The TOBY Xe study

Neuroprotective effects of hypothermia combined with inhaled xenon following perinatal asphyxia

SPONSOR: Imperial College, London
FUNDER: Medical Research Council, UK
STUDY COORDINATION CENTRE: National Perinatal Epidemiology Unit, Oxford, UK

REC reference: 10/H0707/33
EudraCT reference: 200901434411

Study Handbook

Version 2, 30/4/2012
Adverse Events
Record these in the appropriate page of the Daily Log. If the event is ‘serious’, complete the SAE form. See Protocol for the definition of a Serious Adverse Event.

Withdrawal from study treatment
Continue to complete the data collection forms as fully as possible if a baby discontinues treatment early. If the withdrawal is by parental request, please seek their permission to continue data collection.

Transfers
Send a Transfer Pack with the baby to the new hospital and notify the co-ordinating centre of the transfer (01865 289 732).

Deaths
Please complete the data collection forms as fully as possible up to the time of death. A Death Form should also be completed.
## Schedule for Data Collection

<table>
<thead>
<tr>
<th>Hours to Before Randomisation</th>
<th>DAY 1</th>
<th>DAY 2</th>
<th>DAY 3</th>
<th>DAY 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 12</td>
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<td>✓</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>24 - 36</td>
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<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>36 - 48</td>
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<td>✓</td>
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</tr>
<tr>
<td>48 - 60</td>
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<td>60 - 72</td>
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<td>✓</td>
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</tr>
<tr>
<td>72 - 80</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

### Key to Table

- **A**: Indicates data to be recorded on the data collection forms at this time point. Prior to randomisation data should be entered onto the Entry Form. Following randomisation begin entering data in the Daily Log for a period of 80 hours. Once the baby is ready to be discharged, the Discharge Form should be completed.
- **B**: Cooling should be started as soon as possible according to local practice. It must have commenced within 6 hours of birth for eligibility, and should continue for 72 hours unless clinical circumstances require early discontinuation. Please record the time and data at which Passive and Active cooling were started on the front page of the Daily Log.
- **C**: Informed consent should be obtained using the Parent Information Sheet and Consent Form. If consent must be taken by telephone, the Telephone Consent Form should be completed and witnessed by another member of staff.
- **D**: Record all available blood gas analysis results for each 24h period on the appropriate page of the Daily Log. Test should be performed once per 24h, and then as clinically indicated.
- **E**: The Day 1 HIE Score should be completed as soon as possible after randomisation.
- **F**: Record the time and date at which the target rectal temperature (33-34°C) was first reached on the front page of the Daily Log.
- **G**: Please record these hourly readings on the appropriate page of the Daily Log. Data collection should begin at the time of randomisation and continue for a period of 80 hours.
- **H**: If randomised to receive Xenon it should be given for a period of 24 hours at a fixed concentration of 30%. Interruption on clinical grounds is permitted (refer to Study Handbook for further details). If interrupted, xenon must be restarted within 6 hours or not at all.
- **I**: Ideally the consent affirmation discussion should take place within 24 hours of randomisation. Where consent was given over the telephone, it should take place as soon as possible once the parent(s) arrive at the Treatment Centre, and they should be asked to countersign the Telephone Consent Form.
- **J**: Save digital copies of all cranial ultrasound scans and CFM traces. Record these onto a blank CD and return to the Data Co-ordinating Centre together with the Discharge Form.
- **K**: **Blood tests required are**: HB, Hct, Total WBC, Neutrophil Count, Platelet Count, Sodium, Potassium, Creatinine, Glucose, Calcium, CPK, LDH, ALT, Troponin, Thrombin Time, aPTT, INR and Fibrinogen.
- **L**: The Discharge Form contains a scored neurological assessment which should be performed around the time of discharge.
- **M**: For consistency, aim to perform the MRI/MRS scan between 7 - 10 days after birth, where possible. Please ensure the TOBY Xe study number is given to the radiologist performing the scan. Refer to MRI standard operating procedure for further details.

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### Schedule for Data Collection

<table>
<thead>
<tr>
<th>Key Event</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>Xenon (if allocated)</td>
</tr>
<tr>
<td>P</td>
<td>Pulsatility Index</td>
</tr>
<tr>
<td>C</td>
<td>Consent Affirmation Interview</td>
</tr>
<tr>
<td>B</td>
<td>Blood tests</td>
</tr>
<tr>
<td>U</td>
<td>Urine output</td>
</tr>
<tr>
<td>R</td>
<td>Respiratory Function/Ventilator Settings</td>
</tr>
<tr>
<td>C</td>
<td>Cooling equipment/ambient temperature</td>
</tr>
<tr>
<td>H</td>
<td>Heart Rate</td>
</tr>
<tr>
<td>N</td>
<td>Neurological Assessment</td>
</tr>
<tr>
<td>E</td>
<td>ECG</td>
</tr>
<tr>
<td>I</td>
<td>Investigations for sepsis</td>
</tr>
<tr>
<td>M</td>
<td>MRI/MRS Scan</td>
</tr>
</tbody>
</table>

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**Note**: TOBY Study Handbook, Version 1; 23/5/2011

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**See overleaf for key**
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1. Introduction

TOBY Xe is a randomised controlled trial comparing two methods of caring for infants with perinatal asphyxia. It compares intensive care including whole body cooling with intensive care including whole body cooling and inhaled xenon gas.

