



Synopsis

Outcome after Selective early treatment for Closure of patent ductus ARteriosus in preterm babies, a multicentre, masked, randomised placebo-controlled parallel group trial (Baby-OSCAR trial)

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Abstract

Background: In extremely preterm babies, born before 28 weeks' gestation, a large (≥ 1.5 mm in diameter) patent ductus arteriosus present beyond 3 days of age is associated with higher mortality and morbidity than infants without a patent ductus arteriosus. The cyclooxygenase inhibitor ibuprofen may be used to treat patent ductus arteriosus. Whether selective early treatment of a large patent ductus arteriosus with ibuprofen improves health and developmental outcomes is not known.

Methods: We conducted a multicentre, randomised, double-blind, placebo-controlled trial evaluating early treatment (≤ 72 hours after birth) with ibuprofen for a large patent ductus arteriosus in extremely preterm infants. The primary outcome was a composite of death or moderate or severe bronchopulmonary dysplasia at 36 weeks' of post menstrual age. The short-term secondary outcomes included complications of prematurity, patent ductus

arteriosus closure and side effects of treatment. The main long-term outcome was survival without moderate or severe neurodevelopmental impairment, using parent report or classified by blinded end-point review committee at 24 months of corrected age. Other secondary outcomes included survival without respiratory morbidity and duration of oxygen supplementation. A health economic evaluation was undertaken.

Results: A total of 326 infants were randomised to ibuprofen and 327 to placebo. The primary outcome occurred in 220/318 infants (69.2%) in the ibuprofen group and in 202/318 infants (63.5%) in the placebo group (adjusted risk ratio 1.09, 95% confidence interval 0.98 to 1.20; $p = 0.10$). A total of 44 of 323 infants (13.6%) in the ibuprofen group and 33 of 321 infants (10.3%) in the placebo group died by 36 weeks of gestation (adjusted risk ratio 1.32, 95% confidence interval 0.92 to 1.90). Two unforeseeable serious adverse events occurred that were possibly related to ibuprofen.

At 24 months of corrected age, outcome data were available for 263 and 274 children in the ibuprofen and placebo groups, respectively. Survival without moderate to severe neurodevelopmental impairment in the ibuprofen and placebo groups was 131/248 (53.0%) and 134/259 (51.9%), respectively; adjusted risk ratio 1.01 (95% confidence interval 0.86 to 1.18); $p = 0.901$. Survival without respiratory morbidity was 66/210 (31.4%) and 74/220 (33.6%), respectively; adjusted risk ratio 0.92 (95% confidence interval 0.70 to 1.20); $p = 0.536$. Median duration of oxygen supplementation was 76.0 and 78.0 days, respectively.

Conclusion: The risk of death or moderate or severe bronchopulmonary dysplasia at 36 weeks of post menstrual age was not statistically significantly lower for extremely preterm infants randomised to early treatment with ibuprofen compared to placebo. There was no evidence of an improvement in survival without moderate to severe neurodevelopmental impairment or survival without respiratory morbidity at 24 months' corrected age, after selective early treatment of a large patent ductus arteriosus with ibuprofen in children born extremely preterm.

Future work: Future work required includes a trial in babies who are clinically symptomatic and fail to close the patent ductus arteriosus beyond 7 days of age; an individual patient data meta-analysis; follow-up of babies in Baby-OSCAR at 8–10 years of age.

Limitations: Open-label therapy was received by 29.8% of infants in the placebo group, potentially increasing the percentage of infants with patent ductus arteriosus closure in this group. The first dose of trial treatment was administered at a median of 61 hours after birth, later than in other trials.

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Introduction

Ductus arteriosus is a shunt that allows blood from the right ventricle to bypass the fetal lungs to the placenta. In term babies, it closes functionally after birth and is sealed within a few days for transition to adult circulation. In a large number of preterm babies, it does not close spontaneously; this is known as patent ductus arteriosus (PDA).

Rationale and background

Patent ductus arteriosus is a common problem that occurs after an extremely preterm birth, before 28 weeks of gestation, and it is associated with an eightfold increased risk in neonatal mortality¹ and with important short- and long-term morbidities such as bronchopulmonary dysplasia (BPD), necrotising enterocolitis (NEC) and adverse neurodevelopmental outcome.² With improvement in perinatal care, there is an increasing number of extremely preterm babies surviving after being admitted to the neonatal intensive care unit.³ However, the proportion of babies with long-term neurodevelopmental impairment

has remained unchanged despite improvement in neonatal care practices.^{4,5} With improvements in technology and expertise, there is a need for better assessment techniques and management approaches to improve survival and limit the complications of prematurity among this vulnerable group of babies.

Around 7000 extremely preterm babies are born in the UK each year; two-thirds of them will develop a PDA.⁶ The presence of a PDA places an additional burden on level 3 (tertiary) neonatal intensive care services by prolonging the duration of intensive care.⁷ Babies with a PDA require prolonged initial hospitalisation and have ongoing health problems secondary to chronic respiratory disease, systemic complications and adverse neurodevelopmental outcomes. PDA and its associated complications are also a cause of anxiety and distress among parents. A reduction in short-term complications and improvement in survival without serious developmental problems can reduce parental distress, including hospital and healthcare costs. However, there is widespread uncertainty surrounding the management of babies with a PDA, and there is

no agreement as to what should be considered as the best approach.

