TOBY Children Study

School age outcomes following a newborn cooling trial

TOBY Protocol

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Background

Encephalopathy following perinatal asphyxia occurs in about 2-3 full or near full term newborn infants per 1000 births in the UK and is associated with a high risk of death or disability in survivors (1). Until recently, treatment of infants with perinatal asphyxial encephalopathy consisted of maintaining physiological parameters within the normal range and treating seizures with anticonvulsants. No specific treatments were available.

Treatment with hypothermia

Following promising experimental and clinical pilot studies, randomised controlled trials of moderate hypothermia following asphyxia in newborn babies were started. The results of published randomised controlled trials suggest that hypothermia is associated with a modest reduction in death or severe disability at 18 months of age: relative risk 0.76 (95 CI, 0.65-0.89) (2-4). However, estimation of neurodevelopmental outcome at this early stage may be altered on later follow-up, when more precise assessment is possible (5). Although it is likely that severe neuromotor disability will have been correctly identified, less severe impairments are not reliably assessable at 18 months. A recent study of low birth weight infants has established that assessment later in childhood, at about 6-7 years of age, is necessary for accurate comprehensive evaluation of cognitive function, behaviour and learning, fine motor development, attention and psychosocial health, and this is likely to be the case also for other infants with a high risk of cerebral injury (6). Impairments in these functions are a considerable burden to children, their families, and the health care, social and educational services.

Long term outcome following perinatal asphyxial encephalopathy

There have been few studies of infants with encephalopathy which describe outcome for the survivors at school age. In one study of children born in the late 1970s/early 1980s who were followed up to school age, those who had mild encephalopathy were indistinguishable from other neonatal unit admissions or classmates; children with severe encephalopathy either died or survived with severe disability; of those in the moderate encephalopathy group, 5% died and 15% had severe
disability. However, the remaining children with moderate encephalopathy had lower scores of cognition and executive functions compared to the mild encephalopathy and control groups. The authors concluded that following moderate perinatal asphyxial encephalopathy, children without motor disability were at risk of reduced educational functioning (7).

More recently, in a study of children following moderate neonatal encephalopathy in the Trent Region of the UK (8) scores of cognitive and executive ability at school age were reduced in children without motor disabilities and were worse in those with the more severe clinical course in the neonatal period when compared with classmates (Fig 1). These differences were reflected in poorer scholastic attainment in independent National Attainment Tests (Fig 2).

Fig 1: Mean differences in Standardised Scores between children with moderate NE - with (a) less severe and (b) more complex clinical courses and classmates
Therefore children who escape cerebral palsy may still have significant problems in the domains of learning, cognitive function and behaviour which were undetected at 18 months but become apparent at school age. Indeed it is likely that these lesser impairments, which represent the milder end of the clinical spectrum, might be more amenable to treatment with moderate hypothermia than cerebral palsy. Although this still represents improved outcome, the need for educational support is likely to be a key variable in the economic evaluation of the effectiveness of moderate hypothermia. There is also the risk that hypothermia results in improved survival free of cerebral palsy but with increased risk of these important adverse outcomes.

**The TOBY Study**

The TOBY Study was an MRC funded randomised controlled trial of whole body hypothermia for the treatment of perinatal asphyxial encephalopathy. The severity of encephalopathy at randomisation was assessed by amplitude integrated EEG. Recruitment started on December 2002 and completed at the end November 2006, when 325 infants had been enrolled. The primary outcome measure of the TOBY Study was the rate of death or severe disability at 18 months of age. The follow-up rate was >99%. Although the reduction in the combined rate of death and severe disability was not significant (RR: 0.86 [95% CI 0.68-1.07]; P=0.17), cooled infants had an increased rate of survival without neurological abnormality (RR 1.57 [95% CI 1.16-2.12]; P=0.003) (9).
The TOBY Study is the largest trial of therapeutic hypothermia in infants, and therefore provides a unique opportunity to determine more precisely the long term consequences of intervention with hypothermia following perinatal asphyxia, irrespective of the provisional outcomes at 18 months. The earliest we can make robust assessments of cognitive, executive and educational functioning is at 6-7 years.

