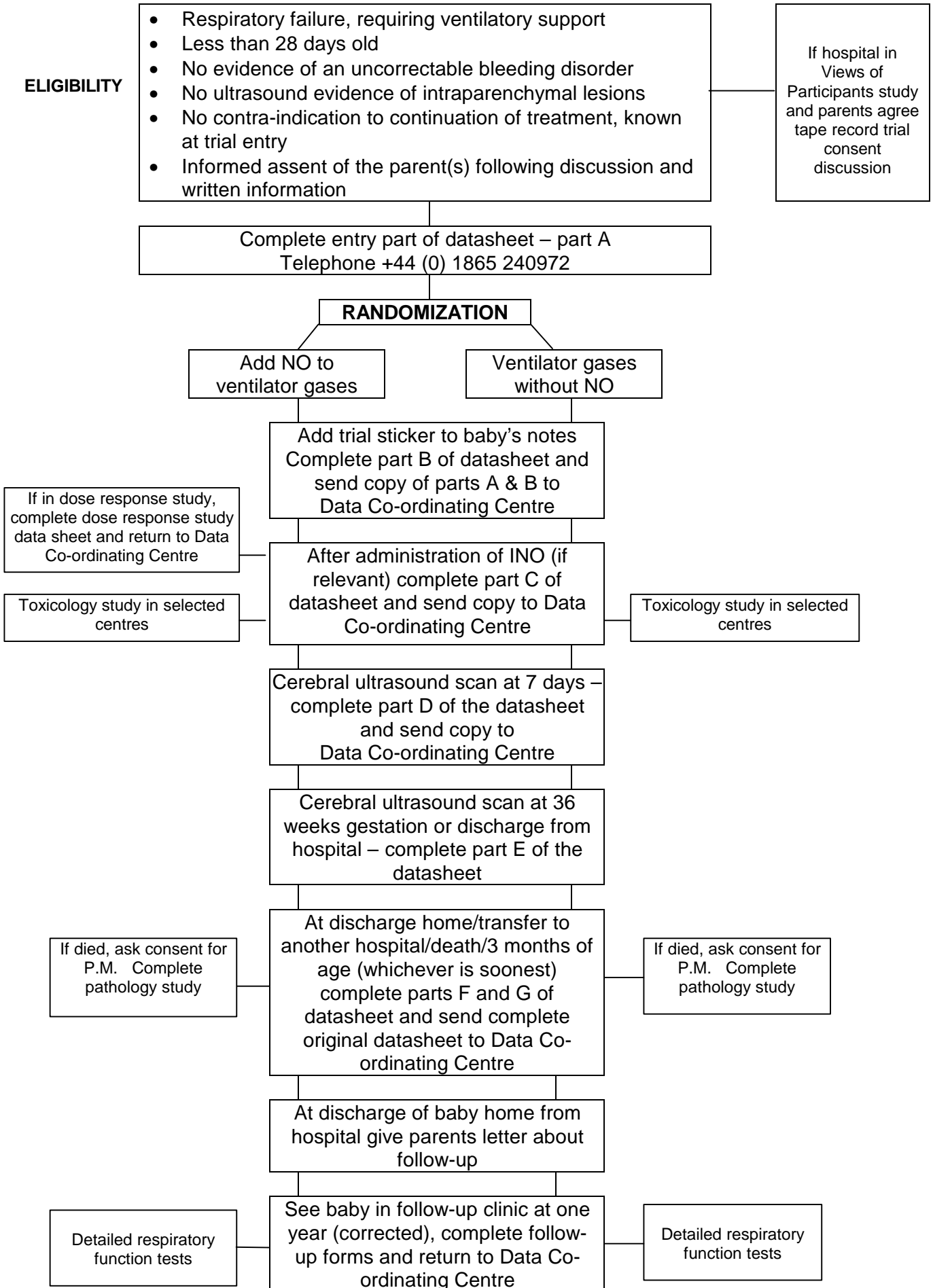# The INNOVO Trial

Neonatal ventilation with **IN**haled **N**itric **O**xide versus **V**entilatory support with**O**ut inhaled nitric oxide for severe respiratory failure:

a multicentre randomized controlled trial

Protocol
June 1999

SUMMARY PROTOCOL

ELIGIBILITY

- Respiratory failure, requiring ventilatory support
- Less than 28 days old
- No evidence of an uncorrectable bleeding disorder
- No ultrasound evidence of intraparenchymal lesions
- No contra-indication to continuation of treatment, known at trial entry
- Informed assent of the parent(s) following discussion and written information