The two medical treatment approaches practised have both been criticised: (1) prophylactic treatment – by treating all preterm babies, this method potentially overtreats a number of babies, exposing them to complications of drug treatment where spontaneous closure could occur and (2) late symptomatic treatment – by delaying treatment until the PDA is symptomatic, the benefits of treatment may be lost with closure occurring too late. Non-interventionists propose a conservative approach of ‘wait and watch’. This conservative or no treatment approach allows the natural course of spontaneous closure of a PDA. Though spontaneous closure is more often seen in babies above 1000g or 28 weeks of gestation, persistent PDA is still a problem in extremely premature babies. A review by Benitz highlighted the absence of benefits of pharmacological closure of PDA and the treatment of PDA being debated even after three decades of intense research enrolling thousands of preterm babies.⁸ Additionally, the safety of the conservative approach has not been proven so far, as there are no long-term data on health and developmental outcomes and the majority of trials were designed to study the efficacy of the active drug in closing a PDA rather than testing the conservative approach with predefined clinical outcome measures. Additionally, there are no data on long-term respiratory outcomes.

The criticism of prophylactic and symptomatic treatment and lack of benefit of the current treatment approaches with uncertainty of the conservative approach among extremely premature babies demand further well-designed studies to resolve the uncertainty regarding the management of PDA. In addition to short-term health outcomes, an assessment of long-term health, developmental and respiratory outcomes and health economic evaluation are needed to guide further practice.

Objectives

The *objective* of this study was to examine whether the pharmacological closure of a large PDA in babies while asymptomatic, identified using bedside echocardiography (a validated objective measure), has a clinically important impact on both short- and long-term outcomes of extremely preterm babies born before and up to 28 completed weeks of gestation – a population at highest risk of adverse outcome as a result of their prematurity.

We aimed to evaluate whether selective early treatment (i.e. within 72 hours) of a large PDA (based on predefined

criteria using bedside echocardiography) using intravenous ibuprofen results in:

1. a 12% absolute risk reduction from 60% to 48% in the incidence of death or BPD at 36 weeks' post menstrual age (PMA) for babies randomised to treatment compared to placebo (primary objective)
2. a reduction in acute morbidities including NEC (Bell stage 2 or 3), severe intraventricular haemorrhage (IVH) (grade 3 or 4), periventricular leukomalacia (PVL), retinopathy of prematurity (requiring treatment), failure of PDA closure requiring rescue treatment, side effects of drug treatment, gastrointestinal bleeding and the duration of intensive care (secondary objectives)
3. improved health and long-term outcomes at 2 years' corrected age, including survival without moderate and severe neurodevelopmental impairment and respiratory morbidity.

We conducted an economic evaluation which took the form of a cost-effectiveness analysis (CEA) alongside the trial. The main economic evaluation took the form of a within-trial CEA performed from the perspective of the NHS/Personal Social Service.⁹ Thus, only direct healthcare costs were included. The main analysis is based on the primary short-term outcome of the trial, which is a composite outcome of deaths avoided and/or cases of moderate or severe BPD eliminated, at 36 weeks of PMA. The results are expressed in terms of incremental cost per additional major outcome averted, where a major outcome is defined as death and/or moderate or severe BPD avoided by 36 weeks of PMA.

A secondary CEA was based on the trial's long-term end point and was reported in terms of cost per survival without moderate or severe neurodevelopmental impairment assessed at 2 years' corrected age.

Methods and data collection

Full details of the proposed study were published as a protocol,^{10,11} which includes details of trial assessments and a flow diagram illustrating the study design.

Design

Multicentre, double-blind, randomised, placebo-controlled trial.

Participants

Babies were recruited from 32 neonatal intensive care units in the UK satisfying the following criteria:-

Inclusion criteria:

- Born at 23 + 0–28 + 6 weeks' gestation.
- < 72-hour old.
- Confirmed by echocardiography to have a large PDA which
 - is at least 1.5 mm in diameter (determined by gain optimised colour Doppler),
- and
 - has unrestrictive pulsatile (left to right) flow [ratio of flow velocity in PDA Maximum (Vmax) to Minimum (Vmin) > 2:1] or, growing flow pattern (< 30% right to left), and no clinical concerns of pulmonary hypertension.
- The responsible clinician is uncertain about whether the baby might benefit from treatment to close the PDA.
- Written informed consent is obtained from the parent(s).

Exclusion criteria:

- No realistic prospect of survival.
- Severe congenital anomaly.
- Clinical or echocardiography suspicion of congenital structural heart disease that contraindicates treatment with ibuprofen.
- Other conditions that would contraindicate the use of ibuprofen (active bleeding especially intracranial or gastrointestinal bleeding, coagulopathy, thrombocytopenia (platelet count < 50,000), renal failure, life threatening infection, pulmonary hypertension, known or suspected necrotising enterocolitis (NEC).
- Indomethacin, ibuprofen, or paracetamol administration after birth.

Interventions

The trial intervention was ibuprofen sodium administered parenterally as a loading dose of 10 mg per kg of body weight, followed by two doses of 5 mg per kg at least 24 hours apart.

The matched placebo was a clear sterile solution of 0.9% sodium chloride administered as an equal volume of 0.9% sodium chloride and with dosing as for the trial intervention. Only one course of ibuprofen or placebo was given.

Randomisation

Dynamic randomisation was performed with a secure web-based system that was created and hosted by the National Perinatal Epidemiology Unit (NPEU) Clinical Trials Unit with 24/7 telephone backup, ensuring concealment of the group assignments. The randomisation program used a probabilistic minimisation algorithm and assigned patients in a 1 : 1 ratio to one of the two groups to ensure

balance with respect to the size of the PDA, gestational age at birth, age, sex, trial site, whether the infant was from a multiple birth, mode of respiratory support and whether inotropes were received. Infants in multiple births underwent randomisation individually.

Blinding

The clinicians, the infants' families and the persons who assessed outcomes were unaware of the randomisation assignments.