This handbook describes practical aspects of the trial. For a detailed description of the background to the study, the scientific aspects of the study and the analysis plan, please see the TOBY Xe Protocol.

1.1 Overview of the study design

More information is available in later sections of this handbook and in the TOBY Xe protocol.

Eligibility and exclusions

Babies are eligible if they are born at 36-43 weeks gestation with evidence of perinatal asphyxia (see Section 2.1 for details of the eligibility criteria). They must be less than 12 hours old at the time they join the study.

Recruitment and randomisation

Eligible infants will be assigned either to “intensive care with cooling” or “intensive care with cooling and inhaled xenon gas” by a web based randomisation service.

Interventions and clinical management

Intensive care with cooling group: intensive care with whole body cooling, with rectal temperature maintained at 33.5 ± 0.5°C.

Intensive care with cooling group and inhaled xenon gas: neonatal intensive care with rectal temperature maintained at 33.5 ± 0.5°C and 30% inhaled xenon gas for 24 hours delivered through a purposely designed TOBY Xe ventilator.

Primary outcome

The primary outcome will be: reduction in Lac/NAA ratio on magnetic resonance spectroscopy or preserved fractional anisotropy measured by TBSS on diffusion weighted magnetic resonance imaging.

Secondary outcomes

These include measures of short-term complications, including death rates.

1.2 Co-ordination of the study

Central co-ordination

TOBY Xe Data Co-ordinating Centre
National Perinatal Epidemiology Unit
Institute of Health Sciences
Old Road
Oxford
OX3 7LF

Tel: 01865 289 732
Fax: 01865 289 740
Email: tobyxe@npeu.ox.ac.uk

Out of hours: 0800 138 5451 for call centre back up
2. Eligibility, Consent And Recruitment

2.1 Inclusion criteria

Eligibility for TOBY Xe requires three sets of criteria to be satisfied (A, B and C).

A. Infants 36 to 43 weeks gestation admitted to the NICU with at least one of the following:

- Apgar score of ≤5 at 10 minutes after birth
- Continued need for resuscitation, including endotracheal or mask ventilation, at 10 minutes after birth
- Acidosis defined as either umbilical cord pH or any arterial, venous or capillary pH within 60 minutes of birth <7.00
- Base Deficit > 15 mmol/L in any blood sample within 60 minutes of birth (arterial, venous or capillary blood)

Infants that meet criteria A will be assessed for whether they meet the neurological abnormality entry criteria (B) by trained personnel:

B. Moderate to severe encephalopathy, consisting of all of the following:

- An altered state of consciousness (lethargy, stupor or coma)
- Hypotonia
- Abnormal reflexes (may include oculomotor or pupillary abnormalities, an absent or weak suck or Moro response)

Infants that meet criteria A & B will be assessed by aEEG (read by trained personnel):

C. At least 30 minutes duration of amplitude integrated EEG recording that shows moderately abnormal or suppressed background aEEG activity or seizures

Every effort should be made to ensure cooling is started within 3 hours and entry to the study is completed before 6-8 hours of age, because there may be rapid attenuation of neuroprotection with a delay in the start of cooling. Infants must be <12 hours of age at the time of randomisation.

2.2 Exclusion criteria

If any of the following apply, the infant must be excluded from the study:
• Treatment with cooling started beyond 6 hours of age
• Infants expected to be >12 hours of age at the time of randomisation
• Infants with ventilator requirements >60%, or requiring HFOV, Nitric Oxide or ECMO therapy
• Attending clinician considers infant not suitable to participate because of major congenital abnormalities, such as diaphragmatic hernia requiring ventilation, or congenital abnormalities suggestive of chromosomal anomaly or other syndromes that include brain dysgenesis
• The infant’s condition appears terminal

2.3 Guidance on the aEEG

The aEEG to determine eligibility will be performed within the Treatment Centre by trained personnel. The aEEG may be performed from one hour of age. If subsequently an abnormal aEEG is recorded before 12 hours of age, the infant then becomes eligible for recruitment.

The aEEG should not be performed within 30 min of IV anticonvulsant therapy as this may cause suppression of EEG activity. In particular, high dose anticonvulsant therapy (e.g. >20mg/kg phenobarbitone) should not be given prior to performing the aEEG.

Guides, tutorials and examples for users of Cerebral Function Monitoring may be found at the following website: [http://cfmusers.wikispaces.com/](http://cfmusers.wikispaces.com/)

2.4 Inborn and Outborn babies

Infants will be recruited both from centres which provide the Xenon treatment ("Treatment Centres"), and from outlying hospitals that refer to these hospitals. All babies recruited to the study, whether they are in the Xenon or non-Xenon group, will be cared for in Treatment Centres. All babies recruited to TOBY Xe from referral hospitals will therefore be transferred to Treatment Centres.

Procedures for recruiting babies at Treatment Centres and referral centres are slightly different (See Sections 2.7 and 2.8).