**Importance of study**

Perinatal asphyxia may have long term consequences on neuropsychological functioning, which may be altered by therapeutic hypothermia. Currently, there is no information on the effect of hypothermia on outcome beyond 18 months of age. The NIH and other experts have expressed concern that therapeutic hypothermia may be introduced into clinical practice without any knowledge of whether the apparent initial benefits are maintained in the longer term, such as at 6 years of age (10, 11). An effective treatment for reducing brain injury following perinatal asphyxia would have major clinical benefits. If longer term follow-up confirms that mild systemic hypothermia is a safe and effective treatment it will be adopted into clinical practice in the NHS and will also be applicable in many other countries, since it is relatively simple and inexpensive to carry out. Hypothermia is already routinely offered following asphyxia in many countries and in the UK mainly on the basis of the results of early outcomes from two trials; in the first two and a half years since the TOBY Study completed enrolment, more than 470 infants from 40 hospitals who received treatment with cooling have been reported to the UK TOBY Cooling Register, which was set up by the TOBY investigators to audit treatment with hypothermia in the UK (12). If hypothermic treatment were shown not to be effective or to be harmful in the longer term, indiscriminate use of this treatment may need to be discouraged.
Study design

Aim

The aim of this study is to determine the effect of therapeutic hypothermia following perinatal asphyxia on neurological and neuropsychological outcomes and also to assess academic attainment and any additional health, societal or educational costs associated with changes in outcome as a result of the intervention.

Summary

We will evaluate the neurological, neuropsychological function and educational attainment of surviving participants of the TOBY Study at 6-7 years of age. The study will commence in September 2009 and continue for 48 months (see timeline in appendix 3). We will use a series of neuropsychological tests and a formal neuromotor assessment to assess and classify disabilities. The primary outcome measure will be survival with an intelligence quotient (IQ) ≥85. Secondary outcomes will include scores on general cognitive and executive function tests, parent and teacher reporting of behavioural measures, scholastic attainment, patterns of disabilities as well as detailed economic and healthcare usage evaluation. We will use standard statistical tests to look for significant differences in these measures between children in the cooled and control groups.

Study plan

Of the 325 participants of the TOBY Study, at 18 months 201 survivors were located in the UK, 20 in Hungary, 13 in Sweden, 2 in Finland and 3 in Israel. We will obtain contact details for these children from our TOBY Study database, the NHS Information Centre and other relevant methods as appropriate. Their parents/carers will be offered a follow up assessment at the local school or an alternative suitable setting. Our intention is that all assessments are carried out by one pair of trained assessors in each country, if possible; it may be necessary to use additional assessors depending on the workload. The assessors will be unaware of trial allocation. The assessment will comprise a structured neurological examination, and a neuropsychological assessment. The assessment will capture areas of neurological, sensory, cognitive,
memory, attention and executive function which represent areas likely to be affected by perinatal asphyxia. Parents will be asked to complete questionnaires which will cover the areas of behaviour, everyday memory, health care usage and demographic information. Teachers will be asked to complete a questionnaire to evaluate educational attainment and behaviour.

**Description of measures to be used:**

**Neurological examination**

A structured neurological examination to detect signs of cerebral palsy and minor neurological dysfunction will be performed (13, 14). Neurological signs will be scored and disabilities classified according to standardised definitions (Appendix 1) (15, 16). Scores will be obtained using the Classification of cerebral palsy (as at 2 years), gross motor function (GMFCS) (17) and manual functions (Manual Ability Classification System [MACS]; www.macs.nu) (18).

**Wechsler Preschool and Primary Scale of Intelligence**


The Wechsler intelligence tests are among the most-widely used and rigorously standardised tests of cognition that sample abilities in several domains. The WPPSI-III (19) (UK 2004 standardised observations for UK children; relevant national standardised observations for other children) evaluates general cognitive performance over the age range 2 years 6 months to 7 years 4 months. The WPPSI-III has a core of subtests achievable by children with minimal motor skills so it can be administered to children with some motor disabilities. The easiest items on the WPPSI-III can capture performance more than 3 standard deviations below the average of children as young as 4 years, which at age 6 years offers a wide choice of items that could be passed by all but the most severely disabled children. WPPSI-III outputs comprise a general measure of IQ (FSIQ) with Verbal (VIQ), non-verbal Performance (PIQ), and Processing Speed (PSQ) quotients together with an optional language score (Global Language Composite) (GLC) that measures receptive and expressive
language. The WPPSI-III yields age-standardised scores with a mean Intelligence Quotient of 100 and a standard deviation of 15. Since the verbal component is very language dependent and language scales have not been re-standardised in non-English populations, and a number of the children may not be English speakers, we will use the non-verbal score as the IQ component of the primary outcome measure.