Outcomes

The primary outcome is a composite of death or moderate or severe BPD assessed at 36 weeks of PMA. The main long-term outcome is survival without moderate or severe neurodevelopmental impairment assessed at 24 months of age corrected for prematurity. Short- and long-term secondary outcomes are listed in the protocol.^{10,11}

Data collection

All of the short-term outcome data for this trial are routine clinical items that were obtained from the clinical notes or local microbiological laboratory records. Clinical information was collected at the following times:

- At trial entry: to confirm eligibility and record baseline demographic and clinical characteristics.
- Recording of major morbidity until discharge from hospital.
- Static data at 36 weeks' PMA or sooner if discharged earlier.
- Data were collected until 24 months' corrected age on death, oxygen supplementation or respiratory support and neurodevelopmental outcomes.

Data for health economic evaluation utilised both resource use and the outcome, which were collected prospectively during the trial using trial-specific case report forms. Data included an initial hospital stay, and by the initial trial end point (36 weeks or earlier), babies were either discharged or transferred to another hospital. In addition, for the secondary analysis, health service use until 2 years, which included the use of primary care services and hospital readmission, was collected through a parent-completed questionnaire. Unit costs for each resource item were identified from several established national sources,^{12,13} and all costs were expressed in 2022–3 Great British pounds. Missing costs were imputed using multiple imputations.¹⁴

Analysis

The statistical analysis plan (SAP) was prepared for the short-term outcomes based on the study plan and primary and short-term outcome measures until discharge.^{15,16} Babies were followed up until 24 months' corrected age for

prematurity as per trial design. A separate SAP was prepared for long-term health outcomes, including neurodevelopment follow-up, respiratory morbidity and mortality till 24 months' corrected age (see [Report Supplementary Material 1](#)).

The total cost during the trial period was estimated by multiplying the resource items used by the corresponding unit cost followed by summation. We calculated the mean total costs and mean total resource use for the babies across trial arms. To address the skewness inherent in most cost data and the concern of economic analyses with mean costs, the bias-corrected and accelerated non-parametric bootstrap methods were used to estimate 95% confidence intervals (CIs) around mean differences by analysing 1000 resamples.¹⁷

Sensitivity analysis was used to quantify the inherent uncertainty relating to assumptions and sampling variations in the methods used and ultimately to assess the generalisability of the results. All results were presented as mean values with standard deviation, and where applicable, as mean differences in costs and effects with 95% CIs.

The incremental cost-effectiveness ratio (ICER) was calculated by dividing the difference in mean total cost between the trial arms by the difference in the number of outcomes avoided. The ICER is a measure that depicts the additional cost ascribed to an additional unit of outcome.

Results summary

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From July 2015 through December 2020, a total of 653 infants underwent randomisation. A total of 326 infants were assigned to receive ibuprofen and 327 were to receive placebo; 324 and 322, respectively, had data available for outcome analyses. A primary outcome event occurred in 220 of 318 infants (69.2%) in the ibuprofen group and in 202 of 318 infants (63.5%) in the placebo group (adjusted risk ratio 1.09, 95% CI 0.98 to 1.20; $p = 0.10$). A total of 44 of 323 infants (13.6%) in the ibuprofen group and 33 of 321 infants (10.3%) in the placebo group died by 36 weeks' gestation (adjusted risk ratio 1.32, 95% CI 0.92 to 1.90). Among the infants who survived to 36 weeks of PMA,

moderate or severe BPD occurred in 176 of 274 (64.2%) in the ibuprofen group and in 169 of 285 (59.3%) in the placebo group (adjusted risk ratio 1.09, 95% CI 0.96 to 1.23). Two unforeseeable serious adverse events occurred that were possibly related to ibuprofen.

At 24 months' corrected age, outcome data analysed by intention-to-treat were available for 537 children: 263 in the ibuprofen group and 274 in the placebo group. Survival without moderate to severe neurodevelopmental impairment in the ibuprofen and placebo groups was 131/248 (53.0%) and 134/259 (51.9%), respectively; adjusted risk ratio 1.01 (95% CI 0.86 to 1.18); $p = 0.901$. Survival without respiratory morbidity was 66/210 (31.4%) and 74/220 (33.6%), respectively; adjusted risk ratio 0.92 (95% CI 0.70 to 1.20); $p = 0.536$. Median duration of oxygen supplementation from randomisation was 76.0 and 78.0 days, respectively.¹⁹

A health economic evaluation conducted alongside the trial showed that ibuprofen was less costly, with an average cost per participant of £126,465 compared to £133,260 [–£6808 (95% CI –£17,154 to £3537)] for placebo, but it was less effective in terms of major outcomes averted with an absolute effect difference of 0.054 (95% CI –0.014 to 0.121).²⁰ The differences in mean cost were mainly attributable to the costs of high dependency care (£2345, 95% CI –£3435 to £8126) and intensive care (£6718, 95% CI –£12,627 to £26,063) which were higher in the placebo arm. The ICER was estimated at £126,846 for an additional case of death, or severe or moderate BPD avoided by 36 weeks of PMA.

Research papers synthesised in the synopsis

Short-term health outcomes

Gupta S, Subhedar NV, Bell JL, Field D, Bowler U, Hutchison E, *et al.* Trial of selective early treatment of patent ductus arteriosus with ibuprofen. *N Engl J Med* 2024;**390**:314–25. <https://doi.org/10.1056/NEJMoa2305582>

Long-term outcomes

Gupta S, O'Connor H, Juczzak E, Subhedar NV, Bowler U, Clarke C, *et al.* Two-year outcomes after selective early treatment of patent ductus arteriosus with ibuprofen in preterm babies: follow-up of Baby-OSCAR -a randomised controlled trial. *eClinicalMedicine* 2025;**87**:103424. <https://doi.org/10.1016/j.eclinm.2025.103424>.

