

The Baby-OSCAR trial: rationale and practicalities



The Baby-OSCAR clinical trial is a new multicentre randomised placebo-controlled trial of ibuprofen treatment for significant patent ductus arteriosus in preterm infants. The main trial is contingent on a successful internal pilot phase, which will assess the practicalities of trial procedures, the equipoise of clinicians and the willingness of parents to enrol their infants into the study. This article describes the Baby-OSCAR trial and offers practical tips for maximising recruitment to clinical trials.

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Patent ductus arteriosus

Patent ductus arteriosus (PDA) is a condition that is caused by a blood vessel called the ductus arteriosus staying open after an infant's birth. During pregnancy, the ductus arteriosus allows blood from the fetal heart to flow to the mother's placenta to get oxygen, bypassing the fetal lungs. Soon after birth, the ductus should close to allow blood to flow to the newborn infant's lungs to get oxygen.

In very premature infants the ductus often takes a long time to close on its own and this can lead to a variety of complications. Clinicians are unsure if early treatment should be given to very premature babies to close a PDA and reduce the risks of complications, or whether it is safer to wait and see if the ductus closes by itself.¹

PDA can be managed medically with ibuprofen; a non-steroidal anti-inflammatory drug routinely used for the symptomatic treatment of pain in children and adults. The current mainstay of treatment, ibuprofen inhibits the synthesis of prostaglandins, which are responsible for maintaining duct patency in the fetus. Their inhibition encourages the ductus arteriosus to close, however, treatment with ibuprofen can itself cause problems because premature infants may not be able to cope with its side effects.² In addition, not all premature babies will have a PDA, and in those that do, the PDA may not be causing any problems. Clinicians are therefore faced with the dilemma of whether to treat with ibuprofen (or other drugs) as a precaution or to wait until symptoms develop, by which time some harm may have already been done.

The Baby-OSCAR trial

Baby-OSCAR (Outcome after Selective early treatment for Closure of patent ductus ARteriosus) is a multicentre, masked, randomised placebo-controlled trial investigating short- and long-term health and economic outcomes of the treatment of a large PDA with ibuprofen in extremely preterm infants within 72 hours of birth. The trial is funded by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme (ISRCTN: 84264977).³

Extremely premature infants born at or before 28 weeks of gestation will be eligible for inclusion in the trial in the first 72 hours following birth if they have a large PDA diagnosed using bedside echocardiography. The echocardiography criteria are carefully chosen to identify babies whose PDAs are unlikely to close spontaneously. Since infants will be identified while they are usually asymptomatic, instituting treatment in this select patient population is called 'selective early treatment' and has the potential benefit of closing the PDA before it has caused substantial damage. Infants will be randomised to receive either the active drug (ibuprofen) used for medical closure of PDA or a matched placebo (normal saline). This allows a fair comparison to robustly answer the clinical question as to whether to treat or not to treat an asymptomatic 'significant' PDA.

The success of the trial not only depends on meeting recruitment and retention targets but, for a fair comparison, open label treatment needs to be kept to a minimum. This has been one of the weaknesses of the trials conducted to date –

patent ductus arteriosus; PDA; preterm; ibuprofen; clinical trial

Juszcak E., Gupta S. The Baby-OSCAR trial: rationale and practicalities. *Infant* 2015; 11(6): 184-86.

1. Baby-OSCAR is a randomised controlled trial to assess whether administration of ibuprofen within 72 hours of birth may help extremely preterm infants with a patent ductus arteriosus.
2. The recruitment target is 730 infants.
3. The trial will be rolled out across the country contingent upon successful completion of an internal pilot study.

open label treatment has ranged from 30–85%.⁴ To minimise this ‘contamination’, the trial protocol sets clinical and echocardiography thresholds that need to be met before considering treatment of a symptomatic PDA.

The Baby-OSCAR trial is one of the largest trials to date on the management of PDA diagnosed using echocardiography and aims to recruit around 730 infants over three years. Unlike previous studies,² this trial is using a primary outcome of mortality or moderate to severe chronic lung disease, plus a number of secondary outcomes including short- and long-term health outcomes. The short-term outcomes include complications of prematurity, side effects of drug, PDA closure and duration of respiratory support and hospital stay. The long-term outcomes include neurodevelopment and respiratory morbidity assessed at two years of age corrected for prematurity, and health economic outcomes are studied for the first time.

Rationale and practicalities

The translation of a clinical question into a successful trial requires support from a large number of clinical centres (both recruiting and continuing care sites), substantial funding and appropriate monitoring. A realistic and pragmatic approach to setting the study timelines and milestones is required in addition to convincing the funder regarding anticipated patient benefits and value for money, while competing with other trials for the patient population. Once funded and underway, the NIHR HTA programme, in this case, requires evidence as to whether the study is feasible before giving the go-ahead for the main phase.

‘When does a study become feasible?’ and ‘How should feasibility be defined?’ are questions that a funder often has to address, more commonly for clinical trials, which tend to involve significant financial outlay. Official definitions vary but, for example, the NIHR Evaluation, Trials and Studies Coordinating Centre (NETSCC) definitions of pilot and feasibility studies are helpful.⁵ A feasibility study is described as a piece of research carried out before a main study in order to answer the question: ‘Can this study be done?’ It is used to estimate important parameters that are needed to design the main study. A pilot study is described as a smaller version of the main study, used to test whether the components of the main

study can all work together. A pilot focuses on the processes of the main study, to ensure that aspects such as recruitment, randomisation, delivery of the intervention and follow-up assessments/outcomes data collection all run smoothly. A pilot study resembles the main study in many ways: the trial in miniature. Data from the pilot phase may contribute to the final analysis; this scenario can be described as an internal pilot.