We will use WPPSI-III to determine language skills in UK in primary English speaking children.

**NEPSY Second Edition**

(NEPSY II)

Further information about memory, executive function and motor skills will be derived from the administration of subtests selected from the domains of the developmental neuropsychological test battery, the NEPSY II (20). In this test standardised scores can be derived from core items, to which may be added supplemental items to derive further information about performance in these domains. Subtest scaled scores, and percentile rankings (presented in 5 groups) are reported as appropriate. We will administer age-appropriate subtests from the attention and executive functioning, visuospatial processing, sensorimotor, and memory and learning domains.

The following items will be administered by the psychologist:

**Attention and executive functioning subtests:**
- Auditory attention (age 5-16)
- Design Fluency (age 5-12)
- Inhibition age (age 5-16)
- Speeded naming [from the Language domain] (age 3-16)
- Memory and Learning subtests:
- Memory for designs, with delay (age 3-16)

**Memory for faces, with delay (age 5-16)**
- Memory for names, with delay (age 5-16)
- Narrative memory (age 3-16)

Subtests to be administered by the paediatrician comprise:
Sensorimotor subtests:
- Fingertip tapping (age 5-16)
- Manual motor sequences (age 3-12)
- Visuo-motor precision (age 3-12)

Visuospatial processing subtests:
- Arrows (age 5-16)
- Block Construction (age 3-16)
- Design copying (age 3-16)
- Geometric puzzles (age 3-16)
- Route Finding (age 5-12)

Working Memory Test Battery for Children
(WMTB-C) (21, 22)

Working memory is a key component of cognitive performance and has been implicated as a specific outcome following neonatal encephalopathy (8) and hypoxia (23, 24). Working memory assessments at school entry are highly effective in predicting attainment levels in Key Stage assessments, special educational needs status and specific learning difficulties including Dyslexia and Specific Language Impairment. We have selected the Working Memory Test Battery for Children (WMTB-C) to assess components of working memory. This is standardised for children aged 5 to 15 years with norms, which are derived from a sample of 750 children from schools in urban and rural locations in the UK. Unlike most baseline assessments, the WMTB-C assesses children’s capacities to learn, rather than what they have already learned. Also, as the tests follow a span procedure in which children spend very little time failing on tasks (which can be a negative experience for them).

Three subtests from the WMTB-C will be used to provide a measure of each component of working memory. These take 15 minutes to complete and are as follows:

Block recall (to assess non-verbal short-term memory).

Digit recall (to assess verbal short-term memory)

Backwards digit recall (to assess central executive function)
Behaviour

The Strengths and Difficulties Questionnaire (SDQ) (www.sdqinfo.com) will be completed by both parents and teachers. Children will be classified with behaviour disorder when both assessments converge. This well respected scale has been translated into most European languages and there are appropriate translations available for our European centres. Differences in behavioural outcome have been demonstrated for children with encephalopathy compared to controls.(8)

Educational attainment

The UK children will be in year 2 of Key Stage 1 and will be tested by their teachers at age 7 in speaking and listening, reading, writing, maths and science. A copy of the attainment record will be sought from the parents. We will also seek information about any special educational needs (SEN) and the utilisation of SEN provision.

Study Outcome

Primary outcome

The primary outcome measure will be the frequency of survival with an IQ≥85 (an IQ of 85 is 1 standard deviation below the standardised mean IQ of normal children).

This endpoint is the most appropriate outcome measure of a long term follow-up study since the aim of whole body cooling in this group of babies is to provide neuroprotection and an endpoint that evaluates survival as well as IQ is preferable to assessment only of the survivors or allocating an arbitrary IQ to the deaths.