Health economic outcomes

Ogwulu CB, Monahan M, Gupta S, Subhedar NV, Bell JL, Field D, *et al.* Economic Evaluation alongside the Trial of Selective Early Treatment of Patent Ductus Arteriosus

with Ibuprofen in Extreme Preterm Babies. *medRxiv* 2025. <https://doi.org/10.1101/2025.06.24.25330184>

Trial protocol

Gupta S, Juszczak E, Hardy P, Subhedar N, Wyllie J, Kelsall W, *et al.* Study protocol: Baby-OSCAR trial: Outcome after Selective early treatment for Closure of patent ductus ARteriosus in preterm babies, a multicentre, masked, randomised placebo-controlled parallel group trial. *BMC Pediatr* 2021;21:100. <https://doi.org/10.1186/s12887-021-02558-7>

Statistical analysis plan for short-term outcomes

Bell JL, Gupta S, Juszczak E, Hardy P, Linsell L. Baby-OSCAR: Outcome after Selective early treatment for Closure of patent ductus ARteriosus in preterm babies – a statistical analysis plan for short-term outcomes. *Trials* 2021;22:368. <https://doi.org/10.1186/s13063-021-05324-3>, 12,

Discussion/interpretation

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Short-term health outcomes

In this double-blind, randomised, placebo-controlled trial involving extremely preterm infants with a large PDA, we found no evidence that early treatment with ibuprofen was associated with a lower incidence of death or moderate or severe BPD at 36 weeks of PMA than placebo. There was no significant between-group difference in either the risk of death or the risk of moderate or severe BPD. Approximately, half the infants we enrolled were born at < 26 weeks' gestation, which is the largest cohort of interest reported in the last 25 years for PDA intervention and is the cohort at greatest risk for a hemodynamically significant PDA. This was the largest trial on selective treatment of a large PDA utilising objective echocardiography assessment. The incidence of death or moderate or severe BPD in our trial was high with early treatment of PDA with ibuprofen but was similar to that in other randomised trials of early pharmacological treatment of PDA. The closure rate of PDA was also similar to other trials of early intervention. Open-label medical therapy for a symptomatic PDA appeared to be less common in this trial than in other

similar trials and occurred almost twice as frequently in the placebo group as in the ibuprofen group.

We found no evidence that ibuprofen resulted in excess serious complications. Unlike Hundscheid *et al.* in the BeNeDuctus trial,²¹ we did not identify an association between ibuprofen therapy and BPD, a finding that might be explained by differences in the trial populations or drug exposure. While most of the infants enrolled in our trial were receiving invasive ventilation, the BeNeDuctus trial mostly enrolled infants who were receiving non-invasive respiratory support. Another important difference was the use of repeated courses (often with high doses) of ibuprofen in the BeNeDuctus trial. Early exposure to high cumulative doses of ibuprofen in infants with a relatively low baseline risk of BPD, as in that trial, may be detrimental.

The PDA closure rate (closed or non-significant PDA; < 1.5mm diameter) at around 3 weeks of age, confirmed by echocardiogram was 55.5% in the ibuprofen group as compared to 37.0% in the placebo group, with an adjusted effect estimate of relative risk 1.50 (95% CI 1.30 to 1.74). This difference is expected as the effect of ibuprofen is to constrict the PDA due to its cyclo-oxygenase inhibitor action. However, the active treatment still could only close PDA in just over 50% of babies who were medically treated with ibuprofen. On the contrary, the closure rate in the placebo arm was 37.0%, which reflects a spontaneous closure rate of PDA. These PDA closure rates at 3 weeks of age are also affected by post-intervention open-label treatment rates (for any indication), which were 14.2% in ibuprofen group and 29.8% in the placebo group, with median age of open treatment (25th, 75th centile) being 11 (8, 17) days and 12 (7, 21) days, respectively. This small separation of closed PDA between the two study groups of treatment versus no treatment could have affected the magnitude of the primary outcome as observed in our study. This has been the limitation of all pragmatic trials to date.

Our trial has limitations. In spite of strict criteria to restrict its use, open-label therapy was received by 29.8% of the infants in the placebo group, the likely effect of which would have been to increase the percentage of infants with PDA closure in this group and make it more difficult to identify the between-group differences in clinical outcomes. We did not meet our enrolment goal of 730 patients, in part because of drug non-availability, changes in clinical practice, competing trials and the effect of the COVID-19 pandemic. Although early assessment and randomisation were encouraged, the first dose of ibuprofen or placebo was administered at a median of 61 hours after birth, which was later than in other similar trials. It is possible that earlier intervention would have achieved more effective ductal closure. The results of this trial, however, are of interest

globally to alert physicians regarding no difference in short-term outcomes of death or moderate to severe BPD between early targeted treatment with ibuprofen versus conservative treatment approach of wait and watch.

Long-term outcomes

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In this trial, there was no evidence of a difference in survival without moderate or severe neurodevelopmental impairment at 24 months' corrected age in extremely preterm born infants, who were randomised to receive early selective treatment of a large PDA with ibuprofen, compared with controls. There were also no significant between-group differences in the individual components of the main long-term outcome, death and moderate or severe neurodevelopmental impairment in survivors, or in measures of respiratory morbidity.