However, assessing the success of an internal pilot study inevitably involves an element of subjectivity – this can result in disagreement with one stakeholder classing a study unfeasible while another stakeholder classes it feasible. The former could be a funder, while the latter is more likely to be a researcher.

Nevertheless, persons submitting grant applications are frequently given the opportunity to propose milestones and more importantly stop/go criteria at some early juncture, often in an internal pilot study. Furthermore, the NIHR expects that when pilot or feasibility studies are proposed by applicants or specified in commissioning briefs, a clear route of progression criteria to the substantive study will be described.

This approach minimises the risk for the funder insofar as a non-viable study may be terminated early before too much resource is invested. However, this approach invokes extra pressure on researchers who need their centres to perform well in the early stages, when under normal circumstances they may be expected to behave atypically when ‘learning the ropes’. This could, in theory, lead to a skewed selection of pilot sites, which, while maximising the chances of proceeding into the main trial, could lead to poor translation when rolled out into a wider group of centres. In addition, another by-product of the system may lead to the research team operating in the knowledge that a poor start may mean a short contract.

The critical foundation stones of any feasible trial are the three Rs – recruitment, retention and results! Poetic license apart, being able to demonstrate that (i) participants will agree to take part and accept randomisation, (ii) clinicians are willing to randomise people into the trial (ie they are willing to accept that they are uncertain as to the best course of action and will not change their behaviour in light of becoming aware of the allocation), (iii) both participants and clinicians will

adhere to the intervention, and (iv) complete outcomes data can be collected, are important metrics of success.

Ensuring successful recruitment

Recruitment is key and without it there is no trial. How can successful recruitment be ensured?

- by picking an important research question that clinicians want to know the answer to. It needs to not only enhance, if not confirm, the evidence base but to potentially change clinical practice and benefit future patients
- by involving user groups, charities and public representatives (PPI, patient and public involvement) to ensure that the trial procedures are acceptable, grounded in common sense and minimise the burden on participants
- by keeping it short and simple (eg trial procedures, web-based randomisation, data collection). The more that trial procedures are embedded in current clinical practice, the better
- by choosing centres carefully.

When choosing recruiting sites, a variety of approaches have been taken over the years:

- past behaviour is the best predictor of future behaviour. Track record speaks volumes as does the presence of a highly motivated, driven and effective leader who will inspire people to join and be a player on ‘Team CNA’ (catchy new acronym)
- use empirical evidence, eg produce a scatter plot of recruitment rates to previous trials and identify consistently good performers
- use a basic test of commitment: request some data (eg on patient throughput, possibly restricted to certain patient subsets) and/or issue forms or checklists (eg request a checklist of healthcare professionals with the requisite GCP training). These approaches will weed out the uncommitted (you may never hear from some again)
- remember that an encouraging response does not always equate to good recruitment
- be mindful of other studies competing for the same patient population
- guard against choosing elite centres. The best recruiting centres may ensure progression into the main trial but overall performance may not translate accordingly
- do not forget the smaller centres – they

may be more committed, have a thriving research culture and actually recruit a greater proportion of eligible participants.

About the trial

The NPEU Clinical Trials Unit at the University of Oxford is coordinating the trial. The co-investigators include clinicians with a keen interest in cardiology and haemodynamics, trial methodologists, statisticians, a developmental psychologist, parent and public representatives and a health economist.

The trial includes an internal pilot phase, which is running from July 2015 until the end of the year, involving five neonatal units:

- Birmingham Women’s Hospital
- James Cook University Hospital
- Liverpool Women’s Hospital
- Norfolk and Norwich University Hospital
- University Hospital of North Tees.

Metrics agreed with the NIHR HTA programme for this trial include recruitment, retention, completeness of data, safety and use of open label medication.

The chief investigator and trial team will

report in these agreed metrics to the independent trial steering committee, which in turn will advise the funder regarding viability of the trial. Only with the funder’s permission will the trial be rolled out into the remaining 20-25 centres.

The number of and composition of feasibility metrics is trial-specific, with the possible exception of recruitment. Even regarding recruitment targets, consistency of approach is lacking from both funders and researchers. Predicted recruitment can be modelled as a percentage of steady state, eg expecting a centre to achieve 25% of target in the first month, 50% in the second, 75% in the third and steady state in the fourth month. Another more statistical approach is to assume recruitment follows a Poisson model – an average recruitment rate can be predicted with a measure of uncertainty such as a 95% confidence interval. Either way, the absolute number of recruits is the currency of success. For Baby-OSCAR, the recruitment target is 730 infants over 42 months (recruitment is for six months in the pilot study and for 36 months in the main trial).

Acknowledgement

Ultimately the success of a research study relies on a great many things, but most importantly, it cannot succeed without the cooperation of altruistically minded participants and, most importantly in the case of neonatal studies, the parents. The authors’ thanks go out to every set of parents who enrol in studies and trust healthcare professionals to take care of their babies.

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