Secondary outcomes

Prespecified Secondary Outcomes:

- Overall IQ (WPPSI III)
- Overall WMTB-C Scale
- Overall SDQ score for behavioural problems
- Overall ADHD Score (Du Paul)
Further outcomes for analysis

We will assess components of all the tests carried out. It is likely that many of the tests will correlate with each other. We will examine for changes in trends in the various assessments to explore the possible influence of therapeutic hypothermia but it is unlikely that any conclusions may be drawn from these secondary analyses.

Study power

We will account for all infants enrolled in the TOBY Study since the death rate is not negligible and may differ between the intervention and control groups. At 18 months follow-up, among the 325 infants recruited, 44% (71/163) in the cooled group survived without neurological abnormality compared to 28% (45/162) in the non-cooled group. We also found that 50% (81/163) of infants in the cooled group survived with a BSID-II Mental Developmental Index score ≥ 85 compared to 37% (60/162) in the non-cooled group. For the intervention to be considered effective in the longer term, we would expect the difference in the proportion of children surviving with an IQ score ≥ 85 at 6-7 years between the two groups to be of similar magnitude (~15%).

Using assumptions based on these data it is possible to examine how the power of a sample size of 325 infants (equal numbers per arm) changes when the underlying event rates vary (Figure 3). The figure shows that a sample of this size would have 80% power to detect an absolute difference of 15% between the two groups with a 2-sided 5% significance level. Each line displays how the power changes for that particular control group event rate compared to cooled group event rates of between 40% and 60%. For example, the blue line (square symbols) charts the change...
in power for a control group event rate of 30%. If the cooled group rate is 45%, then power is 80%, however if the cooled group event rate is higher at 50% then the power is over 90%.

Figure 3: How the power of a total sample size of 325 infants (equal groups) changes in relation to the underlying event rate assumptions with a 2-sided 5% significance level

Statistical Analysis

The primary analysis will be based on comparing all infants allocated to the intervention group with all those allocated to the control group, regardless of what treatment was received, or deviations from protocol. We will calculate the crude relative risk of survival with an IQ score ≥ 85 with corresponding 95% confidence interval (CI). To ascertain whether the treatment effect is consistent across class of severity of encephalopathy, we will perform a test of interaction.

For Normally distributed continuous secondary outcomes we will present the mean difference with 95% CI and analyse using the independent two-sample t test. For skewed continuous secondary outcomes, we will present the median difference (plus 95% CI) and compare groups using rank based methods such as the Mann-Whitney test. For binary and categorical secondary outcomes we will perform Pearson’s Chi-square test.
or Fisher’s Exact test where appropriate and report p values. To quantify the magnitude and direction of the effect we will calculate the crude relative risk with corresponding 95% CI.

We expect sub- or domain scores to be correlated with overall scores e.g. for the WPSSI, NEPSY. We do not plan to perform any formal adjustments for multiple testing, but will present 95% CI with no p-values and employ cautious interpretation.

Secondary analyses will be performed comparing the scores of surviving children who can be assessed (complete case analysis). However we will need to take into account children with missing scores due to (i) logistical reasons, (ii) parental wishes, (iii) children being untested for behavioural reasons or (iv) children being too severely disabled to be assessed. Sensitivity analyses will be performed to assess the robustness of the results by assigning scores to children who could not be tested. Imputing missing values using multiple imputation techniques based on values of the population distribution (taking into account the child’s most important characteristics) would be preferable, but the sample size in this study is too small, hence we will employ various strategies that will be detailed in the Statistical Analysis Plan.

**Economic evaluation (UK)**

We will perform an economic evaluation of whole body hypothermia following perinatal asphyxia. The economic evaluation will be limited to UK children (maximum sample size 193). Cost differences between children allocated to hypothermia and children allocated to normothermia will be identified, measured, valued and combined with long-term outcomes data from this study.

The methods of the economic evaluation are as follows. When the children are 6-7 years of age, parents will be asked to complete a questionnaire which will ascertain their child’s health care resource utilisation over the previous six months. The questionnaire will use previously piloted research instruments based largely upon the MRC funded EPICure study on long term costs following extremely premature birth (25). The data collection will include use of hospital and community health services, social services and education services. Current UK unit costs will be applied to each resource item to value total resource use in each arm of the study. Parents will also be asked to complete the
Health Utilities Index Mark III health survey (26) on behalf of their child. Responses to this health survey will be converted into multi-attribute utility scores using published utility algorithms.

