; Grade III severe ie Blood loss of 250-1000ml with no signs of clinical shock or Grade IV life threatening Blood loss >1000ml; signs of clinical shock Preterm premature rupture of membranes (<37 weeks gestation)
- New onset Pre-eclampsia
- Movement between hospital/unit (only where movement between areas is because of worsening of condition which fulfils the criteria of “serious”. Movement between units/hospitals due to capacity issues will not be reported as an AE)
- Resuscitation at birth and any intervention needed
- Patent ductus arteriosus requiring medical treatment
- Patent ductus arteriosus requiring surgical treatment
- Need for Vasopressor Therapy
- Major congenital anomaly (previously undiagnosed)”.

**Non-reportable as SAE/SARs**

- Pregnancy is part of the inclusion criteria, and so is not considered as an AE or SAE (or reported on a pregnancy reporting form).
- Maternal in-patient admission for birth
- Neonatal admission of the baby

**Reportable as SAE/SARs**

- Maternal death
- Fetal death*
- Neonatal death*
- Maternal life threatening event
- Maternal persistent or significant disability or incapacity
- Major ante partum (pre-birth) or postpartum haemorrhage (>1500 mL), after the time of randomisation
- Other medically important event considered to be an SAE by Investigator*

**If the baby suffers a SAE/SAR a parent-child report form will be completed and reported as described in section 11.6.*

This list will be included in the site training packs, and training on safety reporting requirements will be given as part of the site initiation visits (SIV).

## 11.2 IDENTIFYING AEs AND SAEs

Women will be asked about the occurrence of AEs/SAEs at each attendance for IMP. Open-ended and non-leading verbal questioning of the participant will be used to enquire about AE/SAE occurrence.

After consent, AEs and SAEs will be identified through follow-up data collection. Maternity, birth and neonatal records will be reviewed by the site maternity care team from birth up to hospital discharge or 28 days, whichever is sooner. AEs and SAEs will be identified as part of the data collection, and any events meeting the criteria for AE will be reported. If there is any doubt as to whether a clinical observation is an AE, the event will be recorded.

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

AEs/SAEs will be followed up to resolution, or until the end of the data collection period (hospital discharge or 28 days, whichever is sooner). AE/SAEs that are not resolved at the end of the data collection period will be marked as “ongoing at end of follow-up”.

Parents will be asked to complete the PARCA-R questionnaire at 2 years, but no additional questions on AEs/SAEs will be asked. Any information that is declared which fulfils the criteria for AE/SAEs will be reported as such by the ECTU Trial Manager.

## 11.3 RECORDING AEs AND SAEs

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

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

### 11.3.1 Pre-existing Medical Conditions

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

### 11.3.2 Worsening of the Underlying Condition during the Trial

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

## 11.4 ASSESSMENT OF AEs AND SAEs

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

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

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

### 11.4.1 Assessment of Seriousness

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

### 11.4.2 Assessment of Causality

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

- Unrelated: where an event is not considered to be related to the IMP.
- Possibly Related: The nature of the event, the underlying medical condition, concomitant medication or temporal relationship make it possible that the AE has a causal relationship to the study drug.

Where non Investigational Medicinal Products (NIMPs) e.g. rescue/escape drugs are given: if the AE is considered to be related to an interaction between the IMP and the NIMP, or where the AE might be linked to either the IMP or the NIMP but cannot be

clearly attributed to either one of these, the event will be considered as an AR. Alternative causes such as natural history of the underlying disease, other risk factors and the temporal relationship of the event to the treatment should be considered and investigated. The blind should not be broken for the purpose of making this assessment.

#### 11.4.3 Assessment of Expectedness

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

The event may be classed as either:

**Expected**: the AR is consistent with the toxicity of the IMP listed in the SPC Booklet.

**Unexpected**: the AR is not consistent with the toxicity in the SPC Booklet.

Fatal and life threatening SARs should usually be considered unexpected. Fatal SARs can only be expected for IMPs with an MA in the EU, when it is clearly stated in the list of ARs of the SPC (Section 4.8 of SmPC) that the IMP causes fatal SARs.

#### 11.4.4 Assessment of Severity

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

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

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

**Severe**: an event that prevents normal everyday activities.

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

### 11.5 RECORDING OF AEs

All adverse events for each participant will be recorded on the AE log and will be assigned the appropriate MedDRA Systems Organ Class (SOC) code.

## 11.6 REPORTING OF SAEs/SARs/SUSARs

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

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

The SAE form will be transmitted via email to safety@accord.scot. Only forms in a pdf format will be accepted by ACCORD via email. Where missing information has not been sent to ACCORD after an initial report, ACCORD will contact the Investigator and

request the missing information. The Investigator must respond to these requests in a timely manner.

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

If any SAEs are not to be reported to the Sponsor, they should be listed here.

### 11.7 REGULATORY REPORTING REQUIREMENTS

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

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

ACCORD is responsible for unblinding SUSARs ahead of reporting to the MHRA. Unblinding in managed through the trial database, and the relevant competent individuals within the ACCORDS PhV team will be given access to the database to facilitate unblinding of events.

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

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

### 11.8 FOLLOW UP PROCEDURES

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

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

## 12. TRIAL MANAGEMENT AND OVERSIGHT ARRANGEMENTS

### 12.1 TRIAL MANAGEMENT GROUP

The trial will be coordinated by a Project Management Group, consisting of the grant holders (Chief Investigator, and Trial Implementation), and Trial Management Team in ECTU.