In the Targeted by echocardiographic treatment of the ductus Arteriosus in Preterm infants by Ibuprofen trial, the primary outcome of survival without cerebral palsy, assessed by formal neurological examination, occurred in 71.3% of ibuprofen-treated infants and in 71.6% of controls.²² There were also no significant differences in any developmental domains assessed using the Ages and Stages Questionnaire. The Trial of Indomethacin Prophylaxis in Preterm Infants trial of prophylactic indomethacin reported death or severe neurosensory impairment (defined as cerebral palsy, cognitive delay, deafness or blindness at 18 months' corrected age, as assessed by neurological examination and the Bayley Scales of Infant Development II), which occurred in 46% of very low birthweight infants treated with indomethacin versus 47% of controls. The Ductal Echocardiographic Targeting and Early Closure Trial trial similarly reported no significant differences in the long-term neurodevelopmental outcomes in preterm infants treated early for PDA with indomethacin.

This builds on the short-term clinical outcomes described above, which showed no effect of early selective ibuprofen therapy on death or moderate/severe BPD at 36 weeks' PMA.¹⁸ Death by 36 weeks' PMA occurred more frequently in treated infants, and this tendency towards increased mortality persisted until 24 months' corrected age. Although radiological markers of brain

injury in the neonatal period (severe IVH and PVL) were also more commonly seen in ibuprofen-treated infants, this finding did not translate into an excess of long-term neurodevelopmental sequelae. Potential explanations for a lack of evidence of benefit of early ibuprofen therapy on long-term outcome include the failure to achieve PDA closure rate in approximately half of treated infants and the relatively high open-label medical and surgical intervention rate in the placebo group. Whether earlier effective ductal closure would have resulted in improved long-term outcomes remains unknown.

This is the largest follow-up of a clinical trial cohort reporting long-term data on survival, neurodevelopmental and respiratory outcomes in extremely preterm infants following early ibuprofen therapy for PDA. The long-term outcomes in this trial were assessed in 263 of 318 (83%) and 274 of 315 (87%) infants who received ibuprofen and placebo, respectively. Compared to previous trials, we utilised parent-completed questionnaires to assess outcomes which have been shown to be valid and reliable.

Long-term respiratory outcomes have never been reported for PDA intervention trials and this is the first trial to report these outcomes. Survival without respiratory morbidity was 66/210 (31.4%) in ibuprofen group and 74/220 (33.6%) in placebo group; adjusted risk ratio 0.92 (95% CI 0.70 to 1.20); $p = 0.536$. Median duration of oxygen supplementation from randomisation was 76.0 and 78.0 days, respectively. There were no differences in respiratory long-term outcomes at 2 years' corrected age, which is line with the observed short-term outcome of no statistical difference between the study groups.

Health economic outcomes

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Primary end point of 36 weeks' post menstrual age

The ibuprofen intervention was less costly than placebo, with a cost-saving of £6809 (95% CI -£3537 to £17,154) per baby. However, the intervention was slightly less effective than placebo, with an absolute effect difference of 0.054 (95% CI -0.013 to 0.120). This means that fewer infants achieved the principal outcome of survival at

36 weeks of PMA without moderate or severe BPD in the ibuprofen arm compared to the placebo arm (98 vs. 116, respectively). Given the differences in costs and effects, the point ICER estimate for ibuprofen compared to placebo was calculated at £126,846 per additional case of death, or severe or moderate BPD was avoided by 36 weeks of PMA.

Outcome at 2 years corrected gestational age

The ibuprofen intervention remains less costly and also less effective.

When the uncertainty around all the estimates is incorporated into the analysis, the findings suggest that despite being a potentially cost-saving intervention, the ibuprofen intervention would not be considered to be cost-effective because of the detrimental impact on infants. In some cases, in a health economic evaluation, it can be acceptable to recommend an intervention that is slightly less effective if the resource savings are such that they can be utilised to better effect elsewhere. However, this is rarely the case for interventions to prevent disabilities in newborn babies – as at this time point, there is insufficient evidence to support the likelihood that the detrimental impact on effectiveness is outweighed by the opportunity cost associated with the saving.²³

The health economic limitations included sparse use of health service resources in the follow-up period to 2 years, which did not necessarily indicate missingness but lack of use of healthcare resources. However, there is some uncertainty about this. A longer follow-up period may reveal additional cost and consequences of the disabilities/impairments present and highlight the extent of the degree of differentiation in health service use between the two groups, which would be informative. Our analyses required some pragmatic assumptions regarding the blood volumes and medicines' usage. Nonetheless, our assumptions are supported by existing literature and guidelines, and their relatively low-cost impact is unlikely to have any significant impact on the results.

Patient and public involvement

Parents and the public have been actively involved in all aspects of the trial and, as a direct result, we have been able to ensure that the trial results are applicable to premature babies and their families. Patient and public involvement (PPI) members and charity partners have been actively involved in all aspects of the trial life cycle, including the following:

Trial design and conduct

Parents of extremely premature babies were consulted about the trial synopsis, design and outcome measures

and were asked for their views on the relevance of this trial. After confirming the appropriateness of the research question, the protocol was developed further and a parent was approached to be a co-applicant on the application. In addition, a parent representative, and member of BLISS charity, UK, was approached for her expertise in this area. Both co-applicants have been involved with developing the proposal, coproducing documentation to ensure sensitive and appropriate recruitment material, attending meetings and contributing to all aspects of the trial design and conduct. Our PPI co-applicants have been actively involved in collaborators' days throughout the trial, presenting on PPI updates and training site staff on the importance of trial approach, consent and impact for families.

Trial management

There were two independent parent representatives on the Trial Steering Committee (TSC) providing overall supervision for the trial on behalf of the sponsor and funder. They provided valuable insights on the appropriateness of trial conduct and interpretation of trial results from a parent's perspective.

Analysis and interpretation

Our PPI members have been involved in the interpretation of short- and long-term results, with members coproducing the lay summary of the results and advising on what the results mean for families.