2.5 Mild encephalopathy

The assessment of the baby may not confirm eligibility (i.e. there is only mild encephalopathy). If the baby is still in the referring hospital, it should be managed according to the usual practice of that hospital. If the baby has already been transferred to the Treatment Centre (for example, clinical eligibility criteria met but aEEG is normalising) the attending senior clinician will determine the most appropriate management plan for the baby.

2.6 Consent

Consent for the study should be seen as a continuing process with several stages:

1. Preliminary information about perinatal asphyxia and therapeutic hypothermia will be provided by the clinical team caring for the baby at birth.
2. More detailed information about the study (both the written Parent Information Leaflet and spoken) will be given by the transfer team or the attending team at the Treatment Centre. Face to face, written informed consent will be obtained if it is possible to do so. If neither parent can be present at the Treatment Centre, telephone consent will be obtained by a clinician based in the treatment centre. This will be witnessed by a second member of staff and the Telephone Consent Form completed. Both members of staff will sign the Telephone Consent form and this will be countersigned by the parent(s) at the earliest opportunity when they arrive at the treatment centre.
3. Once a baby has been randomised into the study, information about the trial should continue to be given as and when the parents request it. An appointment with the senior clinician responsible for the baby’s care should be made as soon as possible, ideally within 24 hours, for the parents to discuss participation in detail. At this stage it should be made clear that the parents remain free to withdraw their baby from the study at any time but that if they do withdraw their baby, we would ask them for consent to an MRI examination and to continue follow up.

4. A senior investigator will be available at all times to discuss concerns raised by parents or clinicians during the course of the trial, for example (a) when parents or clinicians at a Treatment Centre wish to withdraw the intervention allocated (b) giving advice to clinicians who are asked by parents to provide Xenon outside the trial (c) giving advice to parents who do not wish to participate in the trial.

5. Information about the study will continue for parents after their baby leaves the neonatal unit or dies. A regular newsletter will be produced giving parents up to date information about the study until it has finished. Experience with other studies in this area suggests that parents of babies who die may want to receive these newsletters, and all parents will be offered the opportunity to receive this information if they wish to. Their preference should be recorded in the Discharge Form (Question 14).

2.7 Recruitment of babies born in Treatment Centres

The baby’s condition should first be stabilised and then assessed for potential eligibility for TOBY Xe. If the baby is considered eligible for TOBY Xe on clinical grounds including the aEEG, the attending clinician should:

1. Inform the parents about perinatal asphyxial encephalopathy and that there is a study, the TOBY Xe study, that may be of interest to them.
2. Inform the TOBY Xe clinician, who will discuss the trial with the parents in more detail and give them the Parent Information Leaflet.
3. If the parents give consent for their baby to participate a Consent Form should be completed and signed by the mother (or father, if married).
4. If the TOBY Xe clinician is not available, the most senior attending clinician can seek consent (this can be a specialist registrar who has received training about the study and the consent procedures from the Lead Investigator).
5. If consent is given, the baby can be randomised into the study (see Section 3).
6. Start the allocated treatment as soon as possible.
7. For babies who are not eligible for the trial because of mild encephalopathy, the parents will be informed that the baby is not eligible but will continue to receive the same standard of care as the infants in the trial.

2.8 Recruitment of babies born in referring hospitals

The baby’s condition should first be stabilised and then assessed for potential eligibility for TOBY Xe. If the baby is considered eligible for TOBY Xe on clinical grounds (criteria A and B; see Section 2.1) and meets none of the exclusion criteria (see Section 2.2) the attending clinician should:

1. Telephone the Neonatal Transport Service (NTS - 020 7407 4999). They will check for the availability of a Xenon cot at one of the Treatment Centres, preferably the closest centre, and discuss with the TOBY Xe clinician whether they can accept the referral.
2. If a Xenon cot is not available, the baby should be treated according to normal hospital practice. Please do not discuss the TOBY Xe study with the parents in this case.
3. If NTS confirms a Xenon cot is available, the local clinicians should give the parents basic information about perinatal asphyxial encephalopathy and that there is a study, the TOBY Xe study, that may be of interest to them.
4. When NTS arrive they will again assess for eligibility and discuss the TOBY Xe study with the parents. The Parent Information Leaflet will be provided. Assent will be obtained for the baby to be transferred to the TOBY Xe Treatment Centre and this transfer will be carried out by NTS.

Treatment with cooling according to local protocol should start as soon as possible, and must have started within 6 hours of birth for eligibility. It is not necessary to delay the start of cooling to recruit a baby into TOBY Xe.

When the infant is admitted to the TOBY Xe Treatment Centre, the following steps will be taken:

1. The baby will be assessed for trial eligibility, including performing the aEEG.
2. During the course of this assessment the TOBY Xe clinician will be discuss the study with the parents in more detail. This may be over the telephone if necessary.
3. If eligibility is confirmed, the parents will be asked for consent for their baby to participate:
   - A Consent Form should be completed and signed by the mother (or father, if married) if the parents can be present at the treatment centre.
   - If neither parent can be present at the treatment centre, telephone consent will be obtained. This will be witnessed by a second member of staff and the Telephone Consent Form completed. Both members of staff will sign the Telephone Consent form, and this will be countersigned by the parent(s) at the earliest opportunity when they arrive at the treatment centre.
4. The baby should then be randomised into the study (see Section 3).
5. The allocated treatment should begin as soon as possible.