The cost and utility data will be incorporated into a decision-analytic model of the long-term cost-effectiveness of whole body hypothermia being constructed as part of the TOBY study. Long-term cost-effectiveness will be expressed in terms of incremental cost per quality-adjusted life year (QALY) gained, as recommended by the National Institute for Health and Clinical Excellence (NICE). Long term costs and health consequences will be discounted to present values using discount rates recommended for health technology appraisal in the UK. We will use non-parametric bootstrap estimation to derive 95% confidence intervals for mean cost and mean utility differences between the study groups and to calculate 95% confidence intervals for incremental cost effectiveness ratios (27). A series of multi-way and probabilistic sensitivity analyses will be undertaken to explore the implications of uncertainty on the incremental cost-effectiveness ratios and to consider the broader issue of the generalisability of the study results. In addition, cost-effectiveness acceptability curves will be constructed using the net benefits approach (28).

Ethics and research governance

We will seek approval from the National Research Ethics Service before commencing the study. There will be no possibility of harm from participating in the study because: This is not a therapeutic trial; All assessments will be done in a suitable environment and by trained personnel. The National Health Service Information Centre (NHS IC) and the National Strategic Tracing Service (NSTS) will be used for contacting individuals.

Data management and preservation

Data management will be similar to that used in the TOBY Study. Specific case report forms (CRF) will be designed for recording the assessments. The CRFs will have unique personal identification numbers that were allocated to each child at randomisation into the TOBY Study. Data
validity will be ensured by using allowable ranges for data items. This study will also utilise the existing TOBY Study dataset. The original TOBY case report forms and the electronic records are stored at the NPEU. Data are stored and used in accordance with the Data Protection Act 1998 and the Freedom of Information Act 2000. Staff utilising the data will have completed Good Clinical Practice Training. Data resulting from this research will be kept indefinitely, and when no longer required for current work they will be archived securely, according to NPEU archiving arrangements in use at that time.

Public engagement

The TOBY Study (31) worked with consumers throughout its course, with representation from SCOPE (www.scope.org.uk) on the Trial Steering Committee and advice from BLISS (www.bliss.org.uk) with the development of Parent Information Leaflets (PILs), for example. The current study involves children rather than infants, so the MCRN Consumer Panel will be consulted about documentation. The Study Steering Committee membership will include a TOBY parent and consumer representative from SCOPE. Families participating in the TOBY Study were asked at the 18 month follow-up appointment whether they would be interested in taking part in future follow-up studies, should funding be obtained. The response was almost universally positive among those who replied to this question.

The Study will have its own website within the NPEU web pages, where the protocol and other documentation such as PILs will be freely available. There will be links to and/or information about relevant consumer groups such as BLISS and SCOPE on this website. Arrangements will be made to make information available on other web sites where appropriate; the study protocol will be published in an open-access journal. The families who take part in this study will be informed individually of the findings, and this information will be published on the study website, which will be freely accessible.
Dissemination

The results of this follow-up study will have importance for all neonatologists caring for babies who have NE, and these babies’ families. If the findings duplicate those reported at the 18 month follow-up they will re-enforce the evidence supporting current clinical practice. If, however, the findings demonstrate a reversal of the situation at 18 months clinical practice might need to be amended as a result.

Hypothermia is a relatively easy and economical intervention that may be widely used worldwide by the time the results of this long term follow-up study are available. Therefore it is important that the findings of this research are widely disseminated. This dissemination strategy will include publication in high impact peer-reviewed journals and presentations at research conferences. In addition, direct communication with a number of policy making organisations will be undertaken. This will include the UK Department of Health and the British Association for Perinatal Medicine and the Royal College of Paediatrics and Child Health. Consumer organisations with an interest in improving neonatal care will also be informed of the study results. We will also encourage the rapid incorporation of the results into relevant Cochrane reviews, including the Reproductive Health Library.