If hospital in Views of Participants study and parents agree tape record trial consent discussion

Complete entry part of datasheet – part A
Telephone +44 (0) 1865 240972

RANDOMIZATION

Add NO to ventilator gases

Ventilator gases without NO

Add trial sticker to baby's notes
Complete part B of datasheet and send copy of parts A & B to Data Co-ordinating Centre

If in dose response study, complete dose response study data sheet and return to Data Co-ordinating Centre

After administration of INO (if relevant) complete part C of datasheet and send copy to Data Co-ordinating Centre

Toxicology study in selected centres

Toxicology study in selected centres

Cerebral ultrasound scan at 7 days – complete part D of the datasheet and send copy to Data Co-ordinating Centre

Cerebral ultrasound scan at 36 weeks gestation or discharge from hospital – complete part E of the datasheet

If died, ask consent for P.M. Complete pathology study

At discharge home/transfer to another hospital/death/3 months of age (whichever is soonest) complete parts F and G of datasheet and send complete original datasheet to Data Co-ordinating Centre

If died, ask consent for P.M. Complete pathology study

At discharge of baby home from hospital give parents letter about follow-up

Detailed respiratory function tests

See baby in follow-up clinic at one year (corrected), complete follow-up forms and return to Data Co-ordinating Centre

Detailed respiratory function tests

Data Co-ordinating Centre

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SUMMARY

The INNOVO Trial is a randomized controlled trial comparing giving ventilatory support with inhaled nitric oxide (INO) against ventilatory support without inhaled nitric oxide for neonates with severe but potentially reversible respiratory failure. The overall hypothesis to be tested is that adding INO to the ventilator gases reduces the risk of substantive adverse clinical outcomes, and is cost-effective. Previous work has suggested that INO can improve oxygenation in the short-term, but little reliable information is yet available about its long-term implications. A pilot INNOVO Trial has been conducted to guide the protocol for the main INNOVO Trial detailed here. Based on this experience the entry criteria will not be restrictive but will be allowed to reflect current clinical practice, with centres recruiting to the preterm, term and near term, or both strata.

The primary outcome measures are (a) death or severe disability at the age of one year (corrected), and (b) death or on supplemental oxygen on the expected date of delivery (or 28 days post-delivery for the full or near term babies). A total sample size of 200 preterm babies (<34 weeks) will be sufficient to reliably detect important effects on these outcomes and the 110 term or near term babies ($\geq$ 34 weeks) recruited over the same period will provide useful data which could be added to meta-analyses.

Sub-studies are also in place to consider other developmental and respiratory outcomes, cost-effectiveness, dose response of preterm babies, pathology, toxicology, respiratory function and views of trial participants.

BACKGROUND

The problem to be addressed in this trial relates to the treatment of a particular group of newborn babies. Whereas the vast majority of babies born in 'developed' countries are healthy at birth, a small proportion are acutely ill. Appropriate and effective treatment at this time is crucial, as it has implications for an entire lifetime. Severe, but potentially reversible respiratory problems in the newborn are a major cause of death and there is an increased risk of subsequent morbidity in survivors. The care of these babies places major burdens on their families, and on the health services, both during the acute illness and in relation to any later problems.

An important aspect of the pathophysiology of lung disease in newborn babies is the persistence of pulmonary vasoconstriction. In utero this is the normal situation, but with the onset of respiration at birth pulmonary vasodilatation should occur leading to a fall in pulmonary vascular resistance and increased pulmonary blood flow. Where the presence of lung disease inhibits the processes involved in initiating this change (e.g. lung expansion, presence of oxygen within the lung) the pulmonary hypertension continues. More rarely persistent pulmonary hypertension of the newborn (PPHN) may arise in mature babies without evidence of lung disease. Modalities for the care of babies affected by pulmonary hypertension, with or without associated lung disease, may include ventilatory support, use of surfactant (particularly for preterm babies), maintenance of systemic blood pressure with inotropes, induction of alkalosis by hyperventilation and bicarbonate, sedation or muscle relaxation and, finally for term or near term babies, extracorporeal membrane oxygenation (ECMO). A variety of vasodilators have been used (e.g. tolazoline, prostacyclin and

magnesium sulphate) to help improve pulmonary blood flow but none has proved consistently effective and all have unwanted side effects, particularly systemic hypotension.