2.9 Requests for treatment with xenon gas outside the study

The parents may decline study entry and request treatment with xenon gas for their baby. As the use of cooling together with xenon gas cooling is experimental, its use outside this study will not be permitted.
Recruitment of a TOBY Xe Baby Born in a Referring Hospital

Eligibility criteria sections A and B are met, and no exclusion criteria apply. Consider starting cooling treatment.

Call NTS. Is a Xenon cot available?

- Yes
  - NTS provide Parent Information Leaflet and obtain parental assent for baby to be transferred to Treatment Centre.
  - Yes
    - Perform aEEG: Eligibility criteria Section C met?
      - Yes
        - The TOBY Xe clinician should discuss the study with the parents by telephone.
      - No
        - Start the allocated treatment as soon as possible.
  - No
    - Baby is not eligible for the study. Standard care should continue and cooling initiated, if appropriate.

Was cooling started within 6 hours of age?

- Yes
  - Randomise BABY. This MUST be done before 12 hours of age.
- No
  - Baby cannot be entered into study. Continue standard care, cooling baby if appropriate.

Notes:

- a) Inclusion criteria are listed in the Protocol (p14) and Handbook (p7).
- b) Exclusion criteria are listed in the Protocol (p14) and Handbook (p7).
- c) Consider starting cooling according to the TOBY Register Protocol. There is no need to delay cooling in order to enrol a baby in TOBY Xe (see Handbook Section 4.3)
- d) Cooling treatment must have been initiated within 6 hours of birth for a baby to be enrolled into TOBY Xe
- e) Telephone consent process must be witnessed by another member of staff
- f) Randomise using the website found at https://rct.npeu.ox.ac.uk/tobyxe
- g) Every effort should be made start cooling within 3 hours and complete study randomisation within 6-8 hours of age. There may be a rapid attenuation of neuroprotection should there be a delay in the start of treatment.
Recruitment of a TOBY Xe Baby Born in a Treatment Centre

Eligibility criteria sections A and B are met, and no exclusion criteria apply. Consider starting cooling treatment.

Perform aEEG: Eligibility criteria Section C met?

Yes

Inform parents about the study, and provide the Parent Information Leaflet. Start cooling if not already done.

No

Baby is not eligible for the study. Standard care should continue and cooling initiated, if appropriate.

Was cooling started within 6 hours of age?

Yes

Obtain written informed consent using the Consent Form and Parent Information Leaflet and complete Sections 1-3 of the Entry Form.

No

Randomise baby. This MUST be done before 12 hours of age.

Start the allocated treatment as soon as possible.

Notes

a) Inclusion criteria are listed in the Protocol (p14) and Handbook (p7).

b) Exclusion criteria are listed in the Protocol (p14) and Handbook (p7).

c) Consider starting cooling according to the TOBY Register Protocol. There is no need to delay cooling in order to enrol a baby in TOBY Xe.

d) Cooling treatment must have been initiated within 6 hours of birth for a baby to be enrolled into TOBY Xe.

e) Randomise using the website found at https://rct.npeu.ox.ac.uk/tobyxe

f) Every effort should be made to start cooling within 3 hours and complete study randomisation within 6-8 hours of age. There may be a rapid attenuation of the neuroprotective effect should there be a delay in the start of treatment.
3. Randomisation

When a baby’s eligibility has been confirmed and informed consent has been obtained, the baby can be randomised into the study. This is achieved by using the web based randomisation service (based at the National Perinatal Epidemiology Unit in Oxford).

3.1 Randomisation Procedure

Please follow these steps:

1. Complete Sections 1 to 3 of the TOBY Xe Entry Form.
2. Log into the randomisation program (found at: https://rct.npeu.ox.ac.uk/tobyxe) by selecting your centre from the drop down list and entering your username and password. The TOBY Xe Co-ordinating Centre will have supplied you with a password for the centre (it is case sensitive).

3. Choose ‘Randomise Baby’ to perform a new randomisation.

4. Answer the questions as shown on screen using the information given on the Entry Form, then click the ‘Continue’ button. If any information on the page is incomplete you will be returned to the first page and the missing or incorrect information will be shown in red.
5. The second page asks you to confirm that you wish to randomise the baby. Click ‘Complete’ to continue. If the randomisation is successful you will be given the baby’s study number and allocated treatment. Please print this page for your records.

If you have made an error when completing the web form, choose ‘Amend’ to correct your entry.

6. Complete Section 4 of the Toby Xe Entry Form, recording the baby’s study number and allocation.

7. Write the baby’s study number on a TOBY Xe Participation label and attach it to the baby’s hospital notes.

8. Commence the allocated treatment as soon as possible. If the baby has been allocated Xenon, this should be started as close as possible to the induction of hypothermia and not later than 12 hours after birth.

9. Once the baby is stabilised, complete the remainder of the Entry Form.

10. Start recording information about the baby’s course on the TOBY Xe Daily Log (use Day 1 to Day 4 in order).

11. Send the completed Entry Form to the TOBY Xe Data Co-ordinating Centre using the FREEPOST envelope provided.
3.2 Problems with randomisation

If you have problems randomising a baby and need assistance, within office hours in the first instance please contact the co-ordinator on 01865 289 732. Out of hours, if your query is urgent please dial 0800 138 5451 to contact a UK call centre that can assist you further with the randomisation. This call centre system for randomising babies is a back up and will always be available, day or night.