Steering Committee Membership

Independent members:
Professor Neil McIntosh (Chair) Veronica Lynch
Caroline Doré Lynne McCabe
Professor Diana Elbourne Dr Alison Salt

Non-independent members:
Dr Denis Azzopardi Ed Juszczak
Professor Peter Brocklehurst Professor Neil Marlow
Professor David Edwards
A Data Monitoring Committee was not set up for this follow-up Study as the cohort is predetermined, there is no treatment intervention for which safety needs to be monitored or that could generate a situation that would necessitate the early cessation of the Study.

**Publication and authorship policy**

All relevant contributors to ensuing publications will be acknowledged. Authorship will be assigned according to journal or ICMJE guidelines (see http://www.icmje.org/). ICMJE suggest that authorship credit should be based on:

1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data;
2) drafting the article or revising it critically for important intellectual content; and
3) final approval of the version to be published.

Authors should meet conditions 1, 2, and 3.

The original grant applicants will qualify for authorship, as long as they continue to be involved in the study, and can also therefore satisfy conditions 2 and 3 above.

A separate document ‘The TOBY Children Study Publication and Authorship Policy’ will provide specific details. Precise formatting of Authors and Acknowledgments may need to change according to the policy of the journal publishing the paper.
<table>
<thead>
<tr>
<th></th>
<th>Definitions</th>
<th>Cognitive</th>
<th>Neuromotor</th>
<th>Vision</th>
<th>Behaviour</th>
<th>Other (e.g., medical condition)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impairment</td>
<td>Problems in body structure or function such as substantial deviation with no loss of function</td>
<td>WPPSI ≥85 and 1 or more NEPSY domain &lt;2.5th centile</td>
<td>Abnormal signs with normal function</td>
<td>Corrected vision with spectacles</td>
<td>SDQ: One or more abnormal sub scores or abnormal total difficulties score</td>
<td>Medical condition that needs medication most days; uses sign language, communicates effectively</td>
</tr>
<tr>
<td>Mild disability</td>
<td>Some loss of function but able to function independently</td>
<td>WPPSI 70-84</td>
<td>GMFCS level 1 Arms: clumsiness of fine movements but independent</td>
<td>Blind in one eye with good vision in the contralateral eye</td>
<td>Parent and teacher overall difficulties (Q26) “Yes” and impact score 0–1 parent and 0–1 teacher</td>
<td>Chronic medical condition requiring &gt;1 admission per 6 months, or causing growth problems, or requiring special diet; epilepsy with &gt;1 generalised fit/month; stoma</td>
</tr>
<tr>
<td>Moderate disability</td>
<td>Aids or assistance needed for some tasks. Moderate difficulty in doing some activities</td>
<td>WPPSI 55-69</td>
<td>GMFCS level 2-3 Arms: able to feed and dress self, but needs aids, or has some difficulty</td>
<td>Seems to have moderately reduced vision but better than severe visual impairment</td>
<td>Parent and teacher overall difficulties (Q26) “Yes” and impact score 2–5 parent and 2 teacher</td>
<td>Medical condition needs supervision most of the time or meeting definition of moderate disability</td>
</tr>
<tr>
<td>Severe disability</td>
<td>Unable to undertake activity without aids or assistance most of the time, or completely dependent on carer</td>
<td>WPPSI &lt;55</td>
<td>GMFCS level 4–5 Arms: Unable to undertake activity without aids or assistance most of the time, or completely dependent on carer ms: needs assistance to feed and dress</td>
<td>Blind OR can only perceive light or light reflecting objects</td>
<td>Parent and teacher overall difficulties (Q26) “Yes” and impact score 6–10 parent and 3–6 teacher</td>
<td>Condition needs supervision/aid constantly - includes continuous home oxygen; communication severely limited</td>
</tr>
</tbody>
</table>
Appendix 2: TOBY Children Study Participants

TOBY recruits 325

Died before 18 month follow-up 86

Died after 18 month follow-up, before TOBY Children Study 6

Declined further participation in TOBY 2

Eligible for invitation to TOBY Children Study 231
Appendix 3: Proposed Timeline for TOBY Children Study

![Proposed Timeline for TOBY Children Study](image-url)
Reference List


Contact information

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