Inhaled nitric oxide (INO) is a promising therapy being used in a growing number of centres as part of the management of such babies. It is a highly diffusible, colourless gas with a vapour density similar to air [1]. The nitric oxide (NO) molecule is considered a 'free radical' because it has an unpaired electron making it able to react with other molecules [2]. NO is synthesised at a variety of sites in the human, including the vascular endothelial cells of the lungs [3]. Endogenous NO production involves NO synthase, an enzyme which oxidises the terminal guanidino nitrogen atoms of the amino acid L-arginine. NO diffuses from the endothelium into the pulmonary vascular smooth muscle where it activates the soluble form of guanylate cyclase and increases the 'second messenger' cyclic guanosine monophosphate, resulting in pulmonary vasodilatation [4]. There is some evidence that NO has an important role in the transition from fetal to 'adult' circulation [5] at birth, and is a contributing factor in the normal decline in pulmonary resistance following delivery [6].

Exogenous NO has the obvious potential to improve pulmonary blood flow. It is also possible that pulmonary efficiency is improved as a result of better matching of ventilation and perfusion. NO has a very short half-life of about one to three seconds[7] with a high affinity for binding with haemoglobin, after which it is quickly inactivated[8], resulting in the formation of methaemoglobin, inorganic nitrate and nitrite[9]. Therefore systemic effects, including hypotension, are unlikely, on theoretical grounds, and this has been confirmed in open studies. There is, however, concern about its toxicity. Under the right conditions nitrogen dioxide and the free radical peroxynitrite may form. Peroxynitrite has been demonstrated to have a variety of adverse effects. High levels of nitrogen dioxide (formed by the combination of NO and oxygen) can be toxic to lung tissues, resulting in severe pulmonary oedema[10]. In addition, NO has the ability to inhibit platelet aggregation, and therefore confers a risk of haemorrhagic complications[11]. High concentrations of NO have been implicated in CNS effects (impaired memory and brainstem conduction time) in rats[12]. Concern has also been expressed about possible carcinogenic effects[13], and inhibition of surfactant[14].

Both case series[15 16 17 18] and trials (see below) indicate that INO may acutely improve oxygenation in babies born preterm (<34 weeks) with respiratory failure complicated by pulmonary hypertension[19], as well as those born at or near term ($\geq$34 weeks – henceforth referred to as 'mature') with PPHN, either as a primary condition of neonatal maladaptation or secondary to other diseases such as hyaline membrane disease (HMD), meconium aspiration, infection, and congenital diaphragmatic hernia. Rigorous information about the implications of these short-term effects on substantive clinical outcomes is, however, not yet available.

Evidence from trials

'Mature' babies. A systematic review was published in the Cochrane Library[20]. The last substantive update was in November 1997. The review was based on 8 trials[21 22 23 24 25 26 27 28], ranging in sample size from 17 to 235. All the trials provided data on the short-term effects on oxygenation, and confirmed that INO can, indeed, lead to significant improvements during treatment and up to one hour afterwards. Not all the trials provided data on substantive clinical outcomes. For instance, based on five of the trials, the review found that INO reduced the requirement for ECMO (Relative Risk (RR) 0.69; 95% Confidence Interval (CI) 0.56 to 0.85), reduced the risk of death or ECMO (RR 0.72 (95% CI 0.60 to 0.87)), but did not suggest any benefit of INO on mortality alone (RR 1.03; 95% CI 0.62 to 1.72), although this CI is wide. A further trial which has not yet been included in the review[29] has come to similar conclusions. No

long term follow up information was available from any of the trials for this review, which did not report data about side-effects and toxicity. Nevertheless, the reviewers conclude: "On the evidence presently available it appears reasonable to use inhaled nitric oxide...for term and near term babies with hypoxic respiratory failure who do not have a diaphragmatic hernia". We have commented on this in the Criticisms section of the Cochrane Library[30], making three main points: (1)There is a need for further information about longer term neurodevelopmental outcomes. (2) Reducing the need for ECMO may not represent an adverse outcome as, appropriately used, it has benefits both for mortality[31] and for respiratory function[32], without leading to greater risk of neuro-developmental problems[33]. In addition it is plausible that delaying the introduction of ECMO whilst INO is tried might, by increasing the time the baby is exposed to hypoxia, increase the rate of neurodevelopmental delay observed in survivors. (3) The effect of INO in reducing the use of ECMO may be an over-estimate as several of the trials were stopped early on the advice of data monitoring committees[34]. Finer and Barrington do temper their conclusions by suggesting the need for further research to assess "what are the long term effects, if any, of INO on the developing lung and on the infant's neurodevelopment…and to evaluate the benefit of INO in premature infants with hypoxic respiratory failure".