3.3 The study number explained

Each of the 130 babies to be randomised into TOBY Xe will be allocated a 4 digit study number. The first 3 digits reflect the order in which babies were randomised, starting at 101 and then issued consecutively by the randomisation program. The fourth digit is a ‘check digit’, which makes it easier to check if a study number has been written down incorrectly.

Please record the baby’s study number wherever it is requested on the data collection forms.

4. Study Interventions

4.1 Intensive care and cooling group

Active cooling to a rectal temperature of 33.5°C will be maintained for 72 hours with a controlled cooling device (usually this will be servo controlled) and following the standard TOBY Register protocol. The rectal temperature will be monitored continuously and recorded hourly on the Daily Log forms for the first 80 hours after randomisation.

4.2 Intensive care with cooling and inhaled xenon group

In addition to active cooling according to the TOBY Register protocol, infants will receive 30% inhaled xenon for 24 hours through the TOBY Xe xenon ventilator following a specific protocol (refer to the Quick Guide to Xenon Ventilation Procedures manual).

4.3 Cooling for infants born in referring hospitals

For infants born in referring hospitals cooling should be started according to the TOBY Register protocol. The infants are nursed prior to transfer with the overhead radiant warmer turned off. During transport the infant should be nursed in a transport incubator. Heart rate and oxygen saturation and the rectal temperature should be monitored continuously and the incubator heater turned on and adjusted if necessary to maintain the rectal temperature between 33 - 34°C. Cooled gel packs may be placed around the infant, if necessary, to maintain the target temperature. Blood pressure should be monitored either continuously if an intra-arterial catheter has been inserted or every 15 minutes by oscillometric technique until arrival at the Treatment Centre.

4.4 Rewarming procedures following the end of the cooling period (72 hours)

When cooling is concluded (72 hours after randomisation, or earlier if clinical circumstances dictate) the rectal temperature should be allowed to rise by no more than 0.25°C per hour, to 37±0.2°C. The thermostat set point of the Tecotherm system can be adjusted as needed, to rewarm the infants. The infant’s temperature must be carefully monitored for at least 4 hours to prevent rebound hyperthermia, as this might be detrimental.
4.5  Xenon ventilation

For detailed guidance on the proper use of the modified Xenon ventilator, refer to the Quick Guide to Xenon Ventilation Procedures manual. Staff must have received appropriate training on the modified Xenon ventilators prior to their use.

4.6  Temporarily halting Xenon treatment

Due to other gases in the oxygen-air mixture, in particular nitrogen, the maximum achievable FiO₂ would be 60%, given with 30% Xenon. The following applies:

- During a baby’s 24 hours of xenon administration, in case of acute deterioration of the baby xenon may be stopped to allow immediate resuscitation or FiO₂ to be increased over 60%
- If the baby’s condition allows, xenon may be re-started after interruption unless the interruption exceeds 6 hours
- Xenon administration will be stopped 24 hours after it was first introduced even if administration is interrupted
- Xenon will be given at 30% or not at all

4.7  Discontinuing Xenon treatment

Treatment with inhaled xenon may be discontinued if the following occur:

- Parents request that their infant is withdrawn from the trial. This request should be discussed with the Centre Lead Investigator whenever possible.
- Attending clinician stops treatment with inhaled xenon. Reasons for early discontinuation of xenon might include clinical, EEG and imaging evidence of severe, irreversible brain injury, or inability to maintain adequate cardiorespiratory support.
- Baby requires treatment with inhaled Nitric Oxide or ECMO

If the parents or the attending paediatrician elect to discontinue treatment with inhaled xenon, then the xenon ventilator should be replaced by a standard ventilator.

4.8  Use of cuffed neonatal endotracheal tubes

For this study it may be necessary to use a cuffed endotracheal tube to avoid excessive loss of Xenon gas. Therefore babies should either be electively intubated using a cuffed tube if the baby is allocated cooling with Xenon or observe for Xe gas usage (displayed on the analyser) and reintubate if the usage is greater than 100 ml/min.

The Rusch 3.5 mm cuffed endotracheal tube is a high volume low pressure cuff. The cuff is inflated through the special porthole with 1-2 mls of air using a 2 ml syringe. Cuff pressure should be checked using a manometer or with the single patient use cuff pressure indicator. The manometer has a ‘green’ safe range (20-25 cm H2O) and the cuff pressure should be adjusted to that range. The cuff pressure should be checked and recorded every 4 hours. It is important that the cuff is deflated by withdrawing the air from the cuff with the syringe before the tube is repositioned or removed.