Patient and public involvement is an important element within the trial team. PPI involvement has increased parental satisfaction in several ways by improving confidence in the trial question and trial team, helping reduce anxiety, providing a greater understanding of parent's needs and developing better relationships with healthcare professionals, and it has the potential to provide positive health effects. Communication with parent advocates is a strength recognised in the NHS, which helps in improving care.

Patient and public involvement representatives were involved in management decisions, promoting the trial, reporting the research and the dissemination of findings.

Equality, diversity and inclusion

Language and terminology

We use the term 'women' and 'mother' throughout the Baby-OSCAR publications to refer to those who are planning to become pregnant, are pregnant and give birth. We acknowledge that not all people who are pregnant and give birth identify as women, and it is important that evidence-based care for maternity, perinatal and postnatal health is inclusive.

Participant representation and generalisability

As the trial was embedded in routine NHS care, it was intended to be inclusive (all babies who met the selection criteria at participating sites were candidates). The study included from the smallest to the largest neonatal intensive care units in the UK. There were no additional clinical visits to routine care for participants. We maximised methods of follow-up, that is, online, postal and phone calls, to be inclusive of parents' preferences for completion while adapting methods throughout the COVID-19 pandemic.

The study enrolled 653 babies from 32 neonatal units in the UK, including babies from all four nations (England, Scotland, Wales and Northern Ireland). A total of 26% of babies had mothers who were from non-White ethnic minority groups and 74% of babies had mothers who were from White ethnic groups [following Office for National Statistics (ONS) ethnic group descriptors]. In ONS data on live births in 2020 (the most recent year of recruitment into the Baby-OSCAR trial),²⁴ 70% of live births were from a White ethnic group, suggesting that babies recruited were broadly representative of the wider population of live births. The mean age of mothers in the Baby-OSCAR trial was within the most common age category reported by the ONS in 2020.²⁵ We are not aware of any published data on ethnicity groupings specifically for babies with significant PDA (between 23⁺⁰ and 28⁺⁶ weeks' gestation) in the UK between 2015 and 2020 to ascertain whether Baby-OSCAR participants were representative of the wider population. No information was collected directly from mothers on their educational or economic status. Deprivation indices derived from participant's home postcodes included a reasonable range, although with an over-representation of babies born to women from the lowest quintile representing least deprived areas compared to ONS data from 2020.²⁴

Our wide geographical diversity of neonatal units, inclusive approach to recruitment and enrolment of a similar proportion of babies of mothers from non-White ethnic minority groups is in keeping with the wider population characteristics of mothers of babies born in the UK and suggest that our research teams enabled participation by a diverse group of babies and that our findings are generalisable.

Team composition

The composition of the team of people involved in delivering the Baby-OSCAR trial was diverse, with the majority being female and representing a range of content expertise from medical, technical, trial management and conduct. People with lived experience and their representatives contributed to the study development, study materials and to discussions of the study results with the TSC and the trial investigators as well as preparation of the Plain language summary.

Impact and learning

The results of this trial have provided neonatologists robust evidence to reflect on the evolving practices over the past two decades. The bedside echocardiography-guided early treatment of PDA was increasingly utilised on the neonatal intensive care units based on the perceived physiological advantages that selective early treatment of PDA before 72 hours of age in extremely preterm babies could reduce the complications due to pulmonary hypercirculation and ductal steal.

The results of this trial not only failed to demonstrate any advantages of this novel approach but also reported a trend towards increased death or BPD by 36 weeks of PMA. This trend in respiratory outcomes, including duration of oxygen supplementation and death, was maintained even at 24-month follow-up. This could be attributed to the intervention itself or the side effects of the ibuprofen, the intervention drug in this trial.

The health economic evaluation further fails to support the intervention after analysing the data until 24 months' corrected age. The findings suggest that despite being a potentially cost-saving intervention, the ibuprofen intervention would not be considered as cost-effective because of the detrimental impact on infants.

The strength of this study lies in the study design which allowed an evaluation of the effect of the intervention in predetermined subgroup analyses by each week of gestational age, size of PDA and mode of respiratory support. None of the subgroup analyses reported any benefit of intervention. The results could, however, be affected by open-label treatment and the closure rate of PDA after intervention.

Research recommendations

1. Future studies could be planned in babies who are clinically symptomatic and fail to close the PDA beyond 7 days of age. These would reflect the severe end of spectrum where closure of PDA could be tested to improve health outcomes. Apart from the presence of PDA, there is an argument to assess cardiac function in babies with PDA to ascertain if the heart is coping with the increased preload. A compromised cardiac function in presence of PDA could indeed be detrimental to health outcomes. Future trials could also consider assessment of cardiac function in babies with PDA to study the effect of intervention for closure of PDA.

2. The trend of increased death in the intervention group observed in our study is also reported in other recent early intervention trials of PDA with similar methodology. This finding is a cause for concern and needs to be evaluated through individual patient data meta-analysis.
3. This cohort of babies enrolled in the trial could be followed at 8–10 years of age to assess the respiratory morbidity and developmental outcomes utilising robust objective methods of clinical assessment. This long-term assessment has never been reported in hemodynamic intervention trials and has a potential to understand the impact of early intervention after extreme preterm birth.

Conclusions

The risk of death or moderate or severe bronchopulmonary dysplasia at 36 weeks of post menstrual age was not statistically significantly lower for extremely preterm infants randomised to early treatment with ibuprofen compared to placebo. There was no evidence of an improvement in survival without moderate to severe neurodevelopmental impairment or survival without respiratory morbidity at 24 months' corrected age, after selective early treatment of a large patent ductus arteriosus with ibuprofen in children born extremely preterm.