More recently the trial Steering Committee discussed the information now available from a single trial [35]. These data showed no evidence of difference in neurodevelopmental and behavioural outcomes in the 87% of surviving babies followed up. As this was a single trial, in a North American setting, the INNOVO Steering Committee decided sufficient uncertainty remained to continue to recruit 'mature' babies into the trial.

b) *Preterm babies.* The systematic review is now published in the Cochrane Library[36]. A search of the Register of controlled trials in this Library identified only one trial[37] which compared the use of INO against conventional management without INO in preterm babies. This trial showed that INO rapidly improved oxygenation, but there was no evidence that this led to improvements in substantive clinical outcomes. Follow up at 30 months does not alter this conclusion (Subhedar, personal communication), although the size of the trial (42 babies) would not have been powerful enough to detect any but the largest effects. Cheung[38] found only 3 of the 24 babies treated with INO were developmentally normal, and in an editorial Rosenberg[39] pleaded for an RCT and "until the results of such a trial are available, use of INO as a salvage therapy must be considered …reckless practice".

INNOVO pilot trial

In the pilot, clinicians recruited babies into the trial if they were uncertain about the benefits of INO for babies in their care. Based on the first 64 babies, 40 were preterm (<34 weeks gestation at birth), and 24 were term or near term. The range of uncertainty in terms of level of severity was very variable, with an inter-quartile oxygenation index range of 17 to 45.

Many centres recruited in both gestational age categories, some recruited only preterm babies, some recruited term or near term babies. Rates of adverse outcomes in preterm babies in the pilot phase were very high, although not so high for 'mature' babies. This led to the conclusion that a definitive trial of preterm babies within a reasonable timeframe was feasible and a trial of 'mature' babies would produce useful data for meta-analysis.

Nitric oxide use

Nitric oxide is becoming well established in neonatal clinical practice, especially for 'mature' babies. For example, a recent survey of the 27 'on-line' centres in the pilot trial asked about 'out-of-trial' use of INO since coming 'on-line'. Twenty replies were received. For preterm babies, although most centres had not used INO at all, or only once over this (variable) period, seven centres had used it more frequently, including a centre which had given INO to over 20 babies in the previous 15 months. For 'mature' babies, eight centres used INO for two or more babies, with two centres using it for more than 20 babies. It seems likely that use will be higher in centres which are not committed to The INNOVO Trial. Overall, this level of use of INO is worrying, given that the evidence from trials shows that the clinical effectiveness of INO has not yet been rigorously tested.

It is therefore imperative that the INNOVO main trial recruits readily to answer the crucial questions about the clinical and cost-effectiveness of INO before the window of opportunity closes.

THE AIMS OF THE TRIAL

The aims of the trial are:

1. To assess the clinical effectiveness and cost-effectiveness of a policy of adding or not adding inhaled nitric oxide (INO) to the ventilator gases of neonates with severe respiratory failure.
2. To conduct relevant sub- studies (see below).

METHODS

Eligibility - hospitals:

Hospitals are eligible to participate if they are accustomed to providing long-term ventilatory support for newborn babies, have facilities for providing INO, and have research ethics committee approval to participate in the trial. Facilities for echocardiography are strongly preferred, in order to be able to exclude babies with congenital heart disease. Before being considered 'on-line' to recruit, centres have to be visited and taken through technicalities and procedures in the Trial Folder by the Trial Research Technician and/or the Trial Co-ordinator.

Detailed technical guidelines are provided in the Trial Folder. The part-time Trial Research Technician at the Clinical Co-ordinating Centre will travel to different centres, and be available to respond to queries in collaboration with the Technical Advisory Group.