Steps to be taken when using the Rusch 3.5 mm cuffed endotracheal tube:

1. Prior to intubation the cuff function should be tested by inflation with 2ml air and deflated by withdrawing the air
2. Intubate according to standard practice. Do not insert the ETT further than the black marker line
3. Inflate cuff with 1-2 ml of air with syringe (or cuff inflator/manometer if available)
4. Attach single patient use cuff pressure indicator to the connector cuff inflation port
5. Check the cuff pressure is at the appropriate level as indicated by the green mark in the indicator (or that the pressure is in the 'green range' in the manometer)
6. Check and record that cuff pressure is in the target range every 4 hours
7. Remember to deflate the cuff if the position of the ETT has to be changed or before the ETT is removed

5. Clinical Care

Treatment Centres will provide a uniform standard of clinical care for all babies in the study, to minimize potential bias that could arise from differential use of co-interventions.

5.1 Seizure therapy

This may be according to local practice, but where possible, seizures, whether noted on aEEG or on clinical signs, should be treated with phenobarbitone 20 mg/kg loading dose over 20 min IV repeated if necessary after 40-60 minutes, followed by 5-10 mg/kg/day. If seizures persist, intravenous midazolam 100 µg/kg followed by 30-100 µg/kg/hour may be added. If further treatment is considered necessary, lignocaine, clonazepam or lorazepam may be used. The time of onset of seizures and all anticonvulsant therapy should be documented on the Daily Log.

5.2 Anti-oedema therapy

Infants in the study must not be treated with steroids or mannitol.

5.3 Analgesic and sedative therapy

Stress may have adverse effects in asphyxiated infants and may influence the therapeutic effect of hypothermia. In addition, neonatal intensive care procedures may cause considerable stress to infants and cooling may also be associated with stress. Signs of distress include tachycardia, facial grimacing and irritability. A heart rate consistently above 100 bpm in cooled infants strongly suggests that the infant is distressed. All ventilated infants should be sedated with intravenous morphine, loading dose 50 µg/kg over 30 minutes followed by 10-40 µg/kg/hour. Non-ventilated infants who appear distressed should also be treated similarly.

5.4 Fluid Management

Renal function is commonly impaired following severe perinatal asphyxia. The infant’s weight, blood creatinine and electrolytes and urine output will guide fluid management. As a guide infants will require about 40-60 ml/kg/day. Infants in renal failure should receive a total of 30 ml/kg/24 hours plus any measured losses. Boluses of 0.9% saline may be required to avoid hypovolaemia if the infant develops diuresis or if vasodilatation occurs during rewarming. Oral feeds may be given as directed by the attending clinician.

5.5 Ventilation

Almost all study infants will initially require mechanical ventilation. Ventilatory care will be managed according to the treating centre standard policy. High frequency oscillation should be changed to standard positive pressure ventilation before randomisation. If this is not possible the infant is excluded from the trial. Blood gases will guide ventilatory requirements; as a guide PaO2 should be maintained between 6-10 KPa and the PaCO2 between 5-7 KPa.
5.6 Cardiovascular support

Alterations in heart rate and blood pressure are common during hypothermia. In general the heart rate is reduced and blood pressure increases with a reduction in body temperature. Most infants with a rectal temperature of 33.5°C will have a heart rate around 100 bpm and a mean blood pressure greater than 40 mmHg. A rapid rise in body temperature may cause hypotension by inducing peripheral vasodilatation. Causes of hypotension should be sought and appropriate treatment provided. For this study treatment with volume replacement and inotropes should be commenced if the mean arterial blood pressure is less than 40 mmHg. A bolus of 10 - 20 mls/kg of normal saline should be given initially, and repeated if necessary. If the blood pressure remains low following treatment with normal saline the infant should be treated with dopamine 5-10 µg/kg/min, and/or dobutamine 5-10 µg/kg/min. Persistent failure of response may be treated by increasing the dose of dopamine and dobutamine up to 20 µg/kg/min, followed by the addition of dexamethasone 250 µg/kg and/or adrenaline 0.1-1.5 µg/kg/min.

5.7 Sepsis

Antibiotic therapy may be given if clinically indicated.

6. Data Collection

A document box will be provided to each Treatment Centre containing the data collection forms and essential documents needed to enrol babies. Please inform the Co-ordinating Centre in Oxford if you need more copies. Study documentation can also be obtained from the TOBY Xe website (https://www.npeu.ox.ac.uk/toby-xe).

6.1 Entry Form

Sections 1-3 of the Entry Form should be completed after a baby has been assessed for eligibility, the study has been discussed with the parents and they have signed a consent form. The information on this part of the form will be needed when using the randomisation website.

The baby’s study number, the allocation and the time of study entry should be entered in Section 4 of the Entry Form following randomisation.

The remainder of the Entry form should be completed as soon as possible after randomisation, and the form should be sent to the TOBY Xe Data Co-ordinating Centre immediately, using the FREEPOST envelopes provided.

6.2 Daily Log

The Daily Log should be completed every hour for the first 80 hours after randomisation. Once complete, the form should be sent to the TOBY Xe Data Co-ordinating Centre, using the FREEPOST envelopes provided.

6.3 Discharge Form

The Discharge Form must be completed when a baby taking part in TOBY Xe is discharged, transferred or dies. Only information relating to the baby’s stay in your unit should be included on this form. If the baby is being transferred (see Section 8), the receiving hospital will complete a Transfer Form relating to the baby’s stay in that unit.