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

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

### 12.2 TRIAL STEERING COMMITTEE

A Trial Steering Committee (TSC) will be established to oversee the conduct and progress of the trial. A TSC Charter will be agreed by all members, and a copy retained in the TMF.

### 12.3 DATA MONITORING COMMITTEE

An independent Data Monitoring Committee (DMC) will be established to oversee the safety of participants in the trial. A DMC Charter will be agreed and signed by all members (including the Sponsor representative. A signed copy will be retained in the TMF.

### 12.4 INSPECTION OF RECORDS

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

### 12.5 RISK ASSESSMENT

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

### 12.6 STUDY MONITORING AND AUDIT

ACCORD clinical trial monitors, or designees, will perform monitoring activities in accordance with the study monitoring plan. This will involve on-site visits and remote monitoring activities as necessary. ACCORD QA personnel, or designees, will perform study audits in accordance with the study audit plan. This will involve investigator site audits, study management audits and facility (including 3rd parties) audits as necessary (delete where not required).

## 13. GOOD CLINICAL PRACTICE

### 13.1 ETHICAL CONDUCT

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

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

### 13.2 REGULATORY COMPLIANCE

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

## 13.3 INVESTIGATOR RESPONSIBILITIES

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

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

### 13.3.1 Informed Consent

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

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

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

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

The Investigator or delegated member of the trial team and the participant will sign and date the Informed Consent Form(s) to confirm that consent has been obtained.

In STOPPIT-3, consent may be recorded by wet ink signature on paper or by electronic signature. The process for filing completed consent forms is as follows;

Wet ink signature: The original will be filed in the Investigator Site File (ISF), women will receive a copy of the signed consent form and a copy will be filed in the participant's medical notes.

Electronic signature: a copy of the signed consent form will be printed and filed in the ISF, a copy given to the woman and a copy filed in the medical notes.

### 13.3.2 Study Site Staff

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

### 13.3.3 Data Recording

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

### 13.3.4 Investigator Documentation

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

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

ISFs. Under certain circumstances the TMF responsibilities may be delegated to the research team by ACCORD.

### 13.3.5 GCP Training

All study staff must hold evidence of appropriate GCP training.

### 13.3.6 Confidentiality

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

### 13.3.7 Data Protection

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

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

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

# 14. STUDY CONDUCT RESPONSIBILITIES

## 14.1 PROTOCOL AMENDMENTS

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

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

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

## 14.2 PROTOCOL NON COMPLIANCE

### 14.2.1 Definitions

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

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

### 14.2.2 Protocol Waivers

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

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

### 14.2.3 Management of Deviations and Violations

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

## 14.3 URGENT SAFETY MEASURES

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

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

## 14.4 SERIOUS BREACH REQUIREMENTS

A serious breach is a breach which is likely to effect to a significant degree:

(a) the safety or physical or mental integrity of the participants of the trial; or

(b) the scientific value of the trial.

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

## 14.5 STUDY RECORD RETENTION

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

## 14.6 END OF STUDY

The end of study is defined as the last participant's last assessment (last 2 year questionnaire).

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

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

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

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

## 14.7 CONTINUATION OF DRUG FOLLOWING THE END OF STUDY

Not applicable

## 14.8 INSURANCE AND INDEMNITY

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

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

- The Protocol has been authored by the Chief Investigator and researchers employed by the University and collaborators. The University has insurance in place (which includes no-fault compensation) for negligent harm caused by poor protocol design by the Chief Investigator and researchers employed by the University.
- Sites participating in the study will be liable for clinical negligence and other negligent harm to individuals taking part in the study and covered by the duty of care owed to them by the sites concerned. The co-sponsors require individual sites participating in the study to arrange for their own insurance or indemnity in respect of these liabilities. Sites which are part of the United Kingdom's National Health Service have the benefit of NHS Indemnity.
- Sites out with the United Kingdom will be responsible for arranging their own indemnity or insurance for their participation in the study, as well as for compliance with local law applicable to their participation in the study.
- The manufacturer supplying IMP has accepted limited liability related to the manufacturing and original packaging of the study drug and to the losses, damages, claims or liabilities incurred by study participants based on known or unknown Adverse Events which arise out of the manufacturing and original packaging of the study drug, but not where there is any modification to the study drug (including without limitation re-packaging and blinding).

# 15. REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

## 15.1 AUTHORSHIP POLICY

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

## 15.2 PUBLICATION

The Clinical Study Report (CSR) will be submitted to the Sponsor and REC within 1 year of the end of the study. Where acceptable, a published journal article may be submitted as the CSR. The Chief Investigator will provide the CSR to ACCORD, for review, prior to finalization. The clinical study report may be used for publication and presentation at scientific meetings.

The STOPPIT publication and dissemination policy describes how trial outputs will be managed, reviewed and disseminated. Investigators have the right to publish orally or in writing the results of the trial, but must do so in accordance with the publication policy.

The results of the study, together with other mandated information, will be uploaded to the European clinical trials database within 1 year of the end of the study.

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

## 15.3 DATA SHARING

The Trial Steering Committee and Data Monitoring Committee will have access to the dataset and oversee analysis, interpretation and reporting of results. The de-identified data that support the findings of this study will be made available upon request to researchers who provide a methodologically sound proposal and whose proposed use of the data has been ethically approved following publication of the primary STOPPIT-3 Trial results.

## 15.4 PEER REVIEW

The protocol has been reviewed by the funder (NIHR HTA), the co-sponsors and the ECTU Senior Management Team.

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