Eligibility – babies:

(1)   Uncertainty by the responsible clinician about whether the baby may benefit from INO. *It is strongly recommended that an echocardiograph is performed on 'mature' babies considered for trial entry. It is also advisable for preterm babies. Apart from babies undergoing*

cardiothoracic surgery and/or with known congenital heart disease, most babies presently being treated with INO will be eligible for entry into the trial.

(2)   Respiratory failure, requiring ventilatory support and administration of surfactant where appropriate. *The severity of illness of the baby will be indicated by the OI at recruitment. The pilot trial has shown considerable variation in the level of severity at which clinicians have felt uncertainty about the benefit of INO.*

(3)   Aged less than 28 days old. *The majority of babies recruited will be less than 72 hours of age, but there may be situations where babies acquire respiratory disease later in the neonatal period.*

(4)   No evidence of an uncorrectable[*] bleeding disorder. *Platelet count must be >50,000 cells per mm^3 plus KPPT must be <72 secs or INR <2.*

(5)   No ultrasound evidence of intra-parenchymal lesions. *i.e. an echodense area (of at least equal echodensity to the choroid plexus or bone) involving the parenchyma of the brain and/or existing parenchymal lesions which are echo-poor, e.g. established porencephalic cysts.*

(6)   No contra-indication to continuation of treatment, known at trial entry. Examples may include severe congenital abnormalities, lethal chromosomal anomalies etc.

Trial entry:

If the baby meets the eligibility criteria, the trial should be discussed with the baby's parents. Try to speak to both parents, if possible. *For centres taking part in the Views of Participants Study, tape the discussion if appropriate and if parents agree to the recording.* Discuss the trial with the parents and give them the Information for Parents leaflet. (NB there are separate versions, one for girls and one for boys). If possible, allow some time for consideration.

If the parent(s) agree to the baby's participation in the trial, complete part A of the trial datasheet (the entry form) and telephone the 24-hours-a-day, 7-days-a-week randomization service on

     01865 240972 (UK centres)   [+ 44 1865 240972 (non-UK centres)].

After eligibility has been confirmed and the entry details have been recorded, a trial number and the random allocation (based on a minimisation algorithm) will be given, either:

     (1) 'Add NO to ventilatory gases' or

     (2) 'Ventilatory support without NO'.

Minimisation is based on the two gestational age groups: <34 weeks and $\geq$ 34 weeks

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[*] Amended from uncorrected to uncorrectable bleeding disorder at Steering Committee meeting held 22nd November 2000

Minimisation categories for the <34 weeks gestational age group

Centre
Principal diagnosis at trial entry: acute preterm lung disease (PLD), chronic PLD, other
Respiratory disease severity at trial entry: $OI^1 < 30, \geq 30$
Postnatal age: ≤ 3, 4-28 days

Minimisation categories for the $\geq$ 34 weeks gestational age group

Centre
Principal diagnosis at trial entry: congenital diaphragmatic hernia, primary persistent pulmonary hypertension of the newborn (PPHN), secondary PPHN, 'other'
Respiratory disease severity at trial entry: $OI <40, \geq 40$
Postnatal age: ≤ 3, 4-28 days

After the allocation has been assigned, inform parent(s) as soon as possible and add a trial sticker to baby's notes.

Outcomes:

The primary outcomes will be:

(1) (a) Death or severe disability at one year of age (corrected)
    (b) Death by one year of age (corrected)
    (c) Severe disability at one year of age (corrected), defined as no/minimal head control or inability to sit unsupported, or no/minimal response to visual stimuli as these have been found to be equivalent to a Developmental Quotient (DQ) of < 50.

(2) (a) Death before discharge from hospital.
    (b) chronic lung disease, defined as being on supplemental oxygen at the expected date of   delivery (preterm stratum) and at 28 days post-delivery ('mature' stratum).

Outcome will be assessed at two points: at discharge from neonatal services (or prior death), and at one year of age (corrected).

Secondary measures of outcome will include:

At discharge from neonatal services (or prior death)

> referral for ECMO support for 'mature' babies
> length of stay in hospital (neonatal unit and other wards)
> length of time on supplemental oxygen (in and out of hospital)
> length of time on ventilatory support

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[1] Oxygenation Index (OI) = (mean airway pressure x FiO_2)/Post-ductal Pa O_2 mm Hg

pneumothorax or other pulmonary airleak
pulmonary haemorrhage
major cerebral abnormality as judged from ultrasound examination
necrotising enterocolitis
treatment of retinopathy of prematurity
infection - suspected or confirmed
age at which oral feeding is established

At the age of one year (corrected)

impairment and disability (neuromotor, vision, hearing, and development)
respiratory problems (symptoms and lung function)
seizures
reduced growth.