Burn all available CFM traces and cranial ultrasound scans onto a blank CD and return to the Data Co-ordinating Centre together with the Discharge Form. Please anonymise these results to initials and study number wherever possible.
6.4 Transfer Form

The Transfer Form should be sent as part of a ‘Transfer Pack’ when a TOBY Xe baby is transferred. The receiving hospital will be asked to only enter information into the Transfer Form that is related to the baby’s stay in their unit. If the baby is transferred again for whatever reason, the TOBY Xe Co-ordinating Centre should be informed, and will provide a Transfer Pack to the new hospital.

6.5 Death Form

A Death Form should be completed for all babies that die whilst enrolled in the Toby Xe trial and returned to the Toby Xe Data-coordinating centre as soon as possible. All deaths will be reviewed by the Chief Investigator. If an autopsy report or death summary is available, please send a copy of this to the Data Co-ordinating Centre using one of the FREEPOST envelopes. Reports should be anonymised and identified by initials and study number only.

6.6 Severe Adverse Event/SUSAR form

This form should be completed for all unexpected Serious Adverse Events and SUSARs, and faxed to the Co-ordinating Centre within 24 hours of staff becoming aware of the event. Please remember to take a photocopy for your records and return the original form to the Co-ordinating Centre in one of the Freepost envelopes.

The SAE/SUSAR Form should not be used for serious adverse events which are ‘expected’. Refer to the Protocol for a list of expected serious adverse events.

6.7 Device Incidents Form

Any incidents involving the Xenon ventilator or associated patient breathing circuit should be reported on this form as soon as possible following the event, and faxed to the Data Co-ordinating Centre in Oxford using the fax number specified. Device incidents will be evaluated on a case by case basis and action taken as appropriate.

6.8 Incident Form

This form should be used to report trial related deviations and serious breaches (see Section 10).

7. Neuroimaging

7.1 Ultrasonography

Cerebral ultrasound should be performed within the first 24 hours after entry to the study and repeated every 24 hours until 80 hours after randomisation. Trained personnel should perform cerebral ultrasonography.

Standard views in coronal and sagittal planes, through the anterior fontanel, can be supplemented with views through the posterior fontanel and pterion, bilaterally, if considered necessary by the examiner.

Cerebral doppler measurement of the Pulsatility Index, of either the anterior or middle cerebral artery, should be performed at 24 hours. Further measurements will be according to local practice.

Digital copies of all standard views should be retained for later review, blinded to study group.
7.2 Magnetic Resonance Imaging

An MRI should be carried out within 15 days from birth. Details are provided in the trial-specific MRI scan standard operating procedure. Local policies for caring of infants requiring MR should be followed.

Please ensure that the radiologist performing the MRI scan is provided with the baby’s study number and date of birth, as it is very important that scans are attributed to the correct study number for analysis.

8. Transfers

8.1 Transfer of a baby recruited to TOBY Xe from your unit

If a baby that is taking part in TOBY Xe is transferred from your unit to another hospital, the TOBY Xe Data Co-ordinating Centre will need to be informed so that all babies can be followed up until discharge from hospital or death. Please follow these procedures:

1. Complete the Discharge Form when the baby is transferred, filling in box ‘b’ (transferred to another hospital) in the Outcome section and giving as many details as possible about the receiving unit. **Include only information about the baby’s stay in your unit on this form.** This form should be returned to the TOBY Xe Data Co-ordinating Centre as soon as possible.
2. A Transfer Pack should accompany the baby to the receiving hospital. This contains a Transfer Form, on which details of the baby’s stay in the receiving hospital will be recorded.
3. Before the baby is transferred, fill in the baby’s identifying details and TOBY Xe study number on the Transfer Pack.
4. Send the Transfer Pack with the baby when it is transferred.

8.2 Transfer of a baby recruited to TOBY Xe into your unit

A baby that has been recruited to TOBY Xe may be transferred to your hospital. If this happens, the TOBY Xe Data Co-ordinating Centre should have been informed by the transferring hospital, and a transfer pack should have been sent with the baby.

Please follow the following procedures:

1. Telephone the TOBY Xe Data Co-ordinating centre to confirm that they have been informed about the baby’s transfer.
2. The baby’s identifying details and study number on the Transfer Pack should have been completed by the transferring hospital. If it has not been completed, please contact the TOBY Xe Data Co-ordinating Centre.
3. When the baby is discharged home, dies or is transferred to another hospital, complete the Transfer Form. **Include only information about the baby’s stay in your unit on this form.** Send the completed form to the TOBY Xe Data Co-ordinating Centre as soon as possible.
4. If the baby is transferred again, please telephone the TOBY Xe Data Co-ordinating Centre to inform them, so that a further Transfer Pack can be supplied to the receiving hospital.
9. Serious Adverse Event Reporting

9.1 Definitions

An **Adverse Event (AE)** is any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product (IMP), whether or not considered related to the IMP.

An **Adverse Drug Reaction (AR)** is an untoward and unintended response to an IMP related to any dose administered. All AEs judged by either the reporting investigator or the sponsor as having reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

An **Unexpected Adverse Reaction (UAR)** is an adverse reaction, the nature or severity of which is not consistent with the applicable product information (Investigator Brochure or SmPC). When the outcome of the adverse reaction is not consistent with the applicable product information, this should also be considered unexpected.