Additional information

CRediT contribution statement

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Acknowledgements

We thank the independent Trial Steering Committee: chair: Michael Weindling (University of Liverpool); members: Eleri Adams (John Radcliffe Hospital, Oxford), Narendra Aladangady (Homerton University Hospital, London), Denis Azzopardi (Imperial College London), Tim Clayton (London School of Hygiene and Tropical Medicine), Ben Snook (lay member), Sophie Welch (lay member); and the independent Data Monitoring Committee: chair: David Edwards (St Thomas' Hospital, London), members: Alan Montgomery (University of Nottingham), Heike Rabe (Royal Alexandra Children's hospital, Brighton).

We thank all the participating families, site research nurses and doctors for their contribution to the trial. We thank all NPEU CTU staff who have worked on the trial, including administration assistants, data assistants, data managers.

We thank the members of the Baby-OSCAR Collaborative Group.

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Wishaw General Hospital	Dr Gopala Krishnan	Denise Vigni

The Baby-OSCAR Collaborative Group

The following investigators, research nurses and hospitals participated in the Baby-OSCAR Study. Sites are listed alphabetically.

Research and Development Department, University Hospital of North Tees, Stockton, UK: Pauline Shephard, Dr Volker Straub, Dr Justin Carter.

Patient data statement

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it is important that there are safeguards to make sure that they are stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives. You can find out more about the background to this citation here: <https://understandingpatientdata.org.uk/data-citation>.

Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to anonymised data may be granted following review.

Ethics statement

Baby-OSCAR received approval from East Midlands – Nottingham 2 Research Ethics Committee on 3 June 2014 (REC ref.: 14/EM/0172) and from the NHS Health Research Authority on 15 November 2016.

Information governance statement

The University of Oxford is committed to handling all personal information in line with the UK Data Protection Act (2018) and the General Data Protection Regulation (EU GDPR) 2016/679. Under the Data Protection legislation, The University of Oxford is the Data Controller, and you can find out more about how we handle personal data, including how to exercise your individual rights and the contact details for our Data Protection Officer here: www.npeu.ox.ac.uk/ctu/privacy-notice#how-we-use-your-personal-data.

Disclosure of interests

Full disclosure of interests: Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at <https://doi.org/10.3310/GJSG2422>.

Primary conflicts of interest: Samir Gupta has received funding from the Baby-OSCAR NIHR HTA grant 11/92/15, has

participated as DMC Chair for the NIHR-funded TOAST Trial, as an independent member of DMC for Erythropoietin Monotherapy in Neonatal Encephalopathy Trial, Chair of the 'Non-Invasive Cardiac Output Monitoring (NICOM)' Special Interest Group of the European Society for Paediatric Research (ESPR) and steering committee member of the 'Neonatologist Performed Echocardiography (NPE)' SIG for ESPR.

Nimish V Subhedar has received a research grant from Beyond Air and an educational grant from Mallinckrodt Pharmaceuticals, Speaker Honorarium and travel expenses from Chiesi Pharmaceuticals and is Chief Investigator of the RePhyNe: Registry of Pulmonary Hypertension in Neonates.

Jennifer L Bell received funding from NIHR HTA grant 11/92/15 (paid to institution).

David Field was the Chair of the Data Safety Monitoring Board (DSMB) for trial of IGF1 in newborn.

Samantha Johnson received funding from NIHR HTA grant 11/92/15 (paid to institution).

Andy King received funding from NIHR HTA grant 11/92/15 (paid to institution).

Louise Linsell received funding from NIHR HTA grant 11/92/15 (paid to institution).

Charles Roehr was President of the European Society for Paediatric Research (ESPR) between 2019 and 2023.

Kayleigh Stanbury received funding from NIHR HTA grant 11/92/15 (paid to institution).

Jonathan Wyllie was part of the wider research team for the ReSTORE trial funded by the NIHR (ISRCTN11359779), received Resuscitation Council UK support to attend Paediatric Academic Societies and to attend the Newborn Life Support ILCOR meeting, participated on the TSC for Paramedic 3 Trial (NIHR131105), is Associate Editor of the Resuscitation Journal from October 2024 and has had roles on the Resuscitation Council UK as Vice President (until 2023) and executive committee member and member of newborn committee.

Edmund Juszczak was a member of CTUs funded by NIHR, HTA General Committee and HTA Commissioning Committee.

Pollyanna Hardy received funding from NIHR HTA grant 11/92/15 (paid to institution) and is a member of the HTA Commissioning Committee.

Ursula Bowler, Charlotte Clarke, Christina Cole, Kerriane Dempster, Clare Edwards, Wilf Kelsell, Ann Kennedy, Marketa

Laube, David Murray, Heather O'Connor, Chidubem Okeke Ogwulu, Justine Pepperall, Tracy Roberts, Sunhil Sinha, Julia Sutton, Richard Welsh, Joy Wiles: none declared.

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This synopsis was published based on current knowledge at the time and date of publication. NIHR is committed to being inclusive and will continually monitor best practice and guidance in relation to terminology and language to ensure that we remain relevant to our stakeholders.

Trial registration

This trial is registered as Current Controlled Trials ISRCTN84264977.

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Award publications

This synopsis provided an overview of the research award *Outcome after Selective Early Closure of Ductus Arteriosus in Extremely Preterm Babies (Baby-OSCAR trial)*.