Neurodevelopmental outcome will be assessed using a brief questionnaire for the local paediatrician caring for the baby to complete in the routine follow-up clinic. In this, information will also be sought on less severe degrees of impairment and disability in all fields of development, impairment and disability (neuromotor, vision, hearing, and development). After discussion with the local paediatrician, parents of appropriate babies able to cope with travel will be invited to bring their baby for a detailed respiratory function tests at London or Leicester.

Analyses will be based on the groups as allocated (the 'intention to treat' principle). All analyses will be stratified by gestational age at trial entry (<34 weeks and ≥34 weeks). Additionally, the primary and principal secondary outcome measures will be stratified for the major prognostic variables: principal diagnosis leading to respiratory distress, postnatal age, and the severity of respiratory disease at trial entry. In this way, some information can be gained about the differential effects of INO in the different categories of babies recruited.

Treatment schedules:

INO dosage

- In **term babies**, gestational age equal to or greater than 34 weeks, the trial starting (and maximal) dosage of INO is 20 ppm, which would then be weaned down, after a 1 hour stabilisation period, to the minimum necessary dosage to sustain a clinically significant response. A response is defined as an increase in post ductal PaO_2 of more than 3 kPa (22.5 mmHg) in the initial 15 minutes of giving INO. The ventilation should remain constant during this initial 15 minutes to prevent outside factors influencing the response.

- In **preterm babies**, gestational age less than 34 weeks, a dose response study is being undertaken to determine the most effective dose. The study will include doses from 5 to 40 ppm. Doses above 40 ppm will not be used.

- For centres not in the dose response study, until the results of the dose response study are available, a dose level starting at 5 ppm will be used. If no satisfactory response is achieved, the dose will be doubled to 10 ppm, then if necessary doubled again to 20 ppm, then again if required to 40 ppm. If at any point, after having achieved a response (an increase in post ductal PaO_2 of more than 3 kPa (22.5 mmHg)), an increase in dose does not produce a further

significant increase in the response, then the dose should be dropped down to the previous level and maintained at that level.

- In **all babies** it is essential that after a period of stabilisation, for the INO dose to be maintained at the lowest possible effective level. Failure to ensure the lowest possible INO dose will result in increased INO and ventilator dependence. It is suggested that reverse dose response weaning is undertaken. This means that the INO dose is repeatedly reduced by approximately 10% every 2-3 minutes until a decrease (2-3 %) in oxygen saturations is noted. The INO should then be increased to the level it was at prior to the decrease in oxygenation. This should be re-evaluated every 12 hours.

- **Non responder** are those babies not showing an increase in post ductal PaO_2 of more than 3 kPa (22.5 mmHg) in the initial 15 minutes of giving INO. Continue on INO, at 5 ppm, for 12 hours and then if there is still no response they should be weaned off INO. Weaning should be carried out in a reverse dose response fashion.

- Some babies, even some of those who appear not to have responded to INO, remain dependant on the INO, so that doses as low as 0.3 ppm may be required for a few days during the final weaning process.

- When **weaning** INO is withdrawn completely it may help to temporarily increase the FiO_2 by up to 40% to finally wean the INO, especially in difficult cases.

- The INO administration circuit should remain attached to the ventilator for a further 24 hours to ensure stability after successful weaning from INO.

N.B. If a baby is randomized to 'the ventilatory support without INO' group, he or she should not receive INO at a later stage i.e. there should be no 'cross-over'.

Data collection:

Data will be collected at five points in time.

1. At trial entry

    Complete part A of the datasheet before telephoning the randomization service and then complete part B of the datasheet as soon as possible after trial entry. Make 2 photocopies of both part A and part B. Pass one of the copies to the local trial neonatal co-ordinator and send the other copy to The INNOVO Trial Data Co-ordinating Centre in the FREEPOST envelope provided in the trial folder. Attach an INNOVO Trial sticker to the baby's notes and place the original datasheet into the baby's notes.

2. At administration of nitric oxide, if relevant. (this part to be completed for all babies whether or not nitric oxide is administered).