An **Serious Adverse Event (SAE)** is any untoward medical occurrence or effect that at any dose:

- Results in death
- Is life-threatening – refers to an event in which the subject 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
- Requires hospitalisation, or prolongation of existing inpatients' hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect

Medical judgement should be exercised in deciding whether an AE/AR is serious in other situations. Important AE/ARs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

A **Suspected Unexpected Serious Adverse Reaction (SUSAR)** is any suspected adverse reaction related to an IMP that is both unexpected and serious.

9.2 Non-serious Adverse Events

The babies enrolled in this study will be very unwell, and consequently many adverse events will be expected. We are specifically interested in collecting non-serious adverse events during the 24h period that inhalational Xenon is administered. These should be recorded in Section 1.9 of the Daily Log. Adverse events occurring outside of this period, that do not meet the criteria of being serious, do not need to be reported on the data collection forms.
9.3 ‘Expected’ Serious Adverse Events

Serious Adverse Events that are considered expected and which may be due to the combination of hypothermia and xenon are:

- Hypertension (mean blood pressure >85 mmHg)*
- Hypotension (mean blood pressure <25 mmHg)*
- Cardiac arrhythmia: severe bradycardia (heart rate <60 bpm), ventricular arrhythmia.
- Inability to achieve adequate ventilation, despite appropriate adjustment of ventilatory settings

These events will be collected on the data collection forms. It is not necessary to complete an SAE/SUSAR form for expected serious adverse events.

9.4 Serious Adverse Events and SUSARs

If an UNEXPECTED serious adverse event occurs, it should be reported to the TOBY Xe Data Co-ordinating Centre within 24 hours, using one of the Serious Adverse Event Report forms. The TOBY Xe Data Co-ordinating Centre will ensure that the TOBY Xe Data Monitoring and Ethics Committee and the Multicentre Research Ethics Committee are informed.

9.5 Deaths

This group of infants is known to have a mortality rate of about 25%. All deaths will be reported on a specific Death Form which will be reviewed by the Chief Investigator. If a death occurs that is considered unexpected it will be reported as such. All deaths will also be reported annually in the Safety Report.

10. Protocol deviations and serious breaches

10.1 Definitions

A trial related deviation is a departure from the approved trial protocol or other trial document or process, from the principles of Good Clinical Practice (GCP) or from any applicable regulatory requirements. Deviation is a general term and includes planned and unplanned deviations and changes made to avoid immediate harm to trial participants. Trial related deviations can be either serious or non-serious, depending on their impact on the safety of trial participants and the integrity of trial data.

A serious breach is a breach which is likely to affect to a significant degree: (a) the safety or physical or mental integrity of the subjects of the trial or (b) the scientific value of the trial.

10.2 Reporting of trial related deviations or serious breaches

All deviations from the protocol, trial procedures, Good Clinical Practice (GCP), or regulatory requirements should be documented on an Incident Form and returned to the TOBY Xe Co-ordinating Centre as soon as possible after the deviation has been identified.
Definitions of terms used in the Data Collection Forms

**Antenatal care.** If mother had any contact with a health professional at any time during this pregnancy, record ‘Yes’.

**Arrhythmia.** Sinus bradycardia below 80 bpm and other arrhythmias identified on ECG

**Delivery complications.** This can include prolapsed cord, abruption, shoulder dystocia, ruptured uterus, head entrapment etc.

**EDD** Use the best estimate (dates or ultrasound) based on a 40 week gestation.

**Hypoglycaemia (infant).** Blood glucose below 2.6mmol/litre

**Hypotension (infant).** Persistent mean blood pressure of < 40mmHg

**Late onset sepsis (>72 hours after birth) confirmed by blood or CSF culture.** Any evidence of infection requiring antibiotic therapy which is confirmed on blood culture.

**Major cerebral anomaly.** Including evidence of parenchymal haemorrhage as determined by ultrasound, ventricular dilatation (defined as >97th centile for gestational age) or the presence of porencephalic cysts or cystic leukomalacia.

**Meconium aspiration syndrome.** The presence of meconium stained liquor at birth and severe respiratory distress within 1 hour of birth and compatible X-ray changes.

**Necrotising enterocolitis.** Any evidence of abdominal distension, bilious aspirates and/or bloody stools (whether or not confirmed by X-ray or laparotomy) sufficient to change management.

**Pregnancy complications.** This can include: pre-eclampsia, maternal seizure, thyroid disorder, diabetes, placenta praevia, known illicit drug use etc.

**Pulmonary airleak.** Any radiologically confirmed airleak (other than pneumothorax) serious enough to affect management (including pulmonary interstitial emphysema, pneumopericardium, pneumoperitoneum and pneumodiastinum).

**Pulmonary haemorrhage.** Copious bloody secretions with clinical deterioration requiring change(s) in ventilatory management.

**Persistent pulmonary hypertension.** Severe hypoxaemia disproportionate to the severity of lung disease and evidence of a right to left shunt.

**Respiratory support.** Use of mechanical ventilation, CPAP or supplementary oxygen. When recording, count part of any day as 1 day.

**Seizures.** Clinical or subclinical, identified on CFM /EEG
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