Other articles published as part of this thread are:

Gupta S, Juszczak E, Hardy P, Subhedar N, Wyllie J, Kelsall W, *et al.* Study protocol: Baby-OSCAR trial: Outcome after Selective early treatment for Closure of patent ductus ARteriosus in preterm babies, a multicentre, masked, randomised placebo controlled parallel group trial. *BMC Pediatr* 2021;21:100. <https://doi.org/10.1186/s12887-021-02558-7>

Bell JL, Gupta S, Juszczak E, Hardy P, Linsell L. Baby-OSCAR: Outcome after Selective early treatment for Closure of patent ductus ARteriosus in preterm babies – a statistical analysis plan for short-term outcomes. *Trials* 2021;22:368. <https://doi.org/10.1186/s13063-021-05324-3>

Gupta S, Subhedar NV, Bell JL, Field D, Bowler U, Hutchison E, *et al.* Trial of selective early treatment of patent ductus

arteriosus with ibuprofen. *N Engl J Med* 2024;390:314-25. <https://doi.org/10.1056/nejmoa2305582>

Gupta S, O'Connor H, Juczzak E, Subhedar NV, Bowler U, Clarke C, *et al.* Two-year outcomes after selective early treatment of patent ductus arteriosus with ibuprofen in preterm babies: follow-up of Baby-OSCAR—a randomised controlled trial. *eClinicalMedicine* 2025;87:103424. <https://doi.org/10.1016/j.eclinm.2025.103424>

For more information about this research, please view the award page (www.fundingawards.nihr.ac.uk/award/11/92/15).

Additional outputs

Juszczak E, Gupta S. Continued uncertainty regarding treatment of patent ductus arteriosus in premature infants and the role of clinical trials. *Semin Fetal Neonatal Med* 2018;23:267–72. <https://doi.org/10.1016/j.siny.2018.03.004>

Gupta S, Juszczak E, Hardy P, Subhedar N, Wyllie J, Kelsall W, *et al.* Correction to: Study protocol: Baby-OSCAR Trial: Outcome after Selective early treatment for Closure of patent ductus ARteriosus in preterm babies, a multicentre, masked, randomised placebo-controlled parallel group trial. *BMC Pediatr* 2021;21:326. <https://doi.org/10.1186/s12887-021-02785-y>

The following was still under review when this synopsis was published. The following preprint version is available for the reader; please be aware this may not have been peer reviewed:

Ogwulu CB, Monahan M, Gupta S, Subhedar NV, Bell JL, Field D, *et al.* Economic Evaluation alongside the Trial of Selective Early Treatment of Patent Ductus Arteriosus with Ibuprofen in Extreme Preterm Babies. *medRxiv* 2025. <https://doi.org/10.1101/2025.06.24.25330184>

Conferences

The results of the Baby-OSCAR trial (short- and long-term outcomes) were presented by SG at the following conferences:

1. PAS 2022, Denver, Colorado, USA, 21–25 April 2022.
2. The Newborn Lung, Buenos Aires, Argentina, 28 March–1 April 2022.
3. 10th Košice Neonatology Conference, Košice, Slovakia, 6–7 June 2022.
4. ProInfantis 2022, Gdansk, Poland, 9–10 June 2022.
5. REaSoN Neonatal Meeting, Warwick, UK, 20 and 21 June 2022.

6. RCPCH Conference 2022, Liverpool, UK, 28–30 June 2022.
7. 12th International congress of UENPS, Krakow, Poland, 2–4 September 2022.
8. BAPM Annual Conference, Manchester, UK, 15–16 September 2022.
9. 9th Congress of the European Academy of Paediatric Societies, EAPS in Barcelona, Spain, 7–11 October 2022.
10. NeoCard-UK Conference, Manchester, UK, 20–21 October 2022.
11. Joint Midlands Neonatal Cardiac Meeting, Leicester, UK, 24 March 2023.
12. 16th European Conference on Pediatric and Neonatal Ventilation, Montreux, Switzerland, 10–13 May 2023.
13. SPIN 2023 Conference, Gdansk, Poland, 9–10 June 2023.
14. RCPCH Conference 2024, Birmingham, UK, 25–27 March 2024.
15. 4th 99 NICU Conference, Lisbon, Portugal, 3–6 April 2024.
16. PAS 2024 in Toronto, Canada, 2–6 May 2024.
17. XI Neonatology Conference, Košice, Slovakia, 4–5 June 2024.
18. XXIX European Congress of Perinatal Medicine, Vienna, Austria, 11–13 September 2024.
19. 10th Congress of the EAPS (EAPS 2024), Vienna, Austria, 17–20 October 2024.

About this synopsis

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List of supplementary material

Report Supplementary Material 1 Baby-OSCAR long term outcomes statistical analysis plan

Supplementary material can be found on the NIHR Journals Library article page (<https://doi.org/10.3310/GJSG2422>).

Supplementary material has been provided by the authors to support the article and any files provided at submission will have been seen by peer reviewers, but not extensively reviewed. Any supplementary material provided at a later stage in the process may not have been peer reviewed.

The supplementary materials (which include but are not limited to related publications, patient information leaflets and questionnaires) are provided to support and contextualise the publication. Every effort has been made to obtain the necessary permissions for reproduction, to credit original sources appropriately, and to respect copyright requirements. However, despite our diligence, we acknowledge the possibility of unintentional omissions or errors and we welcome notifications of any concerns regarding copyright or permissions.

List of abbreviations

BPD	bronchopulmonary dysplasia
CEA	cost-effectiveness analysis
COVID-19	coronavirus disease 2019
ICER	incremental cost-effectiveness ratio
IVH	intraventricular haemorrhage
NEC	necrotising enterocolitis
NPEU	National Perinatal Epidemiology Unit
ONS	Office for National Statistics
PDA	patent ductus arteriosus
PMA	post menstrual age
PPI	patient and public involvement
PVL	periventricular leukomalacia
SAP	statistical analysis plan
TSC	Trial Steering Committee

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