    Complete part C of the trial datasheet, make 2 photocopies. Pass one of the copies to the local trial neonatal co-ordinator and send the other copy to The INNOVO Trial Data Co-ordinating Centre in the FREEPOST envelope provided. If the baby is also enrolled in the dose response study, take the next one from the box of sequentially arranged envelopes.

3. At 7 days after trial entry

A cerebral ultrasound scan should be performed 7 days after trial entry. Complete part D of the datasheet, make 2 photocopies. Pass one of the copies to the local trial neonatal co-ordinator and send the other copy to The INNOVO Trial Data Co-ordinating Centre in the FREEPOST envelope provided.

4.   At discharge home, transfer to another hospital, death or 3 months of age, whichever is soonest

Ensure a cerebral ultrasound is carried out at 36 weeks gestational age (for babies <34 completed weeks gestation at birth) or discharge from hospital (for babies =34 completed weeks gestation at birth) and complete part E of the datasheet.

Complete parts F and G of the datasheet. Make a photocopy of parts E, F and G. Pass the photocopy to the local trial neonatal co-ordinator and send the complete original datasheet to The INNOVO Trial Data Co-ordinating Centre in the FREEPOST envelope provided.

While the baby is in hospital , the local neonatal co-ordinator or named nurse will be contacted regularly by the Data Co-ordinating Centre for brief details about the progress of the baby.

If the baby is transferred to another hospital, please let the staff at the transfer hospital know that the baby is in The INNOVO Trial and that they will be contacted by the Data Co-ordinating Centre.

If the baby dies, follow your usual procedures. If possible, seek consent from the parents for a post-mortem examination, ideally by a paediatric pathologist following Confidential Enquiry into Stillbirths and Deaths in Infancy (CESDI)[40] guidelines and inform the pathologist that the baby is in The INNOVO Trial. The name of your local pathologist is found on the inside back cover of the trial folder, and full details of the pathology study are given in the Trial Folder. A copy of the Stillbirth and Neonatal Death Society (SANDS) *Guidelines for Professionals* is found in the Trial Folder along with copies of the following leaflets: *Support for you when your baby dies (* the SANDS introductory leaflet)*, Mainly for fathers* and a copy of *Saying Goodbye to your baby*.

For centres taking part in the toxicology study, broncho-alveolar lavage fluid[41] from babies randomized in both arms of the trial will be collected.

5.   At one year of age (corrected)

Surviving children will be seen by their local paediatricians who will be asked to complete a trial follow-up datasheet.

Eligible babies will be invited to participate in respiratory function tests. These tests will take place at one of two centres (Hospital for Sick Children at Great Ormond Street, or Leicester Royal Infirmary). Arrangements will be made to pay parents' travel expenses.

Further follow-up is the subject of a separate protocol.

Sample size:

The size of the trial is calculated separately for babies born preterm, and 'mature' babies based on data from the pilot trial.

a) Preterm babies: To detect whether INO reduces the primary outcome of death or severe disability at one year (corrected) from 60% to 40% (i.e. RR of 0.67) with α of 0.05 (2-sided) and 80% power would require a total sample size of approximately 200 babies, which would also allow us to detect a reduction in the short term outcome from 75% to 55%.

b) 'Mature' babies: Assuming recruitment of 'mature' babies ceases at the same time as for preterm babies, a further 86 'mature' babies are likely to have been recruited. The total sample size of 110 (including the 24 recruited in 1997/8) could detect whether INO could reduce the primary outcome of death or severe disability at one year (corrected) from 31.5% to 8.5% (i.e. RR of 0.27) with α of 0.05 (2-sided) and 80% power, although recruitment of 110 'mature' babies would be sufficient to detect a reduction in the short term outcome from 70% to 40%.

Interim analysis:

An independent Data Monitoring Committee (DMC) has already reviewed, in strict confidence, the results of the pilot trial. In the main trial, the DMC will consider at least one further interim analysis of the main trial. In the light of these data, and other evidence from relevant studies, the DMC will inform the Steering Committee, if in their view i) there is proof beyond reasonable doubt that the data indicate that any part of the protocol under investigation is either clearly indicated or contra-indicated, either for all babies or for a particular subgroup, or ii) it is evident that no clear outcome will be obtained with the current trial design. Unless modification or cessation of the protocol is recommended by the DMC, the Steering Committee, collaborators and administrative staff (except those who supply the confidential information) will remain ignorant of the results of the interim analysis.

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